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Anticipating 3rd COVID Wave: If we Sweat in Peace, Less we Bleed in War

Mangesh Tiwaskar¹, Agam Vora²

The word ‘wave’ has always had pleasing connotations related to the sea or watersports. However, in this world hit by the unprecedented Coronavirus Disease 2019 (COVID-19) pandemic, the rise and fall of infections have been denoted as ‘waves,’ rather than sporadic ‘outbreaks’ which puts a different spin on things.¹ The World Health Organization and other international health organizations often refer to “waves” of a pandemic, but no formal definition exists. The latest data from the World Health Organisation (WHO) states that there have been >204 million individuals (207,784,507 confirmed cases as on 17th August 2021) affected by COVID-19 which includes >4 million fatalities (4,370,424 deaths as on 17th August 2021) which boils down to approximately 5 lives lost every minute. On the other hand, the vaccination drives have resulted in >4 billion doses being administered so far, which is heartening.² But by July 2021, out of the countries affected by COVID-19, 63 had already experienced 2 waves, 40 had experienced a single wave and 10 of them had experienced 3 waves or more.¹

International research has applied the epidemic Renormalisation Group (eRG) framework to show that the arrival of the next wave of the pandemic can be mitigated by applying stringent measures to prevent viral transmission in the strolling period in between 2 waves. This is the time when infections grow linearly and appropriate measures taken during that time can stall or delay the subsequent wave. Two crucial strategies which can help in this task involve strict control of internal infected cases (i.e. within the country/region) along with efficient tracking of external infected individuals travelling in (interregional and intercountry travellers).³

Analysis of the COVID-19 wave patterns in Europe showed that the next wave can be delayed by more than 20 or 40 weeks after the ongoing one by controlling the number of new cases per million to <100 or <10 per day, respectively. Thus, instead of putting non-pharmacological interventions in place after the number of infected cases increase substantially, strict implementation of measures should aim to keep the number of newly infected cases at approximately 10 cases/million residents/day to delay the arrival of the next wave.³

India too has been reeling under the assault of the pandemic with the 1st wave sweeping the country from Jan 2020 onwards with nearly 11 million individuals being affected. The 2nd wave which began from mid-February 2021 caught us unawares due to the emergence of newer and more infectious variants of concern of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), mainly the B.1.1.7 (Alpha variant) and B.1.617.2 (Delta variant).⁴

The WHO has warned the world of the emergence of a fresh wave due to the presence of the delta variant in more than 111 countries and has predicted that it may soon become the predominant form of the infection.⁵

A mathematical modelling-based analysis illustrated that four factors may contribute to the rise of the 3rd wave in India—waning immunity, the emergence of a new immune variant with Rₚ = 2.2 which escapes 30% of prior immunity, a more transmissible variant with Rₚ of 4.5 and the release of effective lockdowns. The study also stated that the 3rd wave may not be as severe as the 2nd.⁴

Continuing Medical Education India¹ has put forth some traits which may be observed in the 3rd wave such as:

- The younger age group and children may be affected to a greater extent
- The severity of lung inflammation observed will be greater
- Fatalities may be higher

There is a need for healthcare infrastructure—more hospital beds and intensive care units (ICUs) will be required

On a broader scale, the impending resurgence in cases can be mitigated via multipronged public health strategies such as decentralised organisation of essential health services to ensure that appropriate care reaches the infected quickly, be it quarantine, triage through front-line healthcare services or primary care at the community level. Implementation of a transparent national policy on the pricing and caps placed on all essential health services can ensure access to all.⁷

Marshalling of resources from all sectors of the health system can help form a formidable COVID-19 response team and can include final-year medical/nursing/paramedical students who can be provided with appropriate training and adequate personal protective equipment. A centralised system for procurement and disbursement of vaccines free of charge can improve coverage. Transparency in data collection about the COVID-19 infection and its spread can enable states to foresee impending caseloads so that they can prepare themselves accordingly. Planned lockdowns can help businesses better prepare themselves for an economic downturn and minimise loss of livelihood,⁷ especially since the poorest 20% of households lost all income in the previous lockdowns.⁸

What we now understand is that COVID 19 is here to stay and the only way ahead is to contain its resurgence.

Pandemic preparedness planning and response can influence every aspect

¹Physician and Diabetologist, Shilpa Medical Research Centre, ²Chest Physician, Vora Clinic Mumbai, Maharashtra
of a citizen’s life and several directives have been outlined by the government in this regard. Workplace-related initiatives range from maximisation of work from home options or staggered business hours to Sanitisation/ screening/hygiene, wearing Masks and maintaining Social distancing (SMS) when in the place of business.9

The importance of vaccination cannot be emphasised enough as substantiated by the Indian Council of Medical Research (ICMR) analysis of post-vaccination breakthrough infections (n=677) that showed a predominance of the delta variant across India (except the Northern region) but resulted in decreased disease severity, hospitalisation (9.8%) and mortality (0.4%). Continuous monitoring of post-vaccination breakthrough infections and active genomic surveillance of the new SARS-CoV-2 variants can help tweak the available vaccines or develop new vaccines with greater potential to protect against emerging variant strains.10 However, so far only 8.2% of Indians are fully vaccinated with only 20% having received at least one dose.11 Thus comprehensive vaccination drives across India can help prevent the next wave of infection.

Community-based management in the form of a tiered system of co-ordination between village-level, primary referral centre, district and state-level teams can help ensure protocol adherence even in resource-poor areas. The formation of multi personnel response teams at each level can help in providing education, contact tracing, testing, symptom surveillance, isolation/quarantine facilities, telemedicine and infection control along with psychosocial support as needed.12

Allocation of healthcare resources via predictive analysis can estimate the need for healthcare facilities and help make provision for the same.9 Since the 3rd wave is likely to affect children more severely, preparation of hospital beds, especially to handle paediatric cases is of paramount importance.13 In a constantly evolving clinical management landscape, upskilling of healthcare personnel to keep them updated can help in focussed and optimised care. Containment zones can be established where test positivity is >10% during the previous week or where the occupancy of oxygen-supported or ICU beds is >60%.9

Learning from COVID-19 waves in other countries show that the use of corticosteroids and non-mechanical ventilation were enhanced in hospitalised patients of the 3rd wave vs. the 2nd wave,14 while the ICU admissions and mortality remained unchanged. Swift modifications in clinical management protocols in some patients may thus become the need of the hour.

Facilitating good mental health in healthcare workers and patients can help us respond and recover,15 irrespective of the circumstances. Post-COVID customised rehabilitation of patients can improve their overall quality of life by exercise, repeated practice of rehabilitative activities, psychosocial support and education of the patient and their carers.16 Assessing and providing adequate support to patients suffering from the physical and mental sequelae of the infection can help optimise recovery.

Digital technologies17 can form an integral part of the COVID-19 response paradigm in various ways such as providing epidemiological surveillance by developing digital dashboards, identifying cases swiftly by connected diagnostic devices/sensors, interrupting community transmission via digital contact tracing and mobility-pattern analysis, streamlining overall resource management,7 facilitating public communication via social media platforms, search engines and chatbots and ensuring clinical care via telemedicine.

However, all these strategies can achieve the desired effect only if the basic groundwork is laid by following the test-track-treat-vaccine protocol along with citizen-based initiatives involving the mandatory wearing of a mask in all public places, workplaces and during travel, maintaining social distancing of 6 feet, avoidance of spitting in public spaces, restriction of social/religious gatherings and reduction in community mobility.9

Overall, the arrival of the 3rd wave of COVID-19 may seem like a foregone conclusion but our learnings from the previous two waves can help in restructuring our response to it. Primarily, following simple measures such as SMS at all times while following the test, track and treat protocol along with adequate vaccination can help break the trail of destruction wrought by the disease and minimise the burden on the strained healthcare resources of our country. Lastly, if the several measures outlined by the government are implemented with able support from community-based groups at every tier of our country, from the rural to the urban, we can try to ‘ride’ this wave instead of merely succumbing to it. And we will conclude by quoting that winning efforts will witness sunlight only after great preparedness to prove the fact right that if we sweat in peace, less we bleed in war.

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Glimepiride 1/2/3/4 mg Tablets

SURE-shot BP drop – Nearly 80% patients treated with Olmesartan 40 mg reached target blood pressure < 130/80 mm Hg.


T2DM: Type 2 diabetes mellitus
BP: Blood pressure
Analysis of COVID Deaths: A single Centre Experience in Mumbai Medical College

Vikram Londhey, Neelam Redkar, Sanjay Gulhane, Sameer Yadav, Faisal Memon, Prakash Relwani*, Harshal Joshi

Abstract

Objectives
1. To calculate the mortality rate of COVID 19 at our centre.
2. To study age and sex distribution of COVID 19 deaths.
3. To study the duration of hospital stay with mortality.
4. To study the comorbidities associated with mortality.

Methods: This is a retrospective analytical study of COVID 19 deaths which have occurred from April 2020 to January 2021. Death records of patients who were Confirmed positive cases of COVID 19 infection by Antigen positivity or RT PCR (polymerase chain reaction) or CBNAAT were analysed based on the total number of admissions, total deaths, age and gender distribution; duration of hospital stay, co-morbidities.

Results: There were 763 deaths in our study. Total admissions were 5762. Mortality rate was 13.2%. Out of these 481 were males and 282 females. The mean age of death was in the group of 60-70 years with a median age of 64.8 years. 221 patients had ≥ 3 comorbidities, 162 had ≥ 2 comorbidities. 172 had single comorbidities and 208 no comorbidities.

Conclusions: COVID 19 affects people of all age groups and gender. It neither spares people with comorbidities nor those without any comorbidities. There is no specific therapy for its treatment. Hence Vaccination, and use of masks, social distancing and sanitization are the policies which will help in the long run.

Introduction

Covid 19 which began in Wuhan, China gradually became a pandemic disease. It caused severe morbidity and mortality across the globe. The First case was reported in India on 27th January 2020 and in Mumbai on 12th March 2020. After that the cases started rising tremendously and now we are experiencing the second wave. Till date there have been 105 million cases of Covid 19 globally and 2.28million deaths.1,2 In India, 10.8 million cases have been diagnosed and 1,55,120 deaths. Compared to the total population of India and densely populated cities like Mumbai, the death rate is relatively less as compared to the global scenario. Our institute was looking after Covid as well as non Covid patients during the pandemic. So we decided to analyse our data of deaths and compare it with the global scenario and Indian data.

Aims and Objectives

1. To calculate the mortality rate of COVID 19 at our centre.
2. To study age and sex distribution of COVID 19 deaths.
3. To study the duration of hospital stay with mortality.
4. To study the comorbidities associated with mortality.

Methodology

This is a retrospective analytical study of COVID 19 deaths which have occurred from April 2020 to January 2021 at HBT Medical College and RN Cooper Hospital Mumbai. The data was collected from Medical record department of the institution after obtaining Ethics Committee permission for the study. Since it was analysis of the data from the indoor case papers and no risk was involved, a waiver of consent was granted by the Ethics Committee. Patients who died and who were Confirmed positive cases of COVID 19 infection by Antigen positivity or RT PCR (polymerase chain reaction) or CBNAAT specimen collected by a nasopharyngeal swab were included in the study. The data was analysed based on the total number of admissions, total deaths, age and gender distribution. The deaths were classified as deaths in general wards with oxygen beds or those in the ICU (Intensive Care Unit). The data was analysed to find out the common comorbidities that were associated in individual patients. The number of patients having more than 1 comorbidity were analysed separately and whether any correlation with death with increasing comorbidities was also looked at. The duration of hospital stay

Fig. 1: Total deaths and gender distribution

Deaths= 763
- Males: 481
- Females: 282

1Associate Professor, 2Professor and Head, 3Additional Professor, 4Assistant Professor, HBT Medical College & Dr. R.N. Cooper Hospital, Mumbai, Maharashtra; *Corresponding Author

Received: 01.04.2021; Accepted: 01.07.2021
had ≥ 2 comorbidities. 172 had single patients had ≥ 3 comorbidities, 162 in 22, Atrial fibrillation in 7. 221 Comorbidities like stroke were seen Tuberculosis 5, HIV 3, COPD 27. Other heart disease (IHD) 31, Cancer 19, kidney injury (AKI) 29, Ischaemic Kidney disease (CKD) in 22, Acute hypertension (HTN) 188, Chronic Diabetes Mellitus (DM) 198, Ischaemic heart disease (IHD) 31, Cancer 19, Tuberculosis 5, HIV 3, COPD 27. Other Comorbidities like stroke were seen in 22, Atrial fibrillation in 7. 221 patients had ≥ 3 comorbidities, 162 had ≥ 2 comorbidities. 172 had single comorbidities and 208 no comorbidities (Figure 3).

The deaths which took place based on the duration of admission in the hospital were as follows 209 < 24 hours, 401 > 24 to less than 72 hours, 130 > 72 hours to less than 1 month and 23 patients died after 1 month of hospital stay (Figure 4).

**Discussion**

The mortality rate in India is 1.45%. The deaths are calculated from all the states including Covid care centres where mild to moderate cases are admitted. The mortality rate is lower in centres which were treating mild to moderate cases. DCH and DCHC are referral centres for severe cases needing oxygen/ICU care. Our centre is a tertiary care medical college where seriously ill patients are admitted requiring Intensive care management and high flow oxygen and hence our death rate is high 13.2%. It is lesser than other teaching hospitals in Mumbai. In a retrospective cohort study from China, the mortality of 28% was reported. In a study by Safiya Richardson from US, the death rate reported was 21%. In a postmortem surveillance study from Lusaka Zambia, Lawrence Mwananyanda has reported the death rate to be around 19%.

In a study by Y Lawal, lower mortality rate from Africa as compared to the developed world have been analysed. It was found in this study that positive predictors of covid deaths were population mean age, life expectancy and pre COVID era mortality % of 65 plus individuals. Pre COVID era Cardiovascular mortality rate was a negative predictor of COVID 19 deaths in Africa.

In the present study, 130 patients remained in the hospital and ICU for more than 72 hours and sometimes as long as 1 month before death. There were 23 patients who were hospitalized for more than 1 month before they succumbed to their illness. The average stay in the ICU was 48 hours before death.

Many of the male migrant workers, construction workers were admitted with severe COVID and hence the number of male deaths outnumbers the female deaths. Some unknown male patients brought by police found on the roadside during lockdown added to the number of male deaths.

As many geriatric patients were also admitted with severe Covid infection, the death rate amongst them was higher compared to the younger patients. Geriatric patients had comorbidities like DM, HTN, CKD, Stroke, atrial fibrillation and hence had a higher mortality rate. As the age advanced beyond 55 years the risk of mortality increased; however it was not statistically significant (p=0.08).

The severe cases with Sepsis, Septic shock, Covid pneumonia, pulmonary embolism, myocardial infarction, diabetic ketoacidosis were admitted in the ICU. When the patients were clinically unstable, there was difficulty in maintaining oxygen saturation above 95% and a CT severity index was more than 20/25, these patients required high frequency nasal cannula (HFNC), BIPAP support and Invasive ventilation. These patients were also treated with Remdesivir and Tocilizumab when required on a case to case basis. 59 patients who received Remdesivir died and 27 who received Tocilizumab also died. Patients who had uncontrolled diabetes, uncontrolled hypertension, CKD, electrolyte imbalance were the ones who died despite the ICU care. The commonest electrolyte imbalance was hyponatremia.

Amongst the patients who had TB, 3 were sputum positive pulmonary Tb, one was Tuberculoma with tuberculous...
There were 19 cases who had Cancer. Of them, 7 had prostate, 2 Hepatocellular Ca, 2 Renal tumor, 2 had buccal mucosa Ca, 2 Ca breast, 2 Colonic Ca, 3 Pyriform fossa. Some of them were operated for the current admission.

Two patients had stopped ART 2 months before the admission. All 3 patients of HIV infection had disseminated metastasis to liver, had no primary cancer and were receiving chemotherapy or were inoperable and were advised palliative care. 3 patients had Ca brain, lymph nodes and were advised ventilator support.

In the initial lockdown period, due to late presentation to the hospital and in later stages, due to fear of hospitalization, patients were coming late to the hospital, hence many patients succumbed within first 24 hours of hospitalization. This was mainly seen in the month of May and June 2020. Amongst the hospitalized patients some patients who were in the ‘happy hypoxia’ phase suddenly collapsed in the initial days. Their CT pulmonary angiogram confirmed pulmonary embolism. The Asymptomatic patients as all the referred covid critically ill patients were admitted. Hence a higher rate of mortality as many patients succumbed due to fear of hospitalization. Therefore it would not be wise to conclude that patients without comorbidities do not have the risk of death. Severe COVID infection itself is a risk factor for mortality.

**Limitations**

1. This is a single centre study. It is a retrospective analysis hence only the data which is captured in the indoor papers has been analysed.

2. In patients with severe comorbidities whether the death was related to COVID itself or the underlying comorbidity cannot be ascertained in all the cases.

3. There would be a referral bias as it is a study from a tertiary care centre and hence a higher rate of mortality as many critically ill patients were admitted.

4. There is no control in selecting patients as all the referred covid positive patients were admitted.

**Conclusion**

COVID-19 affects people of all age groups and gender. It neither spares people with comorbidities nor those without any comorbidities. Hence social distancing, proper usage of mask covering the nose and mouth and sanitization will be long lasting self disciplinary measures to curtail the spread of this disease. Prevention is always better than getting affected with the disease. Now, although vaccine is available, the virus is also coming up with newer mutations. Hence we have to be careful about this global pandemic which comes up with some unique surprises every single day!

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### Table 1: Analysis of the Deaths based in duration of hospital stay, number of comorbidities and age in years

<table>
<thead>
<tr>
<th>Total Deaths (N=763)</th>
<th>Males (N=481) 63%</th>
<th>Females (N=282) 37%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death based on duration of Hospital stay</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Within 24 hours (N=209)</td>
<td>153(20.5%)</td>
<td>56(7%)</td>
</tr>
<tr>
<td>&gt;24 hours &lt; 72 hours (N=401)</td>
<td>234(30.6%)</td>
<td>167(21.8%)</td>
</tr>
<tr>
<td>&gt;72 hours upto 1 month (N=130)</td>
<td>84(11%)</td>
<td>46(6%)</td>
</tr>
<tr>
<td>&gt;1 month(N=23)</td>
<td>10(1.3%)</td>
<td>13(1.7%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>No. of Comorbidities</th>
<th>No comorbidities (N=208)</th>
<th>1 comorbidity (N=172)</th>
<th>2 comorbidities (N=162)</th>
<th>3 comorbidities (N=221)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Males</td>
<td>157(20.5%)</td>
<td>104(13.6%)</td>
<td>97(12.7%)</td>
<td>123(16%)</td>
</tr>
<tr>
<td>Females</td>
<td>51(6.6%)</td>
<td>68(9.8%)</td>
<td>65(8.5%)</td>
<td>98(12.8%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Age in years</th>
<th>&lt; 55 (N=255)</th>
<th>55-70 (N=198)</th>
<th>70-80 (N=148)</th>
<th>80-90 (N=137)</th>
<th>&gt; 90 (N=23)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Males</td>
<td>143(18.7%)</td>
<td>110(14.4%)</td>
<td>69(9%)</td>
<td>82(10.7%)</td>
<td>12(1.5%)</td>
</tr>
<tr>
<td>Females</td>
<td>112(14.6%)</td>
<td>88(11.5%)</td>
<td>79(10.3%)</td>
<td>55(7.2%)</td>
<td>11(1.4%)</td>
</tr>
</tbody>
</table>

**References**

3. COVID-19 India. https://www.mohfw.gov.in

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**Office Bearers of Muzaffarpur Branch of Association of Physicians of India for the Year 2021 - 2022**

**Chairman:** Dr. Satish Kr. Singh  
**Hon Secretary:** Dr. Navneet
In high grade fever & pain

Nise
Nimesulide 100 mg tablets

Get well. Sooner...

STARTS ACTION WITHIN
15 MINUTES

References

Nise (Abbreviated Prescribing Information) India

Name of Medicinal Product: Nise (Nimesulide). Dosage form and Strength: Each blistered tablet contains: Nimesulide BP 100 mg Therapeutic Indication: In the short-term treatment of inflammatory conditions including joint disorders such as rheumatoid arthritis, post-traumatic and post-operative painful conditions and fever. Dosage and Administration: The usual adult dose is 100 mg twice daily, orally, given in Special Precautions. Patients with renal impairment: Patients with renal impairment should use nimesulide with caution. Patients with severe renal impairment should probably avoid using nimesulide. Patients with hepatic impairment: Nimesulide should not be administered in moderate to severe hepatic impairment. Use in Asthmatic Patients: As with other NSAIDs, caution should be exercised when using nimesulide in patients with bronchial asthma, Pregnancy and Lactation: Safety and efficacy of nimesulide in pregnancy and lactation women have not been established. Therefore, nimesulide is not indicated for use in pregnant and lactating women. Contra-Indications: Known hypersensitivity to nimesulide. History of hypersensitivity reactions (bronchospasm, rhinitis, urticaria) to aspirin or other NSAIDs. Patients with active peptic ulcer disease. Patients with hepatic or renal impairment. Pregnancy and lactation. Precautions: Caution is advised when administering warfarin and nimesulide concurrently. Unfavorable effects: Among the adverse events reported with nimesulide, the common ones are gastro-intestinal disturbances (epigastric pain, heartburn, nausea, diarrhoea, vomiting), skin reactions (rash, pruritus) and CNS effects (dizziness, somnolence, headache). Nimesulide has been reported to cause hepatic adverse events, ranging from mild abnormal liver function to severe liver injuries including fatal hepatic failure in a few cases. Most of these patients were elderly women. It is reported that this adverse event appears to be idiosyncratic or immunological in nature. Overdose: No information is available on overdosage with nimesulide.

Date: 30 Apr 2018

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Dr. Reddy’s Laboratories Ltd., Global Generics India, 7-1-27, Ameerpet, Hyderabad - 500 016, India. www.drreddys.com
Clinical Spectrum of COVID-19 Cases and their Correlation with S.LDH Levels- An Observational Study from Southeast Rajasthan

Deepak Gupta1*, Ramavtar Sharma2, Bhalachandra Patwardhan3, Rajendra Dutt Mathur4

Abstract

Introduction and Background: The novel coronavirus or commonly referred to as the covid-19, has been a threat to the global health as well as the world economy. It all started from the Wuhan city of china in December 2019, when a cluster of pneumonia cases with severe acute respiratory symptoms were reported with unknown etiology, majority of cases linked to the exposure to wholesale seafood market in Hunan. On January 7th, after the nomenclature of this causative agent was done as Corona Virus Disease 2019, COVID19, the struggles to combat and try to control this illness have only so far been less helpful as more and more countries have exponential proportion of cases. On the other side of the illness are the efforts being done constantly to study the characteristics of the virus, newer treatment agents, expanding testing facilities and finally to find a vaccine as soon as possible.

Although most human coronavirus infections are mild, the epidemics of the two beta corona viruses, severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle East respiratory syndrome coronavirus (MERS-CoV)20-24 have caused more than 10 000 cumulative cases in the past two decades, with mortality rates of 10% for SARS-CoV and 37% for MERS-CoV. The 2019-nCoV has features typical of the coronavirus family and was classified in the beta coronavirus. Four viruses — (HCoV 229E, NL63, OC43, and HKU1) are endemic globally and account for 10% to 30% of upper respiratory tract infections in adults and typically cause common cold symptoms in immunocompetent individuals.

Currently, the patients infected by the novel coronavirus are the main source of infection. Although asymptomatic infected can also be a source. Transmission of the virus happens mainly through respiratory droplets and close contact (defined as that within 1m distance and lasting for several minutes). A possibility of aerosol transmission in a relatively closed environment for a long-time exposure to high concentrations has also not been denied as of yet.

Since the information regarding the illness, the treatment principles have been in constant scrutiny and have been changed dynamically as we get to know more about the virus, studies of covid19 cases would be a major stepping stone in acquiring maximum if not hundred percent knowledge about covid19.

Materials and Methods: An observational retrospective case study was done for a fixed duration of a month i.e from 23/05/2020 to 23/06/2020. Patients satisfying the inclusion and exclusion criteria were included under the study.

Inclusion criteria:
1. Age >40yrs with symptoms of severe acute respiratory Illness (screened as per the symptom suggestive of acute respiratory illness, mohfw.gov.in)
2. Asymptomatic aged >40yrs with comorbidities and in direct contact with confirmed cases of covid19.

Exclusion criteria:
1. Immunocompromised patients.
2. Pregnant patients.
3. Autoimmune disease patients
4. History of psychiatric illness.

The patients were isolated in different wards based on the presence or absence and severity of symptoms. Detailed history, general and systemic examination and investigations were done. Samples of throat and nasal swab were sent for RT-PCR assay of covid19 testing done by Real time reverse transcriptase based PCR. Regular monitoring of patients was done. Treatment given based on the most recent guidelines update by the ICMR and made available by the Ministry of Health and Family Welfare.

Received: 18.09.2020; Accepted: 20.07.2021
Introduction

Epidemics and pandemics from viruses remains a big threat to humans, yet now all the world is facing a new pandemic named covid-19. It all started from the Wuhan city of china in December 2019, when a cluster of pneumonia cases with severe acute respiratory symptoms were reported with unknown etiology, majority of cases linked to the exposure to wholesale seafood market in Hunan.

On January 7, 2020, the causative agent of this pneumonia outbreak a novel coronavirus was isolated and named as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) by the International Committee on Taxonomy of Viruses (ICTV) causing a disease named CORONA VIRUS DISEASE 2019, later on pronounced COVID-19, proceeding which the human to human transmission of the virus was confirmed.1,2

Patients with severe acute respiratory syndrome having pneumonia were called Coronavirus Disease 2019 (COVID-19) by the World Health Organization on February 11, 2020. The WHO then declared Covid-19 as a global pandemic on 11th March 2020.3

Until now the disease has spread rapidly to more than 200 countries and as on the 23rd July 2020 a total case count of 15,380,131 with number of recovered cases being 9,355,496 and number of deaths reported to be 630,334 affecting globally with an adverse impact on mental health, as well as on social and economic status. The first confirmed case of covid-19 in India was diagnosed on 30th January 2020. As of now i.e 23rd July 2020 India is the 3rd most affected country in the world after USA and Brazil with total no of cases being 1,239,684 in which 784,266 have recovered and 29,890 have succumbed.

Statistical Analysis: Data was analysed by using SPSS 22.0 (trial version) software and T test, Chi-square Pierson’s correlation and other appropriate statistical test will be used to analyse the data.

Aims & Objectives: To understand the symptomatology, disease course and complications of covid19.

To study the changes in laboratory parameters in association with severity of illness.

To study the effect of presence of comorbidities with respect to the outcome of covid19

Ethical Considerations: Since it being a retrospective observational study, complete patient confidentiality was being maintained while collecting and analysing the data as well as during the tabulation of the results.

Table 1: Distribution of Study Subjects according to the Age (N=48)

<table>
<thead>
<tr>
<th>Age (in Years)</th>
<th>No.</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>41-50</td>
<td>11</td>
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</tr>
<tr>
<td>51-60</td>
<td>18</td>
<td>37.5</td>
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<tr>
<td>61-70</td>
<td>13</td>
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<tr>
<td>71-80</td>
<td>5</td>
<td>10.4</td>
</tr>
<tr>
<td>&gt;80</td>
<td>1</td>
<td>2.1</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>59.60 (10.53)</td>
<td></td>
</tr>
<tr>
<td>Range</td>
<td>41-84</td>
<td></td>
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Table 2: Descriptive Statistics of various parameters used in the Study (N=48)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Mean</th>
<th>SD</th>
<th>Range</th>
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</thead>
<tbody>
<tr>
<td>HTN</td>
<td>22.9</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asthma</td>
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<td></td>
</tr>
<tr>
<td>CKD</td>
<td>2.1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>COPD</td>
<td>2.1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>DM</td>
<td>18.8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CVA</td>
<td>8.3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CAD</td>
<td>6.3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fracture Femur</td>
<td>2.1</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Fig. 1: Distribution of symptoms

Fig. 2: Distribution of Comorbidities (% of study subjects)

Fig. 4: Distribution of Study Subjects according to the spectrum of illness (N=48)

(HTN-hypertension, CKD-chronic kidney disease, COPD-chronic obstructive pulmonary disease, DM-diabetes mellitus, CAD-coronary artery disease, CVA-cerebrovascular accident)
Coronaviruses belong to the subfamily Coronavirinae, family Coronaviridae, a monophyletic cluster in the order Nidovirales.

Full-genome sequencing and phylogenetic analysis indicated that 2019-nCoV is a distinct clade from the beta corona viruses associated with human severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS).\textsuperscript{13-18}

The name Coronavirus was inspired by the equi-distribution of the spike glycoproteins on the virion surface when viewed under the electron microscope giving the viral particle the appearance of the solar corona. Among the classified coronavirus species, 15 belong to Alphacoronavirus and Beta coronavirus and mainly infect mammals, including humans, pigs, cats, and bats; two belong to Gamma coronavirus and only infect birds; while two belong to Delta coronavirus and infect marine mammals. Among the 15 classified Alphacoronavirus and Beta coronavirus species, 8 are from bats. Bats are considered ideal hosts for both alphacoronaviruses and beta coronaviruses and may play an important role in the ecology and evolution of corona viruses.\textsuperscript{19}

Although most human coronavirus infections are mild, the epidemics of the two beta corona viruses, severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle East respiratory syndrome coronavirus (MERS-CoV)\textsuperscript{20-24} have caused more than 10 000 cumulative cases in the past two decades, with mortality rates of 10% for SARS-CoV and 37% for MERS-CoV.\textsuperscript{25,26}

The 2019-nCoV has features typical of the coronavirus family and was classified in the beta coronavirus. Four viruses — (HCoV 229E, NL63, OC43, and HKU1) are endemic globally and account for 10% to 30% of upper respiratory tract infections in adults and typically cause common cold symptoms in immunocompetent individuals.\textsuperscript{27,28}

Currently, the patients infected by the novel coronavirus are the main source of infection. Although asymptomatic infected can also be a source. Transmission of the virus happens mainly through respiratory droplets and close contact either with high risk exposure or moderate risk exposure deciding the transmissibility (high risk exposure defined as being within 6 feet of an individual with confirmed covid19 infection for more than 10mins while not wearing a mask or a face shield and moderate risk exposure was defined as the same exposure time while wearing a face mask but no eye shield). A possibility of aerosol transmission in a relatively closed environment for a long-time exposure to high concentrations has also not been denied as of yet. As the novel coronavirus can be isolated in feces and urine, transmission from a feces or urine contaminated environment is also a possibility even though is not been included in forming the current guidelines.

Based on the current epidemiological investigation, the incubation period is one to 14 days (mostly 3-7 days). The main symptoms being fever, fatigue, and dry cough. Nasal congestion, runny nose, sore throat, myalgia, and diarrhoea are found in a few cases. Less common symptoms like anosmia, altered taste sensation have also been found in a few cases. Severe patients develop dyspnoea and/or hypoxemia after one week and may progress rapidly to death.\textsuperscript{6,53}

In 20\textsuperscript{th} century, bats have been established as natural hosts of source for many viral originated diseases in humans. In the last 60 years many emerging human viral infections have been linked with bats including lyssa virus, Hendra virus, Nipah virus. Corona virus was not discovered until the breakout of severe acute respiratory syndrome (SARS) in 2005, that led to discovery of coronavirus in bats. The 2019-nCoV has close similarity to the bat coronaviruses, and it has been postulated that bats are the primary source.\textsuperscript{6-12}

Table 2: Descriptive Statistics of various parameters used in the Study (N=48)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Mean</th>
<th>SD</th>
<th>Range</th>
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</thead>
<tbody>
<tr>
<td>RBS</td>
<td>107.59</td>
<td>36.07</td>
<td>48-304</td>
</tr>
<tr>
<td>WBC</td>
<td>7.62</td>
<td>2.98</td>
<td>3.82-21.53</td>
</tr>
<tr>
<td>Neutrophil</td>
<td>64.00</td>
<td>17.80</td>
<td>12.2-94.4</td>
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<tr>
<td>Lymphocyte</td>
<td>21.43</td>
<td>8.10</td>
<td>4.2-39.2</td>
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<tr>
<td>Monocyte</td>
<td>3.32</td>
<td>1.76</td>
<td>0.1-7.0</td>
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<tr>
<td>Eosinophil</td>
<td>3.95</td>
<td>8.34</td>
<td>0-57.4</td>
</tr>
<tr>
<td>Basophil</td>
<td>0.84</td>
<td>0.37</td>
<td>0.2-1.6</td>
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<tr>
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<td>247.93</td>
<td>55.53</td>
<td>82-390</td>
</tr>
<tr>
<td>HGB</td>
<td>13.93</td>
<td>1.57</td>
<td>8.90-16.20</td>
</tr>
<tr>
<td>Blood Urea</td>
<td>33.50</td>
<td>37.88</td>
<td>13-221</td>
</tr>
<tr>
<td>Serum Creatinine</td>
<td>1.11</td>
<td>1.87</td>
<td>0.3-12.9</td>
</tr>
<tr>
<td>SGPT</td>
<td>28.98</td>
<td>17.42</td>
<td>10-107</td>
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<tr>
<td>SGOT</td>
<td>39.77</td>
<td>27.87</td>
<td>18-181</td>
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<tr>
<td>LDH</td>
<td>362.25</td>
<td>100.29</td>
<td>220-624</td>
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<tr>
<td>Sodium</td>
<td>133.39</td>
<td>4.13</td>
<td>123-141</td>
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<tr>
<td>Potassium</td>
<td>4.00</td>
<td>0.35</td>
<td>3.0-6.5</td>
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<tr>
<td>Chloride</td>
<td>99.89</td>
<td>3.97</td>
<td>89-108</td>
</tr>
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</table>

Table 3: Distribution of Study Subjects according to the Investigations (N=48)

<table>
<thead>
<tr>
<th>Investigations</th>
<th>No.</th>
<th>Percent</th>
</tr>
</thead>
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<td>4.2</td>
</tr>
<tr>
<td>Elevated urea</td>
<td>4</td>
<td>8.3</td>
</tr>
<tr>
<td>Normal Creatinine</td>
<td>19</td>
<td>39.6</td>
</tr>
<tr>
<td>Elevated Creatinine</td>
<td>4</td>
<td>8.3</td>
</tr>
<tr>
<td>Elevated SGOT</td>
<td>11</td>
<td>22.9</td>
</tr>
<tr>
<td>Elevated SGPT</td>
<td>8</td>
<td>16.7</td>
</tr>
<tr>
<td>Hyponatremia</td>
<td>36</td>
<td>75.0</td>
</tr>
<tr>
<td>Hypokalemia</td>
<td>9</td>
<td>18.8</td>
</tr>
<tr>
<td>Hyperkalemia</td>
<td>1</td>
<td>2.1</td>
</tr>
<tr>
<td>Normal Chloride</td>
<td>14</td>
<td>29.2</td>
</tr>
<tr>
<td>Hyperchloremia</td>
<td>1</td>
<td>2.1</td>
</tr>
<tr>
<td>Elevated LDH</td>
<td>37</td>
<td>77.1</td>
</tr>
</tbody>
</table>
2. Asymptomatic aged >40yrs with comorbidities and in direct contact with confirmed cases of covid19.

Aims and Objectives

1. To understand the symptomatology, disease course and complications of covid19.
2. To study the changes in laboratory parameters in association with severity of illness.
3. To study the effect of presence of comorbidities with respect to the outcome of covid19.

Results

A total of 48 subjects were studied after fulfilling the inclusion criteria which had 30 male and 18 female cases. 45 subjects were residents of Jhalawar, 2 from Kota and 1 case a migrant from Punjab.

Majority of the cases belonged to the age group of 51-60years (37.5%) with the least percentage of cases being to acute respiratory distress syndrome, septic shock, refractory metabolic acidosis, coagulopathy, multiple organ failure etc. The prognosis is poor for the elderly and patients with chronic underlying diseases. The clinical course of pregnant women with COVID-19 is similar to that of nonpregnant patients of the same age. Symptoms in children are usually mild.29-31

Materials and Methods

Patients who were symptomatic (screened as per the symptom suggestive of acute respiratory illness, mohfw.gov.in) and those who were asymptomatic but with comorbidities (HTN, DM, COPD, MI, CKD) and in direct contact with confirmed cases of covid19 were included under our study. The study duration was 23/05/2020 to 23/06/2020. The patients were isolated in different wards based on the presence or absence and severity of symptoms. Detailed history, general and systemic examination was done following all the necessary SOP’s (standard operating procedures) advised while handling covid19 cases. Routine blood investigations (complete blood count, RFT, LFT, serum electrolytes, S. LDH) ECG, X-RAY and other tests sent as required. Samples of throat and nasal swab were sent for RT-PCR assay of covid19 testing done by Real time reverse transcriptase based PCR. Regular monitoring of patients was done. Discharge was done based on guidelines issued by the MOFHW and post discharge advise was given.

Data regarding the complete clinical and laboratory profile were collected and analysis done by using appropriate statistical methods.

Inclusion criteria

1. Age >40yrs with symptoms of severe acute respiratory illness

Table 4: Association between LDH and Severity of Illness (N=48)

<table>
<thead>
<tr>
<th>LDH</th>
<th>Symptomatic</th>
<th>Pneumonia</th>
<th>AKI</th>
<th>Sepsis</th>
<th>URTI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean</td>
<td>396.63</td>
<td>393.43</td>
<td>460.33</td>
<td>576.00</td>
<td>387.67</td>
</tr>
<tr>
<td>P Value</td>
<td>0.011*</td>
<td>0.376</td>
<td>0.079</td>
<td>0.029*</td>
<td>0.231</td>
</tr>
</tbody>
</table>

Table 5: LDH and its association with Symptoms (N=48)

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Elevated LDH</th>
<th>Mean (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fever</td>
<td>10 (83.3)</td>
<td>402.75 (115.75)</td>
</tr>
<tr>
<td>Sore throat</td>
<td>14 (77.8)</td>
<td>362.44 (94.75)</td>
</tr>
<tr>
<td>Cough</td>
<td>13 (81.3)</td>
<td>374.25 (115.05)</td>
</tr>
<tr>
<td>Expectoration</td>
<td>1 (100.0)</td>
<td>352.00 (100.0)</td>
</tr>
<tr>
<td>Sub</td>
<td>9 (81.8)</td>
<td>395.45 (119.58)</td>
</tr>
<tr>
<td>Chest Pain</td>
<td>4 (80.0)</td>
<td>420.60 (130.39)</td>
</tr>
<tr>
<td>Abdominal Pain</td>
<td>3 (100.0)</td>
<td>451.33 (158.05)</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>3 (100.0)</td>
<td>491.33 (113.23)</td>
</tr>
<tr>
<td>Nausea</td>
<td>6 (100.0)</td>
<td>441.00 (100.60)</td>
</tr>
<tr>
<td>Anosmia</td>
<td>6 (100.0)</td>
<td>370.00 (84.85)</td>
</tr>
<tr>
<td>Altered Taste sensation</td>
<td>6 (66.7)</td>
<td>374.67 (127.38)</td>
</tr>
<tr>
<td>Myalgia/arthralgia</td>
<td>6 (75.0)</td>
<td>392.88 (129.86)</td>
</tr>
<tr>
<td>Altered sensorium</td>
<td>2 (100.0)</td>
<td>446.00 (21.21)</td>
</tr>
</tbody>
</table>

2. Asymptomatic aged >40yrs with comorbidities and in direct contact with confirmed cases of covid19.

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A total of 48 subjects were studied after fulfilling the inclusion criteria which had 30 male and 18 female cases. 45 subjects were residents of Jhalawar, 2 from Kota and 1 case a migrant from Punjab.

Majority of the cases belonged to the age group of 51-60years (37.5%) with the least percentage of cases being...
Among the total subjects, 27 were symptomatic and the remaining asymptomatic. The most common complaint in symptomatic patients was sore throat (37.5%) followed by cough (35.4%), fever (29.2%) and breathlessness (25%). Less common associated symptoms being altered taste sensation, myalgia, anosmia and other GI complaints.

Among the patients without comorbidities, 51.7% of them were asymptomatic and among those with symptoms, majority (57.14%) of them had upper respiratory tract infection (URTI) and only 1 patient had sepsis.

Among the cases with pre-existing disease, only 38.7% of them were asymptomatic and among those having clinical illness, about half of them had URTI (52.63%) and the others had pneumonia.

The most common hemogram report was leucopenia (91.7%), predominantly lymphocytopenia(39.6%) followed by monocytopenia (18.8%), neutropenia (10.4%) and rest of the few cases having leucocytosis.

Amongst the study subjects, 79.2% had a Chest Xray within normal limits. The most common abnormal finding being unilateral pulmonary opacities (consolidation 2.1%, reticulonodular opacity 2.1%, ground glass opacity 2.1%) and ARDS constituting 6.3%.

All the symptomatic patients were given an empirical combination of hydroxychloroquine, azithromycin and oseltamivir. Based on guidelines for the management of severe COVID-19 cases, about 8.3% of cases received Lopinavir/ritonavir therapy. About 37.5% received supportive therapy with iv fluids, 16.7% required O2 therapy, 4.2% were put on CPAP non-invasive ventilation and 2.1% had to be mechanically ventilated. Around 6.3% patients received steroids in view of managing severe sepsis.

A total of 44 cases (91.6%) had complete recovery while 4 cases were undergoing treatment during the course of study. These cases also recovered fully when follow up was done later on. No mortality was observed.

Serum LDH was an important prognostic marker and risk factor correlating the severity of infection. LDH levels were found to be elevated in total of 37 cases (77.1%). S. LDH levels were significantly higher among symptomatic when compared to asymptomatic (p=0.011). And among the symptomatic, the mean values of S. LDH were higher in COVID-19 cases of sepsis and ARDS (p=0.029, significant).

Although serum LDH predicted the severity of the disease, but when the S. LDH levels and the duration of hospital stay were compared, there was no significant difference amongst the severity of illness as LDH levels change dramatically with recovery.

The average duration of hospital stay among both asymptomatic and symptomatic to become negative on throat/nasal swab and recovery of symptoms was around 5-7 days. A longer duration was of course observed among those having severe illness and those having comorbidities.

Discussion

Very few studies have been published regarding clinical profiles of COVID-19. The earliest of its kind in India was the study done by Sudhir Bhandari, Abhishek Bhargava, Shrikant Sharma et al, “Clinical Profile of COVID-19 Infected Patients Admitted in a Tertiary Care Hospital in North India”.3 They studied a total of 21 patients of which 7 were asymptomatic. Among the symptomatic, most common symptom being cough (85.71%) fever (78.57%), myalgia (64.28%). Comparing with our study which revealed, out of 48 cases, 21 were asymptomatic and the most common symptoms observed were sore throat (37.5%), cough (35.4%), fever (29.2%), breathlessness (25%), altered taste sensation (20.8%) and myalgia (18.8%). Their study showed 23.8% patients with abnormal lung infiltrates and rest having a normal x-ray. While our study had 79.2% patients with normal x-ray and most common abnormal pattern being bilateral pulmonary infiltrates (6.3%). Their study had 12 patients with normal x-ray and most common abnormal pattern being bilateral pulmonary infiltrates (6.3%). Our study also revealed elevated SGOT in 11 patients (22.9%) and elevated SGPT in 8 patients (16.7%) when compared to their study which had six patients (28.57%) with derangement in the liver function tests.

A similar study was also done in Delhi by Nitesh Gupta, Sumita Agrawal, Pranav Ish et al to describe the clinical and epidemiological profile of COVID-19 patients in their tertiary care centre.31 Their study observed a mean duration of hospital stay to be 11.54 days as compared to our study having 8.66 days of hospital stay. Out of 21 cases in their study, 11(52.4%) had a history of contact with a positive case in comparison to our observation which had 21 out of 48 cases (43.7%) with a contact history. Just like our study, the most common symptoms were cough, fever, sore throat, breathlessness and headache in descending order of percentages. As observed in our study, the most common comorbidity being hypertension (22.9%), followed by diabetes (18.8%), CVA (8.3%) and CAD (6.3%), their study also revealed 28.6% patients with comorbidities, most common being hypertension and diabetes. Their study showed a normal Xray in 95.2% cases compared to 79.2% in our study. As compared to our study, their observation had only one patient with bilateral consolidation on imaging.

The ideal management protocols were successfully implemented in the region of Bhilwara Rajasthan which became an inspiring example for the entire state and the country in controlling the spread. Arun Gaur1, Surender Kumar Meena2, Ramavtar Bairwa et al conducted a study comparing the clinical and radiological presentation of COVID-19 patients.34 The mean age of patients in this study was slightly younger when compared to that in our study (37.6yrs vs 59.6yrs). And their study also included health care workers infected during their duties. The common symptoms and associated comorbidities observed in their study were similar to the findings in our study. In addition to hypertension, diabetes and CAD they
also had a RA, CHD and COPD affected cases as well. The blood counts in their study had 9 out of 26 (34.61%) with leucopenia as compared to a higher percentage of cases of leucopenia in our study (91.7%). The chest imaging done was normal in 76.92% cases comparable to our observation of 79.2%. Based on the spectrum of illness, oseltamivir and chloroquine was given all 26 cases, azithromycin to 24, and the lopinavir/ritonavir given to only 3 cases out of which 2 patients died. Owing to a slightly different patient composition in our study, all 48 cases had received azithromycin, oseltamivir and HCQ. Broad spectrum antibiotics given to 17 cases with suspected superimposed bacterial infection. The lopinavir/ritonavir had been given to 4 cases with severe manifestations, although no mortality was observed in our study.

One of the earliest studies regarding LDH being a prognostic factor in the severity of the illness was done from the analysis of retrospective data obtained of 47 patients from Renmin Hospital of Wuhan University. While comparing non-severe and severe covid19 cases they observed higher values of AST, ALT, LDH, CRP, D-dimer and Troponin I among severe cases. Among the other values, LDH was found to be of more statistical significance and S. LDH level was considered to be a risk factor for rule out severity of covid19 patients (OR 1.02, P<0.05). Even our study had similar observations in the LDH values which were significantly elevated among those with symptoms as compared to the asymptomatic (p 0.011) and among the clinical illness, LDH levels were significantly higher among those having sepsis and ARDS (p 0.029). Their study also observed a positive correlation of LDH with CRP, AST, BNP and cTnI, while negative correlation with lymphocyte count.

A study on similar lines was done by Mei-ying Wu, Lin Yao, Yi Wang et al for the clinical evaluation of potential usefulness of serum LDH in 2019 novel coronavirus pneumonia. And they found significant differences in LDH levels between non-severe and severe group (p<0.05 vs p=0.029 in our study).

A similar study was conducted at RUHS, Jaipur by Arvind Kumar Sharma, Asrar Ahmed2, Vaseem Naheed Baig et al comparing cases and controls of hospitalized covid 19 patients. In the study, the mean age was younger as compared to that in our study (35.1+-16.6yrs vs 59.6+-10.53yrs). most of the cases observed were asymptomatic with less than 105 having symptoms (in our study, 43.7% were asymptomatic). The mean hospital stay duration was about 19 days as compared to ours which was 8.66+-4.73 days.

A study conducted studying the clinical characteristics of covid19 patients by Lei Pan, MD, PhD1,2, Mi Mu, MD et al, they observed 50.5% cases with gastrointestinal symptoms like decreased appetite (78.6%), diarrhoea (34%), vomiting (3.9%) and abdominal pain (1.9%). Our study here too reported a few cases with associated gastrointestinal complaints like nausea (12.5%), diarrhoea (6.3%) and altered taste sensation (20.8%), although these symptoms had no significant effect on the outcome of the disease.

Similar non respiratory symptoms were also found in a study done by Andrea Giacomelli, Laura Pezzati, Federico Conti, Dario Bernacchi et al, where patients were provided with self questionnaire and a cross sectional study revealed 33.9% had both altered smell and taste sensation, 5.1% had hyposmia alone and 8.5% had GI symptoms.

A collective retrospective study was done throughout China collecting data from patients of covid19 under the coordination of the National Health Commission. The study included a total of 1590 cases from around 575 hospitals. Mean age was 48.9 years. 686 (42.7%) patients were female. The most common symptom was fever on or after hospitalisation (88.0%), followed by dry cough (70.2%), fatigue (42.8%) and productive cough (36.0%). At least one abnormal chest CT manifestation (including ground-glass opacities, pulmonary infiltrates and interstitial disorders) was identified in >70% of patients as compared to our study where 6.3% had bilateral pulmonary infiltrates, 6.3% had consolidation features, 2.1% had reticulonodular infiltrates. Severe cases accounted for 16.0% of the study population. Just as in our study, even their observations had hypertension, cardiovascular diseases, diabetes, COPD and CKD as common comorbidities.

Dawei Wang, MD; Bo Hu, MD; Chang Hu, MD; Fangfang Zhu, MD et al published a study about clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus-infected pneumonia in Wuhan, China which included 138 hospitalized patients. Most patients received antiviral therapy (oseltamivir, 124 [89.9%]), and many received antibiotic therapy (moxifloxacin, 89 [64.4%]; ceftriaxone, 34 [24.6%]; azithromycin, 25 [18.1%]) and glucocorticoid therapy (62 [44.9%]). 4 patients (11.1%) received high-flow oxygen and 15 (44.4%) received non-invasive ventilation. Invasive mechanical ventilation was required in 17 patients (47.2%). In our study, 100% had received azithromycin, oseltamivir, HCQ whereas 8.3% received lopinavir/ritonavir, 35.4% had received broad spectrum antibiotics, 2 cases had NIV, 1 case was on mechanical ventilation and 6.3% received steroids. Numerous lab abnormalities were observed in severe covid ICU cases as compared to non-ICU cases like, decreased lymphocytes, prolonged PT, elevated LDH similar to observations in our study where 91.7% had leucopenia and 77.15 had increased LDH mostly in severe symptomatic cases.

**Conclusion**

A total of 48 cases were considered in our study based on the inclusion criteria.

The mean age of presentation being in the range of 51-60yrs, with a male predominance (62.5%). Majority of them belonged to local district of Jhalawar with a couple of cases being those of migrants.

The most common symptoms were fever, cough, breathlessness along with a few having associated GI symptoms and atypical complaints of altered taste and smell sensation. Hypertension, Diabetes, CVA and CAD were among the common comorbidities associated. With regards to the spectrum of illness, most of them included under study were asymptomatic (43.7%) and among those having clinical illness, majority of them (37.5%) had URTI with a few cases presenting with lobar consolidation and 3 cases had bilateral pulmonary infiltrates.

All cases were prescribed a cocktail regime of HCQ, oseltamivir, azithromycin (as per the guidelines issued during the duration when the study was being done) with 35.4% receiving additional antibiotics and 4 cases with severe illness receiving
lopinavir/ritonavir and 3 requiring assisted ventilation (2 patients on NIV, 1 patient on mechanical ventilation).

As per the laboratory parameters, leucopenia was the common blood count abnormality. Higher levels of elevations of AST, ALT and LDH were found among severe covid19 cases when compared to mild to moderate illness, although statistical significance was found only in the case of S. LDH levels. No mortality was reported.

Limitations of Study

1. The age group selected under study was skewed in terms of under representation of the younger and very elderly population.
2. Many of the young asymptomatic cases didn't undergo any investigation and hence comparisons couldn't be drawn between the symptomatic and asymptomatic.
3. The complete coagulability profile couldn't be done of all the cases under study.
4. Due to the dynamically changing guidelines of covid19 management protocol, the prognosis of mild, moderate and severe cases couldn't be accurately compared.
5. Since the advent of the pandemic, there have been several speculations regarding the mode of transmission, with droplet mode being the most accepted and proven one. As far as the clinical history of cases studied here was concerned, among the patients who were symptomatic, the source of illness could seldom be traced. And among the asymptomatic group, the details of time duration and the presence of close contact was appreciated in only a few cases. Hence our study couldn’t really add any significant points regarding the transmissibility of the disease.
6. Even though a pandemic, a much larger sample size and a longer duration of study would have given a more broader perspective regarding the illness.
7. Special group of population like pregnant, children etc weren’t considered in our study.

References

Chest Computed Tomography (CT) Severity Score Assessment to Explore Association between Tuberculosis and COVID-19 Pneumonia for Assessing the TB Bulwark against Moderate to Severe COVID-19 Infection

Rajaram Sharma1*, Sambhav Lodha2, Ritu Mehta3, Sunil Chugh4, Girish Mathur5

Abstract

Importance & Objective: First case of Covid-19 pneumonia was reported in Wuhan and soon it became pandemic.1 Pulmonary tuberculosis (TB) is mainly a disease of tropical and poor countries like India.2 Initially, it wasn't clear how these two diseases will interact with each other. We tried to determine if TB has any impact on course and prognosis of Covid-19 pneumonia.

Design & Setting: In this retrospective analytical study, data of 7774 patients were collected from various state government owned hospitals of India. Chest CT scans were reviewed for present or past stigmata of pulmonary TB, CORADS and CT severity score. Statistical analysis was done for class wise frequency distribution and association of attributes were calculated.

Results: 95.01% Patients with Covid-19 pneumonia didn’t have CT signs of history of active or old healed pulmonary TB, while 4.99% had it. In first group 44.85% mild, 36.17% moderate and 13.98% had severe disease, while in second group figure is 3.39% 1.21% and 0.40% respectively. Probability of TB providing immunity against developing moderate or severe form of Covid-19 pneumonia is 0.6778.

Conclusions: Patients with active or past history of TB are less prone to develop moderate or severe form of Covid-19 pneumonia. It may be the reason for less mortality in health resource poor India as compared to Europe or America.

Introduction

There has not been an outbreak of any communicable diseases in recent years anywhere in the world which is comparable to Covid-19 in terms of number of cases, mortality rate and geographical spread. COVID 19 (SARS-CoV-2) with common symptoms of fever and cough, culminating in breathing problems is a type of respiratory infection. More than 210 countries of the world have been affected with varying magnitude of intensity. The first case of novel Covid-19 has been from the Hubei province of China on 17th November 2019, which subsequently became the epicenter of this disease.3 The virus mainly causes flu like illness that may lead to acute respiratory distress syndrome (ARDS). The World Health Organization (WHO) labeled it as COVID-19.2,4 With the gradual reporting of cases in other countries, curfews, quarantines, stay-at-home orders, shutdowns, lockdowns and such other restrictions on free movement of people were imposed by many countries to prevent the fast spread of the severe acute respiratory syndrome SARS-CoV-2 which causes Covid-19. In April 2020 with its global spread, it was declared a pandemic.5 Till the time of the writing, there have been 116,521,281 cases registered with 2,589,548 mortalities.6 The corresponding figure for India is; 1,12,44,786 confirmed cases with 1,57,930 deaths.

The SARS-CoV-2 virus mainly affects respiratory tract and causes flu like symptoms, i.e., fever, myalgia, sore throat, breathing difficulties and pneumonia.7 Multi organ failure and death can happen in severe cases. Severity and prognosis of the disease depends on demographic factors and co-morbidities.8

CT provides a detailed and thorough assessment of the pulmonary involvement, which has greatly helped in diagnosing false negative cases. It thus, helps in assessing patient triage, prognosis, treatment monitoring and evaluation of post recovery residual fibrosis. The COVID-19 Reporting and Data System (CO-RADS) and the CT Severity Score (CTSS) developed by the Radiological Society of the Netherlands (NVvR) provide an objective and systematic pattern of reporting, which is reproducible across the world. It ranges from CO-RADS-1 of very low suspicion to CO-RADS-5 of very high suspicion, while CO-RADS-6 suggests RT-PCR positive cases. CT severity score is calculated upon the percentage of involvement of lung lobes. CT severity score ranges from 1 to 25, depending upon degree of involvement, mild score is 1-8, moderate is 9-15 and severe is 16-25.8

Tuberculosis is caused by Mycobacterium tuberculosis (M.tb.), a bacterial pathogen from Mycobacteriaceae family. It can have a latent infection to florid disseminated
involved. The most common system involved is respiratory system.9 According to WHO, there have been more than 10.0 million incident cases of TB in India, which in the subcontinent have shown a significantly higher morbidity and mortality. Approximately one fourth of world’s population is infected with M.t.b.10 As per the WHO India ranks higher in the prevalence of active or latent TB cases.11

Chest CT scan has high sensitivity for diagnosing pulmonary TB in high prevalence countries like India. Signs of active disease include multiple centrilobular nodules, tree-in-bud pattern of distribution, irregular thick-walled cavities, consolidations, pleural effusions or mediastinal lymphadenopathy.12 Healed TB is characterized by thin-walled cavities, pulmonary fibrosis, calcified granulomas or calcified pleural thickening.12

During this pandemic many studies have described protective effects of Bacillus Calmette-Guerin (BCG) vaccine in reducing COVID-19 associated mortality. The full mechanism is however not thoroughly understood and yet remains unexplained; however there have been suggestions that link BCG vaccine to trigger non-specific innate immunity, which is thought to be protective against Covid-19 pneumonia. Few studies have focused on finding association between latent tuberculosis infection (LTBI) and Covid-19 pneumonia. However, all these studies have been focused upon epidemiological data, rather than direct individual observation on chest CT scan.13,14 The present study is based on the data of chest CT scans, including Covid-19 patients, which provides more objective findings and hence a better radiological understanding.

### Aim

The study is meant to assess immunomodulatory effects of TB in preventing and reducing the severity of covid-19 pneumonia in Indian population by assessing chest CT scans data of patients with and without Covid-19 infection.

### Objectives

1. To examine the association of incidence of Covid-19 pneumonia with CT severity score in patients undergoing chest CT scan in state government owned hospitals of India.
2. To calculate the extent of healed or active pulmonary TB in patients undergoing chest CT scan in state government owned hospitals of India.
3. To work out the probability and other statistical measures to know if TB provides immunity against Covid-19 pneumonia.

### Methodology

The present study is a retrospective analytical study based on chest CT scan data. The chest CT scan data of 7774 patients from various state government hospitals were collected from 1st June to 30th November. The data pertains to all patients referred for Chest CT scan from various districts of Rajasthan and Bihar states, during the above-mentioned time period. The peak of covid-19 pneumonia in peripheral districts started from June 2020 and hence 1st June is selected as the starting point to minimize the chances of non covid-19 atypical pneumonia cases. The mutant strain of Covid-19 was first identified in early December 2020, characteristics of which are not fully known; therefore, the CT scan data till 30th November is included for the purpose of analysis. CT scan machines in these hospitals have been installed under public-private partnership scheme of concerned state governments. Reporting of all the cases is done at single nodal center via means of teleradiology. Fully experienced and trained Radiologists have reported these CT chest scans in a common agreeable standard format, to maintain homogeneity in reporting. CT chests reports have been archived from the system and analyzed. The analysis is focused on cases of old healed TB, active TB, any signs of TB with Covid-19 pneumonia and only
Table 4: Estimate of probability of TB and Covid-19 pneumonia cases with CT severity score

<table>
<thead>
<tr>
<th>CT severity score with morbidity combination</th>
<th>Number of cases</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild CTSS and only Covid-19 pneumonia</td>
<td>1338</td>
<td>44.85%</td>
</tr>
<tr>
<td>Mild CTSS and pulmonary TB and Covid-19 pneumonia</td>
<td>101</td>
<td>3.39%</td>
</tr>
<tr>
<td>Moderate CTSS and only Covid-19 pneumonia</td>
<td>1079</td>
<td>36.17%</td>
</tr>
<tr>
<td>Moderate CTSS and pulmonary TB and Covid-19 pneumonia</td>
<td>36</td>
<td>1.21%</td>
</tr>
<tr>
<td>Severe CTSS and only Covid-19 pneumonia</td>
<td>417</td>
<td>13.98%</td>
</tr>
<tr>
<td>Severe CTSS and pulmonary TB and Covid-19 pneumonia</td>
<td>12</td>
<td>0.40%</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>Total</td>
<td>2983</td>
</tr>
<tr>
<td></td>
<td>100%</td>
<td></td>
</tr>
</tbody>
</table>

Covid-19 pneumonia. Class wise frequency distribution and Chi-square test for association of attributes had been carried out.

Results

Out of total chest CT scans 68.92% were males and 31.08% were females. Out of total chest CT scan 10.17% had active TB and 11.19% had signs of healed/old TB. Out of total chest CT scans 38.37% had signs of Covid-19 pneumonia. Out of total 2983 Covid-19 pneumonia cases only 4.99 % had Covid-19 with signs of any form of TB and remaining 95.01 % had only Covid-19 disease (Tables 1, 2).

Mean of CTSS in group with CT signs of active or Old TB is 7.3. Probability of having mild grade of Covid-19 pneumonia with TB is 0.6778. Probability of having moderate grade of Covid -19 pneumonia with TB is 0.2416. Probability of having severe grade of Covid -19 pneumonia with TB is only 0.08.

Probability of TB providing immunity from developing moderate or severe form of Covid-19 pneumonia is only 0.08. (Tables 3, 4).

The chi-square test or association of CTSS with and without TB is significant implying presence of TB pulls down in the severity of covid-19 Pneumonia.

Discussion

Covid-19 has impaired family life, reduced social harmony, distorted household income, disrupted education of children and marginalized religious faiths.

TB is endemic in many resource poor countries, like India. According to health ministry notification 2019, there were more than 2.4 million cases of TB in India.

It is estimated that about 40% of the Indian population is infected with the TB bacteria, the vast majority of whom have latent TB rather than TB disease.15

There were similar suggestions from other part of the world, that BCG vaccine has rendered some form of unexplained immunity against Covid-19 infection.15

Additionally, we have also observed that patients coming from same family, living in a common house had different CT severity scores, as in patients with CT stigmata of old healed or active TB having shown an overall lesser CTSS compared to the other family members.

Other studies have suggested that active or latent TB also provides some protection against Covid-19 pneumonia. However, none of these studies has involved chest CT as an objective marker for confirmation of old healed or active pulmonary TB. We have done this study with data attributed from chest CT of 7774 patients. Our study hence, is the first of its kind in the world as per literature. We didn’t rely on the data made available by government or WHO to calculate the association. We observed all the findings on chest CT scan by ourselves, which makes this study more authentic.

Protection from moderate or severe form of covid-19 pneumonia is probably from cross immunity. However, the mechanism of this cross immunity is not fully known till now. This maybe the reason of having the 2 nd highest number of confirmed Covid19 cases, India still sees a much lower mortality rate as compared to USA and Europe. This relation is observed with the particular strain (SARS-CoV2 belonging to the beta-corona virus genera-HCoV- NL63); same may not apply with its mutant strains.

Conclusion

Findings of our study suggest that old healed or active pulmonary TB provide protection against getting moderate and severe form of Covid-19 pneumonia, using objective criteria derived from chest CT scan.

Limitations

We could derive a statistical significance between history of old healed TB or active TB providing immunity against Covid-19 pneumonia, however we aren’t fully capable to explain this association.

The study involves patients from different geographic, social and economic categories, which might have unknown confounding effect.

References

Study of COVID-19 Infection, its Severity and Outcome in COVID-19 Vaccinated People at Tertiary Health Care Center, North West Rajasthan

Aman Thathai1, Rekha Gahlot2, Narendra Kumar Gahlot3, Ravindra B4, Man Mahendra Singh5, Prem Prakash5, Virendra Pal Singh6, Hardik Bajaj7, Aditya Kochar7*, Sanjay Kumar Kochar8

12nd Year Resident, General Medicine, 2Associate Professor, Anatomy, 3Assistant Professor, Emergency Medicine, 43rd Year Resident, General Medicine, 52nd Year Resident, General Medicine, 6Assistant Professor, PSM, 7 Intern, 8Senior Professor, General Medicine, Sardar Patel Medical College and Associated Group of Hospital, Bikaner, Rajasthan; *Corresponding Author

Objective: Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the causative agent of corona virus-induced disease 19 (COVID-19) that was declared as a global pandemic in March 2020 by the world health organization (WHO). Two vaccines were granted for emergency use by the Central Drugs Standard Control Organization (CDSCO) in India, Covishield® (AstraZeneca’s vaccine manufactured by Serum Institute of India) and Covaxin® (manufactured by Bharat Biotech Limited). Sputnik - V has been granted EUA in the month of April 2021. The purpose of this study is to determine the association of COVID-19 infection, its severity and outcome in COVID-19 vaccinated people.

Methods: This was a hospital based prospective cohort study done between March to June 2021 at PBM & Associated Group of Hospitals (AGH), Bikaner, Raj. Total 1028 COVID suspected cases consulted in COVID OPD or hospitalized under department of medicine, out of which 146 satisfied the inclusion and exclusion criteria, out of these 146, first 100 cases who gave consent for part of study were selected.

Results: Among 100 COVID-19 infected cases, 49 received first dose while rest got both doses. After first dose of vaccination 42.86% had mild and 32.65% had severe clinical infection while after both doses 80.39% had mild and 11.76% had severe clinical infection. On evaluation of HRCT Chest, after first dose 8.16% had normal & 40.82% were in severe category while those who got both doses it was 52.82% & 3.92% respectively. Among 49 who got first dose, 10.20% recovered on just home based treatment without any need of hospitalization, while 89.8% got admitted in dedicated COVID hospital out of which 73.47% got recovered and 16.33% died. Among 51 who got both the doses, 66.67% recovered on just home based treatment, while 33.33% required hospitalization out of which 25.49% got recovered and 7.84% died.

Conclusion: After 2nd dose of vaccine there is a significant risk reduction in need of hospitalization and getting severe infection and mortality when compared with first dose only.

Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the causative agent of corona virus-induced disease 19 (COVID-19) was first reported in December 2019, in Hubei Province, China, from where it spread rapidly to all over the globe. COVID-19 was declared as a global pandemic in March 2020 by the world health organization (WHO). In India first case of COVID-19 infection was reported from Kerala, on January 30, 2020. Most people with COVID-19 have mild illnesses or asymptomatic, while approximately 14% develop severe disease that requires hospital admission and oxygen therapy, and 5% patients need an Intensive Care Unit (ICU) treatment.

Two vaccines were granted for emergency use by the Central Drugs Standard Control Organization (CDSCO) in India, Covishield® (AstraZeneca’s vaccine manufactured by Serum Institute of India) and Covaxin® (manufactured by Bharat Biotech Limited). Sputnik - V has been granted EUA in the month of April 2021.

The purpose of this study is to determine the association of COVID 19 infection, its severity and outcome in COVID 19 vaccinated people at tertiary healthcare center, Bikaner, Rajasthan.

Material and Methods

This was a hospital based prospective cohort study carried out between March to June 2021 at P.B.M. & Associated Group of Hospitals, Bikaner, Rajasthan, with sample size of 100 selected via convenient sampling. Total 1028 cases consulted in COVID OPD or hospitalized under department of medicine, out of which only 146 satisfied the inclusion and exclusion criteria among them first 100 cases who gave consent for being part of study were selected.

In this study, exposure is taken as COVID-19 infection after first or both doses of COVID-19 vaccine and outcome is taken as recovery at home based treatment or need of hospitalization leading to recovery or death of participant.

Inclusion Criteria

1. Patient should be vaccinated by first or both dose of COVID-19 vaccine.
2. Patient should be RTPCR COVID-19 positive or clinical suspicion and radiological evidence of COVID-19 infection.

3. No history of COVID-19 infection in past.

Exclusion Criteria
1. Age less than 18 years.
2. Those who refused to give consent.

Primary predictors
Severity is defined on the basis of clinical status of patients (Table 1) and radiological HRCT Chest Score (Table 2) of COVID-19 infection.

Statistical analysis
Differences in COVID-19 infection and its severity following first and second dose of COVID-19 vaccination was compared, using chi square test for categorical variables and ANOVA for continuous variables. The level of significance was kept at 95% for all statistical analysis, p value <0.05 was taken as statistically significant. It was then exported into SPSS 17.0 software.

Results

Table 1: Severity according to clinical status

<table>
<thead>
<tr>
<th>Severity</th>
<th>Clinical status</th>
<th>Respiratory rate</th>
<th>SPO2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild</td>
<td>Respiratory rate &lt;24/min &amp; SPO2 &gt;94% room air</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Moderate</td>
<td>Respiratory rate 20-30/min or SPO2 90-94% room air</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Severe</td>
<td>Respiratory rate &gt;30/min or spo2 &lt;90% room air or less than &lt;94% with oxygen or ARDS or septic shock</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 2: Severity according to HRCT Chest Score

<table>
<thead>
<tr>
<th>Severity</th>
<th>HRCT chest score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild</td>
<td>1-8</td>
</tr>
<tr>
<td>Moderate</td>
<td>9-15</td>
</tr>
<tr>
<td>Severe</td>
<td>More than 15</td>
</tr>
</tbody>
</table>

Among 100 cases, 49 cases were vaccinated for first dose only while 51 cases for both the doses. 44(89.80%) out of 49 cases who got only first dose were vaccinated with Covishield while 5(10.20%) got Covaxine. Similarly for both doses, 50(98.04%) out of 51 got Covishield while only 1(1.96%) got Covaxine (Figures 1, 2).

Among 100 cases, 63 were males and rest females. In our sample of 100 cases, 38 were health care workers while rests were general population. Out of 100 cases tested for RTPCR 73 turned positive of which 30 (41%) got one dose while 43 (58.9%) got both doses of vaccine. Rest 27 cases were negative on RTPCR but HRCT Chest strongly suggestive of COVID-19 infection. Patients were categorized based on their clinical status. In 49 patients who got only first dose, 21 (42.86%) had mild infection, 12 (24.49%) had moderate and 16 (32.65%) landed up with severe infection. In 51 cases who got both doses, 41 (80.39%) had mild infection, 4 (7.84%) had moderate while 6 (11.76%) had severe COVID-19 infection (Figure 3). On the basis of HRCT Chest Scoring, 49 patients who got only first dose 4 (8.16%) had normal HRCT Chest but confirmed RT-PCR positive, while 15 (30.61%), 18(36.73%), and 20(40.82%) cases were categorized into mild, moderate and severe respectively. Among 51 who received both doses of vaccine, 30(58.82%) had a normal HRCT Chest, while 10(19.61%), 9(17.65%) and 2(3.92%) cases were categorized into Mild, Moderate and severe respectively (Figure 4 and Table 3).

On analyzing age groups we observed that 80% of cases <45 years age, 7% of 45-60 years and none of age >60 years recovered on just home based treatment. While only 20% of <45 years needed hospitalization but the number grew to 66.67% and 70% in ages 45-60 years and >60 years respectively. There was no mortality noted in cases <45 years of age which grew exponentially to 10% in 45-60 years and 30% in >60 years. This gives a clue that the effectiveness of vaccine is more in younger population as compared to older age groups (Table 4).

This is also suggestive from data that out of 38 HCWs, 92.1% recovered on just home based treatment and 7.90%...
Among 51 who got both the doses, 34 (66.67%) recovered on just home based treatment without any need of hospitalization, while 17 (33.33%) got admitted in dedicated COVID hospital, out of which 13 (25.49%) got recovered and 4 (7.84%) died (Figure 6).

Mean age of all the patients who died is 68.08 years with male to female ratio of 5:1. Out of 12 died, 8 (66.66%) had received only first dose of vaccine, while 4 (33.33%) died even after receiving both doses of vaccine. Mean duration of onset of symptoms after last dose of vaccination was 22 days. 8 (66.66%) had RTPCR positive report, while 4 (33.33%) had RTPCR negative report but HRCT Chest suggestive of COVID-19 infection. Of 12 patient, 7 (58.33%) had co-morbidities like asthma, diabetes, hypertension, COPD, etc., rest 5 (41.66%) had no co-morbidities. On the basis of clinical parameters, 2 (16.66%) had moderate infection while 10 (83.33%) were categorized as severe. On basis of HRCT Chest, 5 (41.66%) and 7 (58.33%) were categorized as moderate and severe respectively (Table 5).

**Discussion**

Currently, the vaccine development efforts have started to come to fruition as some of the leading vaccine candidates have shown positive results in the prevention of clinical disease.8-10 In this study we observed that, there is a risk of COVID-19 infection even after vaccination & clinicians should have high level of suspicion of reported symptoms and avoid dismissing complaints as vaccine related until true infection is ruled out.

When we compared clinical severity in COVID 19 infected patients we observed that after single dose 42.86% had mild infection, 24.49% had moderate and 32.65% had severe infection while after both doses 80.39% had mild infection, 7.84% had moderate and just 11.6% had severe infection.

On comparing outcome, we observed that after first dose, only 10.20% patients recovered on Home based treatment and 89.33% needed hospitalization out of which 16.33% died, while after both the doses 66.67% patients recovered without need of hospitalization, and 33.33% needed admission out of which only 7.84% died. This data is not in concordance with the study done in AIIMS, New Delhi which reported no deaths in post vaccination COVID-19 infected cases11 but other study carried out in PGIMER Chandigarh reported deaths per thousand with a single dose was 0.25 and with both doses, it was 0.05 signifying less mortality after both dose as in concordance with our study.

This whole data emphasizes that there is a significant reduction in morbidity as well as mortality after both doses as compared to only first dose.
dose as observed in other studies also, so there is a need for boosting up vaccination programme for both the doses so as to reduce the burden on already overwhelmed health system as well as to reduce the treatment expenses. On analyzing effect of co morbidities on outcome it was observed that out of 12 deaths, 58.33% had associated co morbidities, maximum of Hypertension and Diabetes, and 41.66% had no associated co morbidity. Along with the need for reduction of modifiable risk factors, people with no co morbidities should stay vigilant as they are also at a significant risk of getting severe infection and even death.

Despite sufficient evidences available that vaccination prevents from getting severe infection and hospitalization, there are still risk of getting COVID-19 infection and even hospitalization emphasizing the need of following universal health precautions even after vaccination. This study enjoys the benefit of being carried out in the period of peak of second wave of COVID-19 and limitation of being a single center study so it is difficult to generalise the result on population.

Acknowledgements

We are grateful to Dr. Naval Kishore Gupta, Principal CMO, Medical & Health department, Bikaner, Raj and Dr. Inder Puri, Associate Professor, Department of Neurology for his valuable advice. We further give thanks to all participants for giving us consent to use this data for study.

Table 5: Distribution of deaths according to different variables

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Age</th>
<th>Gender</th>
<th>Vaccination Status</th>
<th>Duration*</th>
<th>RT PCR Status</th>
<th>Co Morbidities</th>
<th>Severity*</th>
<th>Category on HRCT Chest</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>69</td>
<td>Male</td>
<td>First Dose</td>
<td>30</td>
<td>Positive</td>
<td>HTN</td>
<td>Severe</td>
<td>Severe</td>
<td>Died</td>
</tr>
<tr>
<td>2</td>
<td>45</td>
<td>Male</td>
<td>First Dose</td>
<td>1</td>
<td>Positive</td>
<td>None</td>
<td>Moderate</td>
<td>Died</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>85</td>
<td>Male</td>
<td>First Dose</td>
<td>18</td>
<td>Positive</td>
<td>None</td>
<td>Severe</td>
<td>Died</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>66</td>
<td>Male</td>
<td>First Dose</td>
<td>44</td>
<td>Positive</td>
<td>HTN</td>
<td>Severe</td>
<td>Died</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>73</td>
<td>Male</td>
<td>First Dose</td>
<td>41</td>
<td>Negative</td>
<td>None</td>
<td>Moderate</td>
<td>Died</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>57</td>
<td>Male</td>
<td>First Dose</td>
<td>2</td>
<td>Negative</td>
<td>COPD</td>
<td>Severe</td>
<td>Died</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>62</td>
<td>Female</td>
<td>First Dose</td>
<td>23</td>
<td>Negative</td>
<td>Diabetes</td>
<td>Moderate</td>
<td>Died</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>65</td>
<td>Male</td>
<td>First Dose</td>
<td>7</td>
<td>Positive</td>
<td>Asthma</td>
<td>Severe</td>
<td>Died</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>76</td>
<td>Male</td>
<td>Both Doses</td>
<td>28</td>
<td>Positive</td>
<td>Hypertension, Diabetes, Chronic liver disease</td>
<td>Severe</td>
<td>Died</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>77</td>
<td>Male</td>
<td>Both Doses</td>
<td>9</td>
<td>Negative</td>
<td>Hypertension, Diabetes</td>
<td>Moderate</td>
<td>Died</td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>56</td>
<td>Female</td>
<td>Both Doses</td>
<td>22</td>
<td>Negative</td>
<td>None</td>
<td>Severe</td>
<td>Died</td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>86</td>
<td>Male</td>
<td>Both Doses</td>
<td>41</td>
<td>Positive</td>
<td>None</td>
<td>Moderate</td>
<td>Died</td>
<td></td>
</tr>
</tbody>
</table>

*Duration of onset of symptoms after last dose of COVID–19 vaccination (days); *Severity based on clinical parameters.

References
An Epidemiological Case Control Multi-centre Trial on Cerebral Venous Sinus Thrombosis in Western Maharashtra, India

Anand Alurkar1, Rajani Amin2, Pradeep Divate3, Suyog Doshi4, Soma Das5, Nasali Ichaporia6, Rahul Kulkarni7, Satish Nirhale8, Shripad Pujari9, Arati Ranade10, Hemant Sant11, Mangesh Udar12, Rustom Wadia13

Abstract

Introduction: Cerebral Sino-Venous thrombosis (CSVT) is common in India; this country has a heterogeneous population. Genetically and physiognomically this population differs in their diet as well as in their environment. Despite these differences CSVT has been described from all quarters of India; a common factor embracing all these patients could be nutrition.

Objectives: An epidemiological, case-control, multi-centre trial was carried out in patients of CSVT. A common factor underlying this could be nutrition which has not been highlighted in several studies. Hence, we studied the nutritional aspects of these patients.

Method: 63 patients of CSVT and 62 controls enrolled prospectively and followed for a year were investigated with special emphasis on their nutritional status.

Results: The triceps skin fold thickness, energy baseline, serum Proteins, Albumin, Hemogram and Platelet counts were lower in patients than in the controls while serum Homocysteine, carbohydrates and fats were higher in patients than in controls.

Conclusion: The results of this study confirm nutritional deficiencies in patients of CSVT and it begs the question of whether nutrition in any way is causal in CSVT. Larger multi-centric trials will help establishing causality. The study also shows that routine evaluation of thrombophila factors and immunological tests are not necessary in CSVT.

Introduction

CSVT is common in India; though epidemiological studies are unavailable, large hospital-based studies give an impression that the incidence is distinctly more than in the Western world.1,2 CSVT has been described not only from India but also in neighboring countries like Pakistan and China.3,4 India has been populated by admixture of Aryans, Dravidians, Mongolians and aboriginals; besides a commixture of races has occurred due to invasions by Moghuls, Huns, Greeks and Portuguese altogether totaling 300 endogamous groups. Genetically and physiognomically this population differs in their diet as well as in their environment. Despite all these differences CSVT has been described from all the regions of India; a common factor embracing all these patients could be nutrition. We therefore studied the nutritional aspect of CSVT patients from Western Maharashtra. A case control study to find etiologies of CSVT was therefore undertaken. The primary aim was to compare percentage of CSVT patients with nutritional deficiencies and those with abnormal thrombotic profile as compared to controls. The secondary outcome looked at short and long-term disability, death and incidence of recurrence.

Material and Methods

Patients diagnosed with CSVT between December 2012 and March 2014 in six academic hospitals were enrolled prospectively and followed up for twelve months. Simultaneously, a control arm of participants from hospital out-patients with minor illnesses or somatoform disorders, (including those as per the discretion of principal investigator), were recruited as controls. The protocol was approved by the Ethics committee. The trial was registered with Clinical Trial Registry of India (CTRI/2013/01/0032980). Sample size was determined using power equation. A sample size of 240 (120 per group using a 1:1 ratio of cases to controls) is required for the detection of a significant difference between the two groups. However, only 125 subjects (63 patients and 62 controls) were enrolled in this first phase of the study for interim analysis.

Outcomes were assessed using Modified Glasgow Coma Scale and modified Rankin Scale (mRS). Secondary outcome was classified according to the modified Rankin Scale as complete recovery (mRS 0 to 1), partial recovery, independent (mRS ≤2), dependent (mRS 3 to 5) and death (mRS 6). Relevant laboratory parameters were performed in all confirmed cases and controls shown in Tables 3, 4.

Inclusion Criteria

1. Individuals between 18 and 65 years of age.
2. CSVT confirmed by MRV or CTV.

References

1KEM Hospital and Apollo Hospital, Pune, Maharashtra; ‘BJ Medical College and Navale Medical College, Pune, Maharashtra; ‘KEM Hospital and Sahyadri Speciality Hospital, Pune, Maharashtra; ‘Bharati Vidyapeeth Medical College and Sahyadri Speciality Hospital, Pune, Maharashtra; ‘Jehangir Clinical Development Centre, Pune, Maharashtra; ‘Apollo Hospital, Pune, Maharashtra; ‘Deenanath Mangeshkar Hospital, Pune, Maharashtra; ‘DY Patil Medical College, Pune, Maharashtra; ‘Deenanath Mangeshkar Hospital, Pune, Maharashtra; ‘Jehangir Clinical Development Centre, Pune, Maharashtra; ‘Sahyadri Speciality Hospital, Pune, Maharashtra; ‘Ruby Hall, Pune, Maharashtra; ‘Corresponding Author

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Treatment given

Patients were treated with low molecular weight heparin (LMWH) for five to seven days followed by oral anticoagulation (Vitamin K antagonists) with a target International Normalized Ratio (INR) of 2–3 for a period of 6 months.

Statistical Analysis

All analyses were performed using SPSS software version 11.5 for Windows. Odds ratios (ORs) and 95% confidence intervals (CIs) are used as a measure of the association between CSVT and nutritional assessment as well as various types of thrombophilia. Fisher exact test was applied for categorical data and Student’s t-test or ANOVA for continuous data. For the outcome of death or dependence at the end of follow up, survival analysis was performed using Kaplan-Meier and Cox regression statistics.

Results

The mode of onset was acute (< 48 hours) in 27 patients (42.86%), sub-acute (> 48 hours- 30 days) in 32 (50.79%), and chronic (> 30 days) in 04 (6.35%).

Patients’ mean age was 35+10.51 years and 33% were women. Majority of the patients were vegetarians (77%).

Baseline characteristics, Clinical features and Outcome at discharge and follow up

Table 1 highlights the baseline characteristics, clinical features and percentage of patients with CSVT.

The score of mRS between 0-2 was considered as good and ≥ 3 as poor outcome. At the time of discharge, 54 (85.7%) had a good outcome and only four (6.3%) had in-hospital mortality. A total of 53 patients were followed up till the end of the study. At the end of follow-up of 1 year, 52 patients (98.1%) had no symptoms and had no significant disability. The commonest drug use associated with CSVT in women was oral contraceptives (29%). The commonest symptom seen in CSVT comprised of headache (85.71%) and seizures (31.7%). A total of 14.2% patients showed poor outcome percentage of patients with CSVT.

The commonest symptom seen in CSVT was headache (85.71%) and seizures (31.7%). A total of 14.2% patients showed poor outcome percentage of patients with CSVT.

Table 1: Base line characteristics, Clinical features and Outcome at discharge

<table>
<thead>
<tr>
<th>Parameters</th>
<th>No. of Patients</th>
<th>Outcome at discharge N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N=63 (%)</td>
<td>mRS* (0-2) Good</td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 30 years</td>
<td>23 (36.5)</td>
<td>17 (73.9)</td>
</tr>
<tr>
<td>&gt; 30 years</td>
<td>40 (63.4)</td>
<td>37 (92.5)</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>43 (66.1)</td>
<td>38 (60.3)</td>
</tr>
<tr>
<td>Female</td>
<td>20 (31.7)</td>
<td>16 (80)</td>
</tr>
<tr>
<td>Clinical Features</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>54 (85.71)</td>
<td>47 (87)</td>
</tr>
<tr>
<td>Right sided neck pain</td>
<td>4 (6.3)</td>
<td>3 (75)</td>
</tr>
<tr>
<td>Vomiting on and off</td>
<td>27 (42.8)</td>
<td>21 (77.7)</td>
</tr>
<tr>
<td>Aphasia</td>
<td>10 (15.87)</td>
<td>8 (80)</td>
</tr>
<tr>
<td>Nausea</td>
<td>7 (11.11)</td>
<td>5 (71.4)</td>
</tr>
<tr>
<td>Seizures-Generalised/Focal</td>
<td>20 (31.74)</td>
<td>19 (95)</td>
</tr>
<tr>
<td>Tingling sensation in limbs</td>
<td>7 (11.11)</td>
<td>7 (100)</td>
</tr>
<tr>
<td>Diplopia</td>
<td>7 (11.11)</td>
<td>6 (85.7)</td>
</tr>
<tr>
<td>Fever</td>
<td>9 (14.29)</td>
<td>8 (88.8)</td>
</tr>
<tr>
<td>Hemiparesis</td>
<td>19 (30.3)</td>
<td>9 (47.3)</td>
</tr>
<tr>
<td>Modified Glasgow coma score**</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3 – 8</td>
<td>63 (100)</td>
<td>54 (85.7)</td>
</tr>
<tr>
<td>9 -12</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>13-15</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Localisations of Thrombosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thrombosis of the right transverse</td>
<td>26 (41)</td>
<td>22 (84.6)</td>
</tr>
<tr>
<td>Sigmoid sinus</td>
<td>38 (60.3)</td>
<td>34 (89.4)</td>
</tr>
<tr>
<td>Thrombosis of the entire superior Sagittal sinus</td>
<td>39 (61.9)</td>
<td>35 (89.7)</td>
</tr>
<tr>
<td>Thrombosis of the Left transverse</td>
<td>20 (31.7)</td>
<td>16 (80)</td>
</tr>
<tr>
<td>Extensive leptomeningeval enhancement</td>
<td>1 (1.5)</td>
<td>1 (100)</td>
</tr>
<tr>
<td>Generalised cerebral Oedema</td>
<td>6 (9.5)</td>
<td>6 (100)</td>
</tr>
<tr>
<td>Straight Sinus Thrombosis</td>
<td>8 (12.6)</td>
<td>7 (87.5)</td>
</tr>
<tr>
<td>Both transverse Sinus</td>
<td>5 (7.9)</td>
<td>5 (100)</td>
</tr>
</tbody>
</table>

*Modified Rankin Scale:

<table>
<thead>
<tr>
<th>Score</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>No symptoms at all</td>
</tr>
<tr>
<td>1</td>
<td>No significant disability despite symptoms; able to carry out all usual duties and activities</td>
</tr>
<tr>
<td>2</td>
<td>Slight disability; unable to carry out all previous activities, but able to look after own affairs without assistance</td>
</tr>
<tr>
<td>3</td>
<td>Moderate disability; requiring some help, but able to walk without assistance</td>
</tr>
<tr>
<td>4</td>
<td>Moderately severe disability; unable to walk without assistance and unable to attend to own bodily needs without assistance</td>
</tr>
<tr>
<td>5</td>
<td>Severe disability; bedridden, incontinent and requiring constant nursing care and attention</td>
</tr>
<tr>
<td>6</td>
<td>Dead</td>
</tr>
</tbody>
</table>

**Modified Glasgow coma score:

<table>
<thead>
<tr>
<th>Score</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>3-8</td>
<td>Severe Loss of Consciousness</td>
</tr>
<tr>
<td>9-12</td>
<td>Moderate Loss of Consciousness</td>
</tr>
<tr>
<td>13-15</td>
<td>Mild Loss of Consciousness/ normal</td>
</tr>
</tbody>
</table>

Exclusion Criteria

1. Any known associated condition (such as cancer) and terminal illness with poor prognosis.
2. Recent (< 2 weeks) major surgical procedure or severe cranial trauma.
3. Patients who are unlikely to abide by protocol requirements.
4. Patients who are currently participating or had participated in other interventional study for last 30 days prior to their enrolment.
5. Patients who are willing to or likely to comply with all study requirements.

3. Age, gender and economically matched healthy individuals from community without any neurological conditions or previous history of thrombosis or CSVT willing to participate as controls.

4. Patients or authorized representative must be able and willing to provide written informed consent.

5. Patients who are willing to or likely to comply with all study requirements.
transverse sinus (41% right and 31% left). Multiple sinuses were involved in 90% of cases.

**General Characteristics of study group**

The general characteristics of study cohort are shown in Table 2.

**Plasma levels of various nutritional and thrombotic parameters**

The results of laboratory parameters are tabulated in Table 3. Significantly low values were observed between cases than control for total Cholesterol, hemoglobin, platelet count, total Proteins, Albumin, and Transferrin; the pre-albumin levels were non-significantly low; whereas vitamin B12, Protein S, homocysteine levels, prothrombin Time and WBC count were higher than controls. The higher levels of B12 were due to inadvertent administration of the vitamin preparation before admission or after admission to the hospital before withdrawal of the blood sample.

The data was re-arranged in Table 4 below to segregate number of cases and controls falling under normal, below normal and above normal ranges for those parameters which showed significant difference as per Table 3 above.

The values for parameters like ANA, dsDNA, APLA, Lupus anticoagulant were negative for all patients and controls. AT III was within range while protein S levels were higher than

---

### Table 2: Group Characteristics

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Cases</th>
<th>Control</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>SBP (mm of Hg) N</td>
<td>63</td>
<td>62</td>
<td>0.604</td>
</tr>
<tr>
<td>Mean</td>
<td>127.59</td>
<td>126.15</td>
<td></td>
</tr>
<tr>
<td>SD</td>
<td>15.42</td>
<td>15.62</td>
<td></td>
</tr>
<tr>
<td>DBP (mm of Hg) N</td>
<td>63</td>
<td>62</td>
<td>0.884</td>
</tr>
<tr>
<td>Mean</td>
<td>80.13</td>
<td>80.39</td>
<td></td>
</tr>
<tr>
<td>SD</td>
<td>10.29</td>
<td>9.67</td>
<td></td>
</tr>
<tr>
<td>Height N</td>
<td>63</td>
<td>62</td>
<td>0.672</td>
</tr>
<tr>
<td>Mean</td>
<td>164.44</td>
<td>163.66</td>
<td></td>
</tr>
<tr>
<td>SD</td>
<td>9.80</td>
<td>10.79</td>
<td></td>
</tr>
<tr>
<td>Head Circumference (cm) N</td>
<td>63</td>
<td>62</td>
<td>0.823</td>
</tr>
<tr>
<td>Mean</td>
<td>55.06</td>
<td>54.90</td>
<td></td>
</tr>
<tr>
<td>SD</td>
<td>4.27</td>
<td>3.70</td>
<td></td>
</tr>
<tr>
<td>Weight (kg) N</td>
<td>63</td>
<td>62</td>
<td>0.2</td>
</tr>
<tr>
<td>Mean</td>
<td>66.44</td>
<td>70.42</td>
<td></td>
</tr>
<tr>
<td>SD</td>
<td>18.82</td>
<td>15.56</td>
<td></td>
</tr>
<tr>
<td>Waist Circumference (cm) N</td>
<td>63</td>
<td>62</td>
<td>0.306</td>
</tr>
<tr>
<td>Mean</td>
<td>86.02</td>
<td>88.29</td>
<td></td>
</tr>
<tr>
<td>SD</td>
<td>12.88</td>
<td>11.84</td>
<td></td>
</tr>
<tr>
<td>Triceps Skin Fold (cm) N</td>
<td>63</td>
<td>62</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Mean</td>
<td>16.06</td>
<td>20.35</td>
<td></td>
</tr>
<tr>
<td>SD</td>
<td>5.38</td>
<td>6.93</td>
<td></td>
</tr>
<tr>
<td>BMI (kg/m²) N</td>
<td>63</td>
<td>62</td>
<td>0.735</td>
</tr>
<tr>
<td>Mean</td>
<td>25.67</td>
<td>26.16</td>
<td></td>
</tr>
<tr>
<td>SD</td>
<td>10.23</td>
<td>5.33</td>
<td></td>
</tr>
<tr>
<td>Energy Baseline N</td>
<td>54</td>
<td>62</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Mean</td>
<td>1455.28</td>
<td>1261.85</td>
<td></td>
</tr>
<tr>
<td>SD</td>
<td>255.86</td>
<td>187.26</td>
<td></td>
</tr>
<tr>
<td>Protein (gms)_Baseline N</td>
<td>54</td>
<td>62</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Mean</td>
<td>45.22</td>
<td>39.55</td>
<td></td>
</tr>
<tr>
<td>SD</td>
<td>10.32</td>
<td>6.77</td>
<td></td>
</tr>
<tr>
<td>CHO (gms)_Baseline N</td>
<td>54</td>
<td>62</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Mean</td>
<td>189.13</td>
<td>154.68</td>
<td></td>
</tr>
<tr>
<td>SD</td>
<td>40.96</td>
<td>40.38</td>
<td></td>
</tr>
<tr>
<td>Fat (Gms)_Baseline N</td>
<td>54</td>
<td>62</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Mean</td>
<td>42.74</td>
<td>34.26</td>
<td></td>
</tr>
<tr>
<td>SD</td>
<td>9.47</td>
<td>7.16</td>
<td></td>
</tr>
</tbody>
</table>

**Note:** P values mentioned show significant differences in the corresponding parameter values between the patients and controls group based on Student’s t-test. Cut off level of significance was decided to be 0.05.

### Table 3: Group Statistics for various laboratory parameters

<table>
<thead>
<tr>
<th>Group</th>
<th>Cases</th>
<th>Controls</th>
<th>P-value</th>
<th>Normal Values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Cholesterol (mg/dl) N</td>
<td>22</td>
<td>62</td>
<td>0.003</td>
<td>&lt; 200</td>
</tr>
<tr>
<td>Mean</td>
<td>160.27</td>
<td>194.82</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SD</td>
<td>45.53</td>
<td>36.02</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HDL Cholesterol (mg/dl) N</td>
<td>22</td>
<td>62</td>
<td>0.979</td>
<td>&gt; 60</td>
</tr>
<tr>
<td>Mean</td>
<td>40.91</td>
<td>41.02</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SD</td>
<td>17.71</td>
<td>13.00</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Triglycerides (mg/dl) N</td>
<td>21</td>
<td>62</td>
<td>0.9</td>
<td>Below 150</td>
</tr>
<tr>
<td>Mean</td>
<td>131.52</td>
<td>133.50</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SD</td>
<td>58.73</td>
<td>70.57</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PT (s) N</td>
<td>61</td>
<td>62</td>
<td>&lt; 0.001</td>
<td>10.5-13.0</td>
</tr>
<tr>
<td>Mean</td>
<td>14.84</td>
<td>11.29</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SD</td>
<td>6.01</td>
<td>0.56</td>
<td></td>
<td></td>
</tr>
<tr>
<td>INR N</td>
<td>55</td>
<td>62</td>
<td>0.068</td>
<td>0.85-1.15</td>
</tr>
<tr>
<td>Mean</td>
<td>2.47</td>
<td>1.16</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SD</td>
<td>5.09</td>
<td>1.30</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Haemoglobin (gm/dl) N</td>
<td>58</td>
<td>62</td>
<td>0.01</td>
<td>Male: 14-17.5</td>
</tr>
<tr>
<td>Mean</td>
<td>12.74</td>
<td>14.07</td>
<td></td>
<td>Female: 12.3-15.3</td>
</tr>
<tr>
<td>SD</td>
<td>3.46</td>
<td>1.77</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Platelet count (/cumm) N</td>
<td>56</td>
<td>62</td>
<td>0.006</td>
<td>1,50,000-4,50,000</td>
</tr>
<tr>
<td>Mean</td>
<td>235250.00</td>
<td>284677.42</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SD</td>
<td>119099.88</td>
<td>65880.86</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total WBC count (/cumm) N</td>
<td>54</td>
<td>62</td>
<td>0.024</td>
<td>4500-10000</td>
</tr>
<tr>
<td>Mean</td>
<td>12951.95</td>
<td>7195.32</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SD</td>
<td>16968.10</td>
<td>1764.14</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total Proteins (gm/dl) N</td>
<td>39</td>
<td>62</td>
<td>&lt; 0.001</td>
<td>6.4- 8.2</td>
</tr>
<tr>
<td>Mean</td>
<td>6.72</td>
<td>7.81</td>
<td></td>
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</tr>
<tr>
<td>SD</td>
<td>0.76</td>
<td>0.44</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Albumin (gm/ dl) N</td>
<td>39</td>
<td>62</td>
<td>0.004</td>
<td>3.4- 5.0</td>
</tr>
<tr>
<td>Mean</td>
<td>3.90</td>
<td>4.26</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SD</td>
<td>0.68</td>
<td>0.38</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Folic acid (nmol/L) N</td>
<td>63</td>
<td>62</td>
<td>0.104</td>
<td>2.34-17.56 ng/ml</td>
</tr>
<tr>
<td>Mean</td>
<td>6.64</td>
<td>6.54</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SD</td>
<td>4.70</td>
<td>3.07</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Homocysteine (µmol/L) N</td>
<td>63</td>
<td>62</td>
<td>&lt; 0.001</td>
<td>5.08-15.39</td>
</tr>
<tr>
<td>Mean</td>
<td>29.62</td>
<td>21.40</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SD</td>
<td>16.71</td>
<td>13.41</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Transferrin (mg/dl) N</td>
<td>63</td>
<td>62</td>
<td>&lt; 0.001</td>
<td>200-360</td>
</tr>
<tr>
<td>Mean</td>
<td>285.24</td>
<td>319.84</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SD</td>
<td>55.10</td>
<td>43.12</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AT_III N</td>
<td>63</td>
<td>62</td>
<td>&lt; 0.001</td>
<td>20-250</td>
</tr>
<tr>
<td>Mean</td>
<td>331.60</td>
<td>341.02</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SD</td>
<td>118.01</td>
<td>108.26</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vitamin B12 N</td>
<td>58</td>
<td>58</td>
<td>0.015</td>
<td>Adult: 200 - 835 Adult &gt; 60 Years: 110 - 800</td>
</tr>
<tr>
<td>Mean</td>
<td>613.68</td>
<td>297.05</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SD</td>
<td>932.03</td>
<td>231.51</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ferritin N</td>
<td>56</td>
<td>58</td>
<td>0.173</td>
<td>Male: 20-250</td>
</tr>
<tr>
<td>Mean</td>
<td>115.14</td>
<td>35.29</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SD</td>
<td>428.96</td>
<td>63.35</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre_Albumin N</td>
<td>60</td>
<td>61</td>
<td>0.720</td>
<td>15-36</td>
</tr>
<tr>
<td>Mean</td>
<td>30.34</td>
<td>32.14</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SD</td>
<td>30.48</td>
<td>24.45</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Protein_S N</td>
<td>63</td>
<td>61</td>
<td>&lt; 0.001</td>
<td>16.1-32.2</td>
</tr>
<tr>
<td>Mean</td>
<td>51.31</td>
<td>32.98</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SD</td>
<td>19.58</td>
<td>11.65</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Note:** P values mentioned show significant differences in the corresponding parameter values between the patients and controls group based on Student’s t-test. Cut off level of significance was decided to be 0.05.
controls. Protein C and Factor V Leiden Mutation were not analyzed.

**Discussion**

CSVT is caused by many factors and has varied presentations. Our literature scan showed scarcity in articles mentioning the role of nutrition in CSVT. In this prospective case control study, we have tried to look into nutrition as a contributory factor to the happening of CSVT. Its’ ubiquitous occurrence in all parts of this country and other Asian countries lead us to hypothesize that nutrition could in some way be looked into as a contributory factor amongst many.

In the present study males predominated over females (66 Vs 31%). In most of the studies the females outnumbered males due to inclusion of puerperal CSVT. In the present series no case of puerperal CVT occurred; the reason perhaps is that the study was carried out in tertiary centers and not in primary general hospital settings. Besides, it is our impression that puerperal CSVT is declining possibly due to better antenatal care and nutrition. Similar experience has been quoted by one of the large studies from South India. In their study, out of 428 patients of CSVT 42 (9.8%), suffered from post-partum venous thrombosis.

The patients and controls did not differ in their weight, height and head circumference meaning thereby that the nutritional deficiencies occurred mostly after their full physical development. The triceps skin fold thickness was significantly low in patients as compared to controls (mean 16.06 Vs 20.35 < 0.001) suggesting low body fat. The energy baseline was more in patients compared to controls (<0.001). The two major constituents of food – Carbohydrates and Fats fared significantly better than controls; serum proteins and albumin were however lower than in controls (< 0.001 and 0.004 respectively). The Homocysteine levels were higher in patients than controls; out of the three vitamins (Folic acid, Vitamin B12 and Pyridoxine), Folic acid levels were normal while that of Vitamin B12 were higher – due, probably, to intravenous administration of the vitamins before withdrawal of blood. The homocysteine levels take averagely 4-6 weeks to normalize after administration of the vitamins; it may therefore be surmised that low vitamin B12 or pyridoxine (not evaluated in this study) levels prior to injectables may have contributed to the high levels of homocysteine. The autoimmune and the thrombophilia work up was essentially noncontributory (Protein C and Factor V Leiden Mutation has not been carried out). The thrombophilia work-up, barring some selected situations, is unnecessary as has been reiterated in European Cerebral Venous Thrombosis Guidelines.

Some of the observational studies from India showed hyperhomocysteinemia in patients of CSVT and lower levels of B6; the authors of this observational study claim it to be a risk factor for CSVT. In the landmark publication of International Study on Cerebral Vein and Dural Sinus Thrombosis (ISCVT), out of 624 patients, 28 (4.5%) showed hyperhomocysteinemia. The American Heart and Stroke Association (AHA/ASA) based on five case control studies concluded that “Hyperhomocysteinemia is a risk factor for deep vein thrombosis (DVT) and stroke but has not been clearly associated with an increased risk of CSVT”. The question whether raised homocysteine is an associated factor or is causal in CSVT is unsettled.

CSVT has very low recurrence rate of 2.2 %; therefore, unlike ischemic stroke, secondary prevention trials are not executable. It is generally observed that barring few weeks after discharge, the patients continue to adhere their original – pre illness – pattern of food intake. It is enigmatic therefore why the recurrence rate remains low. CSVT in most of the patients therefore seems to be a one-time event.

How does nutrition affect the venous coagulation? The literature on this subject is sparse and the results controversial. Data about the relationship of diet to venous thromboembolism (VTE) risk is gathered from venous thrombosis in war time conditions with food rationing. Studies of diet and lifestyle factors, lipid profiles, inflammation markers, and coagulation variables were assessed in patients of VTE and controls. In Norway during World War II, the incidence of post-operative thrombosis declined considerably and was attributed to rationing of food with resultant increased intake of micronutrients and omega-3 fatty acid and decrease of calories, meat and fats. After the end of war in 1944, with cessation of rationing of food the incidence of thrombosis again rose. In a prospective study over 12 years studying 14,962 middle-aged adults it was noted that diet including more plant food and fish and less red and processed meat is associated with a lower incidence of VTE. These studies are dealing with peripheral venous thrombosis whose etiopathogenesis differs from that of CSVT and therefore may not be extrapolated to CSVT.

In the present study, some facts have come out into view: low hemoglobin, low serum proteins, reduced triceps skin fold thickness and high homocysteine were observed as compared to controls suggesting subtle nutritional deficiencies in patients suffering from CSVT.

**Limitations of the present work**

This study is underpowered to suggest any guidance; perhaps larger institutionalized case control work may shed further light on the role on nutrition in CSVT. Secondly, even to our surprise, no case of puerperal CSVT was included in this work. It may perhaps be suggested that puerperal CSVT, non-puerperal CSVT and women with normal deliveries may be compared; this is in order to note any differences in their clinical and investigatory profile. This is in order to note differences, if any, in the causative factors including nutrition.

**Conclusions**

Results of this preliminary study confirm nutritional deficiencies in patients of CSVT and it begs the question of whether nutrition in any way is causal in CSVT. Larger multicentric trials may perhaps help us in establishing a causal relationship. The study also shows that routine evaluation of thrombophilia factors and immunological tests are not necessary in the management of CSVT.

**Acknowledgements**

The above work was financially supported by Pfizer India Pvt Ltd. and we are grateful to them.

We thank the management of Jehangir Clinical Development Centre (JCDC) for providing the staff and infrastructure.
Table 4: Observations for various laboratory parameters in cases and control

<table>
<thead>
<tr>
<th>Parameter (Normal values)</th>
<th>Group</th>
<th>Cases (N)</th>
<th>Control (N)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Cholesterol (&lt; 200 mg/dl)</td>
<td>Normal</td>
<td>21</td>
<td>56</td>
</tr>
<tr>
<td></td>
<td>Below Normal</td>
<td>00</td>
<td>00</td>
</tr>
<tr>
<td></td>
<td>Above Normal</td>
<td>01</td>
<td>07</td>
</tr>
<tr>
<td></td>
<td>Total</td>
<td>22</td>
<td>63</td>
</tr>
<tr>
<td>PT group (10.5-13.0 s)</td>
<td>Normal</td>
<td>25</td>
<td>61</td>
</tr>
<tr>
<td></td>
<td>Below Normal</td>
<td>06</td>
<td>00</td>
</tr>
<tr>
<td></td>
<td>Above Normal</td>
<td>31</td>
<td>01</td>
</tr>
<tr>
<td></td>
<td>Total</td>
<td>62</td>
<td>62</td>
</tr>
<tr>
<td>Haemoglobin (Male: 14-17.5; Female: 12.3-15.3 gm/dl)</td>
<td>Normal</td>
<td>21</td>
<td>43</td>
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References

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For Gram –ve Sepsis,

Sepsivac®
(Heat killed Mw)

Save More Lives

An adjunct therapy in Gram-ve Sepsis

Significant reduction in

- Mortality by 11%¹
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- Days of hospital stay²
- Days on ventilator²
- Days of ICU stay²

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(0.1 ml intradermal at 3 different sites)

Approved by DCGI

Maxima

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3. SOFA — Sequential Organ Failure Assessment
4. PS No. 1006/10/1964B4
Aims and Objectives of Study

1. To identify clinical and biochemical factors related with low testosterone levels and hypogonadism.
2. To establish correlation of hypogonadism with coronary artery disease in male patients with type 2 diabetes mellitus (T2DM).

Materials and Methods

Study subjects

100 men (50 each eugonadal and hypogonadal), aged 28–85 (mean 56.7±11.6 years) with type 2 diabetes mellitus, attending diabetes clinic OPD at a tertiary care hospital, were included in the study.

Patients with type 1 diabetes mellitus, acute concurrent disease and on previous treatment with androgens were excluded. All patients gave written informed consent to participate in the study and the Government Medical College, Kota Ethics Committee approved the study protocol.

Biochemical measurements

Blood samples were drawn simultaneously for all the measurements between 8 AM and 9 AM after overnight fast. We analyzed fasting blood glucose, HbA1c, serum creatinine, serum albumin, lipid profile: total cholesterol, low and high-density lipoprotein cholesterol (LDL-C and HDL-C, respectively), triglycerides, liver function tests such as alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma-glutamyl transpeptidase (GGT), glomerular filtration rate (eGFR) with MDRD formula adjusted for body surface area, hormone measurements: TT was measured with a chemiluminescence assay, SHBG was measured with a
chemiluminescence assay, cFT was defined using Vermeulen’s formula (Vermeulen et al.).

Two cut-offs were used to define hypogonadism: serum total testosterone < 10.4 nmol/L according to the guidelines of the Endocrine Society (Bhasin et al.) or Calculated free testosterone (cFT) of 226 pmol/L (0.03 ng/mL) (Wang et al.). Values of TT below 8 nmol/L were considered as severe hypogonadism. Symptoms of hypogonadism were assessed using the validated Androgen Deficiency in the Aging Male (ADAM) questionnaire of the Saint Louis University (Morley et al.).

Diagnosis of complications and comorbidities

Diagnosis of DM-2 was previously established in patients attending the diabetes clinic OPD. The diagnosis of coronary artery disease was made by previously established diagnosis of coronary artery disease by CT or angiography and confirmed with corresponding specialist. The diagnosis of retinopathy, neuropathy, peripheral artery disease, and cerebrovascular disease was obtained after written diagnostic reports from the corresponding specialists. The diagnosis of chronic kidney disease was established after two eGFR lower than 60 mL/min/1.73 m² BSA. Anemia was defined by haemoglobin levels <13.5 g/dL. The diagnosis of abnormal liver function tests was established when AST and/or ALT and/or GGT had a value at least 1.5-fold the higher limit of reference, in two different analyses. Patients were classified as smokers (usual consumers in the last 3 months) or non-smokers. Alcohol consumption allowed classifying the patients as drinkers (≥2 standard alcohol units per day) or non-drinkers.

Method of collection and analysis of Data

We identified male patients in diabetes clinic OPD having T2DM who were meeting the inclusion criteria for our study (i.e. All T2DM males without any acute concurrent illness and not taking androgens previously). All those patients who met the inclusion criteria were administered the ADAM questionnaire to identify likely candidates with hypogonadism due to any cause. We collected samples for baseline biochemical parameters from these patients who had clinical symptoms of hypogonadism based on ADAM questionnaire out of which some were found to have hypogonadism whereas others had normal testosterone values. 50 patients with hypogonadism (based on serum testosterone levels) and T2DM were selected for study. An equal number of eugonadal patients with T2DM were taken as controls. We aimed to identify the differences in baseline physical and biochemical parameters any difference in prevalent co-morbid conditions in the two groups.

Statistical tools

For descriptive analysis, variables were checked for normal distribution with the Kolmogorov–Smirnov test. The variables with normal distribution were reported as mean and standard deviation (SD). Non-normally distributed variables were reported as median and interquartile range. Qualitative variables were presented as percentages. The comparisons of qualitative variables were performed using Pearson’s chi-squared test. Quantitative variables were correlated using Pearson’s coefficient of correlation. Risk assessment of significant quantitative variables was done using multivariable logistic regression analysis. Statistical analyses were performed using Statistical Package for the Social Sciences (SPSS) version 26.0.

Results

We divided the patient data collected in two main groups namely eugonadal and hypogonadal with equal number of patients in each category. After taking mean (SD) of quantifiable date and prevalence (%) of non-quantifiable data
we were able to find out the parameters which have a significant difference in p-value (<0.05) as shown in Table 1.

**Comparison of the two study groups**

Based on the above table we can observe that the prevalence of coronary artery disease is high in males with type 2 diabetes mellitus and hypogonadism as compared to those with eugonadism (p=0.0324). We tried to evaluate whether there is a statistically significant correlation between hypogonadism and coronary artery disease in these patients. The factors associated with hypogonadism have been discussed further:

A. Relation of Aging, duration of diabetes, BMI and waist circumference with Serum Testosterone levels

Age of patient correlated inversely with TT (R = -0.316, p = 0.013), cFT (R= 0.334, p = 0.011) and BT (R = -0.289, p=0.003) (Figure 1). Aging in male patients with type 2 diabetes mellitus leads to decrease in TT, cFT and BT serum levels in our study. The prevalence of hypogonadism increased with aging: 18.1% (≤50 years), 11.5% (51–60), 19% (61–70), and 27.7% (>70 years), p = 0.007. The prevalence of severe hypogonadism also increased significantly with aging: 9.2% (≤50 years), 6.4% (51–60), 12% (61–70), and 21.5% (>70 years), p = 0.009.

While age of patient has a significant negative correlation with serum testosterone, the duration of time for which a person has had T2DM does not affect this TT (R = -0.107, p = 0.386), cFT (R = -0.195, p = 0.146) and BT (R = -0.130, p = 0.197) levels. The values of TT and cFT may decline slightly with increasing duration of diabetes but it is not statistically significant.

An increase in waist circumference negatively correlated with TT (R = -0.262, p = 0.008), cFT (R = -0.255, p = 0.010) and BT (R = -0.130, p = 0.197) levels i.e., testosterone values declined as the waist circumference increased.

**Although the prevalence of hypogonadism was found to increase with increasing BMI e.g., in the four quartiles of BMI (≤19 kg/m2, 20–24 kg/m2, 25– 29 kg/m2, ≥30 kg/m2) was: 38.1%, 49.9%, 50% and 70%, respectively, BMI was not found to be independently correlated with TT (R = -0.116, p = 0.290), cFT (R = -0.088, p = 0.350) and BT (R = 0.009, p = 0.920) levels in our study.**

B. Relation of biochemical indices with Serum Testosterone levels

Fasting blood sugar level was found to have a negative correlation with TT (R = -0.262, p = 0.047), cFT (R = -0.262, p = 0.048) i.e. low TT and cFT were associated with raised FBS (Figure 2). There was a statistically significant difference between eugonadal and hypogonadal men in relation to FBS i.e., eugonadal vs hypogonadal [128.8_47.4 vs 178.4_81.2 mg/dL, p = 0.0003]. HbA1c does not have a statistically significant association with TT (R = -0.15, p = 0.26) and cFT (R = -0.16, p = 0.23).

Raised Serum triglyceride is a major risk factor for CAD and it was found to have a negative correlation with TT (R = -0.268, p = 0.048), cFT (R = -0.26, p = 0.049) levels. There was no statistically significant difference between the two subgroups in relation to HDL-C and LDL-C levels.T2DM patients with low testosterone levels were much more likely to have a deranged lipid profile with the level of triglycerides mainly deranged while not having a significant effect on LDL-C and HDL-C.

When the level of eGFR in a patient with T2DM was correlated with TT and cFT we found that TT and cFT had a correlation with eGFR (R = 0.178, p = 0.013; R = 0.159, p = 0.034 respectively) showing that low eGFR is associated with hypogonadism in T2DM males. Patients with an eGFR < 60 mL/min/1.73 m² had significantly lower TT and cFT than patients with eGFR ≥ 60 mL/min/1.73 m². The prevalence of hypogonadism (TT ≤ 10.4 nmol/L) and severe hypogonadism (TT ≤ 8 nmol/L) was higher in T2DM males with low eGFR (<60 mL/min/1.73 m²) than in those with ≥60 mL/min/1.73 m²: 46% vs. 32%, p < 0.005 and 35.6% vs. 23%, p < 0.05, respectively.

Haemoglobin level was not found to have a correlation with TT (R = 0.046, p = 0.053) and cFT (R = 0.041, p = 0.058).

C. Relation of Chronic diseases with Serum Testosterone levels for T2DM males

We found a statistically significant difference in the prevalence of CAD between hypogonadal and eugonadal T2DM males. No difference was found in the prevalence of macroalbuminuria, retinopathy, stroke, abnormal LFT and hypertension. There are biochemical variables which are interdependent such as low eGFR, waist circumference, lipid profile, poor glycemic control which may contribute to both hypogonadism and CAD. Poor glycemic control may lead to early progression of diabetic nephropathy and lead to low eGFR. Our study groups did not differ on BMI, LDL-C, HDL-C, prevalence of hypertension or smoking status.

**Correlation of statistically significant biologic variables (p<0.05) and testosterone levels with CAD by multivariable logistic regression (to account for interdependence of risk factors)**

After applying multivariate regression analysis on our study, we found that prevalence of CAD in a patient with diabetes is associated with waist circumference, fasting blood sugar, serum triglycerides and eGFR. Age of patient and HbA1c values.
are not significantly correlated with prevalence of CAD. Also we found an increased prevalence of CAD in patients with low serum testosterone levels (p=0.032) showing increased risk of CAD in patients with hypogonadism. From the above Table 3 we can conclude that a male patient with T2DM and hypogonadism will have 1.33 times or 33% higher odds of having CAD as compared to a eugonadal male patient with T2DM.

**Discussion**

Several studies in the past have shown evidence of hypogonadism in T2DM males.10 No such association has been found in T1DM males.11 While studies in the past have linked hypogonadism and CAD in general population no previous study to our knowledge has tried to establish a quantitative association between hypogonadism and CAD in T2DM male population.

In this study, we compared two subgroups of male patients with type 2 diabetes i.e. those with normal serum testosterone levels (eugonadal) and those with reduced serum testosterone levels (hypogonadal). The testosterone levels were compared with physical and biochemical parameters as well as with the prevalence of chronic diseases in the two groups.

We found that testosterone indices among Indian T2DM males have a negative correlation with age, waist circumference, fasting blood sugar, serum triglycerides (p<0.05). A small negative correlation was found for duration of diabetes, LDL-C and haemoglobin levels but it was not statistically significant when adjusted for confounding variables. Patients with low eGFR, which is commonly seen in diabetic nephropathy were found to have lower testosterone levels as compared to those with normal eGFR(p<0.05). Uraemia, seen in men with advanced renal failure, inhibits the Luteinising hormone (LH) receptor in Leydig cells.12 This leads to reduced activation of G-protein coupled receptors and decreased cAMP production which leads to low testosterone production and subsequent hypogonadism. Further, these low testosterone levels fail to stimulate production of gonadotropins (LH and FSH) suggesting a distortion of the hypothalamic-pituitary axis. The drugs commonly used in diabetes mellitus patients such as statins, ACE inhibitors and ARBs also affect testosterone production.13

Several studies have shown a stronger correlation of waist circumference with hypogonadism as compared to BMI with hypogonadism.14 In our study we found a significant correlation of waist circumference with hypogonadism (p<0.05) but did not find a correlation between BMI and hypogonadism (p>0.05). This has been observed in some previous studies in non-Caucasian population.15 This may be explained by the fact that the characteristic obesity in Asian-Indian phenotype is remarkably different from those in Caucasian phenotype. While a peripheral predominant distribution of fat is commonly seen in Caucasian population (centrifugal obesity), the pattern of fat distribution in Indian population is visceral predominant (centripetal obesity). This visceral predominant fat leads to significantly increased waist circumference. As such, BMI may not have a significant independent correlation with hypogonadism in Indian population.

A study by Liu et al16 suggested that testosterone levels were consistently lower in men with CAD. In patients with coronary disease testosterone deficiency is common and impacts significantly negatively on survival.17 Gurunani et al18 showed that low testosterone was an independent predictor of severity of CAD. Upon comparison of chronic diseases in T2DM patients in the two subgroups we found that the prevalence of coronary artery disease was significantly higher in T2DM males with hypogonadism as compared to those without hypogonadism (p=0.032). Further we tried to evaluate whether this high prevalence of CAD in hypogonadal male patients with T2DM is an independent association or secondary to other factors such as fasting blood sugar, triglycerides, waist circumference and eGFR which are significantly altered in hypogonadal male patients with type 2 diabetes. After multiplying the odds of all positive and negative factors we found that in hypogonadal males with T2DM there is 33% higher odds of CAD as compared to eugonadal males with T2DM.

Serum Testosterone has several effects on the cardiovascular system including those on the coronary arteries. Animal studies point to its role in vasodilation.19 It has been suggested that testosterone may trigger vasodilatation via endothelial-independent non-genomic means, given its rapid onset, though potentiation by genomic means via the classical androgen receptor (AR) cannot be excluded.18,20 Inhibition of voltage-operated calcium channels (VOCCs) and/or activation of potassium channels on smooth muscle cells is also significant. Testosterone also upregulates the expression of endothelial nitric oxide synthase (eNOS), the enzyme responsible for synthesising nitric oxide (NO). NO in turn brings about the relaxation of SMCs and subsequent vasodilatation by activating guanylate cyclase which produces cGMP, which in turn activates cGMP-dependent protein kinase (PKG). PKG phosphorylates and activates sarcoplasmic reticulum-ATPase (SERCA) which results in augmentation of calcium levels in the sarcoplasmic reticulum leading to vasodilatation.21

Intima Media Thickness is a feature of atherosclerosis. A study by Soisson et al22 showed an inverse relationship between total testosterone and intima media thickness. They imply a preventive role of endogenous testosterone in coronary artery disease. In another study conducted on rats, the infarct size after myocardial infarction in orchiectomised mice was larger as compared to orchiectomised plus testosterone treated mice which suggested a role of testosterone in vascular reperfusion.23

India, with 69.2 million people with T2DM, is the country with 2nd highest number of people living with diabetes mellitus worldwide. Approximately 20.7% of Indian males with T2DM suffer from hypogonadism.24 Taking this into account and values from our study, approximately 7–8 million male patients with type 2 diabetes mellitus in India are suffering from hypogonadism and 0.5 million are predicted to have increased risk of coronary artery disease that can primarily be attributed to hypogonadism. In a recent study in veterans with documented low testosterone levels, testosterone replacement therapy (TRT) lead to lower risk of MI (HR=0.82)25. By that measure, we predict that by addressing
the prevalent hypogonadism in T2DM male population, up to 125000 coronary events may be prevented in future. Long term trials and meta-analysis are required to further assess the efficacy of TRT in cardiovascular disease prevention in T2DM males with hypogonadism.

**Conclusion**

There is definite evidence that low testosterone levels are associated with increased risk of cardiovascular disease in non-diabetic male patients.\(^4\)\(^\text{15}-\text{18}\) Diabetes is associated with several risk factors for hypogonadism and prevalence of hypogonadism in males with T2DM is higher as compared to non-diabetic counterparts.\(^\text{19}\) We have shown a statistically significant correlation between the testosterone levels in male patients with the prevalence of coronary artery disease in our study. Further, testosterone has been found to be as a risk factor for coronary artery disease in men with T2DM in our study by calculating the odds ratio (1.33) for CAD in T2DM males with hypogonadism as compared eugonadal males. Among men with androgen deficiency, testosterone replacement therapy is associated with a lower risk of cardiovascular outcomes.\(^\text{20}\)

There was a reduction in acute MI, revascularisation, sudden cardiac death, unstable angina and all-cause mortality in hypogonadal patients who have ever taken testosterone treatment.\(^\text{21}\) Therefore further research is needed for testosterone replacement therapy in males with type 2 diabetes with androgen deficiency in relation to prevention of coronary artery disease.

**Limitations of the Study**

1. Sample size of the study population is not large.
2. Patients with hypogonadism and T2DM have been compared with eugonadal T2DM patients due to observational nature of the study. A prospective case control study with subjects without type 2 diabetes mellitus as control is required to further establish a causal association.

3. The study population is not matched for age, glycemic control and waist circumference all of which are related to both T2DM and hypogonadism. We have tried to overcome this limitation by calculating the odds of each of risk factor for CAD and adjusting for odds of each risk factor.

**Compliance with Ethical Standards**

1. Written informed consent was taken from all participants involved in the study.
2. Ethical clearance was granted by institutional ethics committee of Government Medical College, Kota vide letter no. F.3/(Acad-II)/Plan/2019/1262 dated 14/06/2019.
3. No funding was received by the any of the authors for this study.

**References**

15. Huang F: Is a Previously or Currently Reduced Testosterone Level in Male Patients with Type 2 Diabetes Mellitus a Risk Factor for the Development of Coronary Artery Disease? A Systematic Review and Meta-analysis. Diabetes Ther 2018; 9:1061–1072.
Beneficial Primary Outcomes of Metabolic Surgery with Changes in Telomere Length and Mitochondrial DNA in Obese Asian Indians with Dysglycemia

Sundaramoorthy Chandru1,2, Paramasivam Prabhu3, Muthuswamy Balasubramanyam1,4, Radhakrishnan Subhashini1, Mangesh Tiwaskar2, Thyparambil Aravindakshan Pramodkumar1, Rajendra Pradeepa1, Ranjit Mohan Anjana1, Viswanathan Mohan1*

Abstract

Introduction: Although metabolic surgery has been shown to offer beneficial primary outcome results in obese individuals / obese Type 2 diabetes mellitus (T2DM) patients, there is paucity of information on the underlying mechanisms. In the recent years, estimations of non-invasive molecular parameters viz., telomere length and mtDNA copy number (mtDNAcn) assume significance as robust biomarkers. However, there is lack of evidence about this especially, in the Indian context. To assess the changes in the telomere length and mtDNAcn levels after metabolic surgery in obese Asian Indians with dysglycemia along with routine measurements of anthropometry, glycemic/lipidimic parameters and inflammatory markers.

Methods: This study is a prospective one-year follow-up study of 16 obese individuals with dysglycemia who underwent metabolic surgery at a tertiary diabetes centre in South India. Telomere length, mtDNAcn, serum adiponectin, glycaemic/haemoglobin and high-sensitivity C-reactive protein (hs-CRP) levels were analysed before surgery and at 6 and 12 months after surgery.

Results: There was a significant reduction in weight (p<0.001), BMI (p<0.001), waist circumference (p<0.001), fasting and postprandial glucose (p<0.05), HbA1c (p<0.001), triglycerides (p<0.05), hs-CRP (p<0.05) and increase in serum adiponectin (p<0.05) at 6 and 12 months post-surgery compared to the preoperative status. There was a significant reduction in mtDNAcn (p<0.001) and a significant increase in telomere length (p<0.001) at 6 and 12 months post-surgical surgery.

Conclusion: We report an increase in telomere length and decrease in circulatory mtDNA copy number levels at 6 and 12 months post metabolic surgery in obese individuals with T2DM in India.

Introduction

Type 2 diabetes mellitus (T2DM) has a strong association with obesity and unhealthy lifestyle regardless of genetic predisposition. Obesity is a complex multi-factorial disease that has genetic, behavioural, environmental and socio-economic origins leading to an increase in morbidity and mortality. Nitrogen compounds, free radicals and reactive oxygen species (ROS) are needed in low concentration for normal cell functioning, intracellular signalling and cell redox state. However there is an excess production of ROS and free radicals in certain disease conditions like T2DM and obesity. Higher concentration of ROS and free radicals can damage cellular proteins, lipids, carbohydrates, DNA and other cellular structures and impair cell function.

Higher circulating levels of triglycerides in obesity and T2DM leads to excess infiltration and accumulation of triglycerides in the peripheral tissues and this excess in triglycerides is shown to induce mitochondrial (mt) dysfunction, increase oxidative stress and impair energy substrate metabolism as well as oxidative phosphorylation. Oxidative stress is known to cause cellular injury and release excess amount of mtDNA fragments into the circulation.

Telomere length is determined by genetic factors but throughout human life it is also influenced by various non-genetic factors. Longest and shortest telomere length are present at birth and old age, respectively.

Aging is associated with a progressive shortening of telomere length and it varies with the type of the cell and mitotic tissue. Telomere length was reported to shortened in both type 1 diabetes mellitus (T1DM) and T2DM as well as in obesity states.

Apart from diabetes and obesity, studies have also reported that telomere shortening is associated with impaired glucose tolerance, atherosclerosis, hypertension, dyslipidemia, diabetic kidney disease, insulin resistance and non-alcoholic fatty liver disease (NAFLD).

Metabolic surgery is an effective strategy to reduce both obesity and metabolic syndrome.
diabetes by altering or reversing various path-physiological mechanisms. Studies have shown the effects of metabolic surgery in rescuing the cell from oxidative stress and delaying the progression of biological aging. There is a lacuna of data among the obese Asian Indians with dysglycemia with regard to oxidative stress. The potential associations between telomere length and mitochondrial DNA copy number (mtDNAcn) with diabetes has been studied cross-sectionally. Prospective studies in this field are scarce, with very few reporting that telomere length is increased after bariatric surgery compared to before. The current study aimed to evaluate the benefits of metabolic surgery with a special emphasis on changes in telomere length and mtDNAcn, a year after surgery in obese Asian Indians with dysglycemia.

**Methods Study Design**

This is a prospective observational study of individuals with dysglycemia who underwent metabolic surgery between November 2013 and March 2019. A total of 36 individuals with pre diabetes or type 2 diabetes were recruited, who underwent metabolic surgery at a tertiary referral centre for diabetes in Chennai, South India. For purpose of this study sixteen (14 T2DM and 2 prediabetes, male 6 and female 10) individuals who agreed to take part in subset of studies and willing to give additional blood samples for analyzing various biochemical parameters were included in the present study. Written informed consent was obtained from all the study participants. All study procedures were conducted in accordance with the declaration of the Helsinki and approved by the Ethical Committee of Madras Diabetes Research Foundation, Chennai India (MDRF/NCT/07-02/2014).

All the individuals underwent pre-operative, multi-disciplinary evaluation by a bariatric surgeon, physician, anaesthetist, psychologist and dietician prior to surgery. Diabetes history, medications, risk factors and co morbidities associated with obesity were recorded.

**Anthropometry and blood pressure measurements**

Anthropometric measurements including weight, height, and waist circumference were measured using the standard techniques. Height (in cm) was measured using a stadiometer (SECA Model 214, Seca GmbH Co, Hamburg, Germany). Weight (in kg) was measured with an electronic weighing scale (SECA Model 807, Seca GmbH Co, Hamburg, Germany) that was kept on a firm horizontal flat surface. Waist circumference was measured at the smallest horizontal girth between the costal margins and the iliac crest at the end of expiration. Blood pressure was recorded in the sitting position in the right arm to the nearest 1 mmHg using a mercury sphygmomanometer (Diamond Deluxe, Pune, Maharashtra, India). Two readings were taken 5 min apart and their mean was taken as the blood pressure.

**Biochemical investigations**

Biochemical analysis was done at our laboratory which is certified by the College of American Pathologist and the National Accreditation Board for Testing and Calibration Laboratories. A fasting venous blood sample was collected after an overnight fast of at least 10 hours for the estimation of fasting glucose and lipids and, after a standard South Indian breakfast, a 2 hour postprandial sample was obtained for postprandial plasma glucose estimation. Plasma glucose levels were analyzed by the hexokinase method, serum cholesterol by cholesterol oxidase peroxidase amidopryline method, serum triglyceride by the glycerolphosphate oxidase-peroxidase-amidopryline method, high density lipoprotein (HDL) cholesterol by direct method- immunoinhibition method, hs-CRP by immunoturbidimetry measured using Beckman Coulter AU680 (Fullerton, CA, USA) and Beckman kits. Low-density lipoprotein (LDL) cholesterol was calculated using the Friedewald formula. HbA1c was measured by high-performance liquid chromatography using the Variant II Turbo (Bio-Rad, Hercules, CA, USA). The intra and inter-assay coefficients of variation for the biochemical assays ranged between <3.1 and 7.6%.

**Adiponectin measurements**

Adiponectin was measured by quantitative sandwich enzyme-linked-immune sorbent assay technique (ELISA) (Adiponectin: Cusabio: Houston, USA). In brief, a monoclonal antibody specific to Adiponectin has been pre-coated onto a microplate. Standards and samples are pipetted into the wells and any Adiponectin present is bound by the immobilized antibody. After removing any unbound substances, a biotin-conjugated antibody specific for Adiponectin is added to the wells. Following a wash to remove any unbound avidin-enzyme reagent, a substrate solution is added to the wells and colour develops in proportion to the amount of Adiponectin bound in the initial step. The colour development is stopped and the intensity of the color is measured at 450 nm. The values are expressed in (ng/ml). The intra- and inter-assay coefficients of variation were <8% and <10%, respectively.

**Surgical technique**

Of the 16 individuals, 9 underwent Restrictive procedure- Laparoscopic sleeve gastrectomy (SG) and 7 underwent Gastro intestinal diversionary procedures- Laparoscopic Rouxen-Y gastric bypass (RYGB). The type of metabolic surgery was decided by the bariatric surgeon depending upon the duration of diabetes and other comorbid conditions of the patient. DNA was quantified using Nanodrop One (Thermo Scientific) and was stored at -20°C.

**Human serum DNA isolation**

Serum DNA was isolated using commercially available serum/plasma DNA isolation kit (#ab15893; abcam). Briefly, 500µL of serum sample was added into mixture 20 µL digestion and 500µL of DNA isolation buffer. The resultant cocktail was mixed properly and incubated at 65°C for 10 minutes. After that, 500 µL of above mixture was added into column tube and centrifuged at 12000 rpm for 30 seconds and discarded flow through. Then F-spin column tube was washed with 70% and 90% ethanol by centrifuged at 12000rpm for 20 seconds respectively. Finally, DNA was eluted by adding 20 µL DNA elution solution into F-spin column tube and centrifuged at 12000 rpm for 30 seconds. DNA was quantified using Nanodrop One (Thermo Scientific) and DNA was stored at -20°C.

**Telomere length measurement**

Relative telomere length was determined by Real-time PCR approach as previously described by with minor modifications. This method measures
The factor by which the ratio of telomere repeat copy number to single - gene copy number differs between asample and that of a reference DNA sample. PCR amplification was achieved using telomere (T) and single copy gene, 36B4 (encodes acidic ribosomal phosphoprotein) primers (S) which serves as a quantitative control. The mean telomere repeat gene sequence (T) to a reference single copy gene (S) was calculated to determine the relative telomere length.

Quantification mitochondrial DNA (mt DNA) copy number: Human mitochondrial DNA (mt DNA) monitoring primer Set (Takara Bio Inc, Kusatsu, Shiga, Japan) was purchased from Takara and the experiment was carried out as per manufacture’s instruction. In brief, 20 ng of DNA and Nuclear DNA primers (SLCO2B1 and SERPIN1A1) and mitochondrial primers (ND1 -NADH dehydrogenase subunit 1- and ND5) were added to SYBR green master mix (Clontech Laboratories, Mountain View, USA) and Quantitative PCR was performed on the Roche Light Cycler 96 (Roche GmbH, Mannheim, Germany). Relative quantification of mitochondrial DNA was determined using the ‘ct’ values for mtDNA and nDNA and data was expressed as mean mtDNAcn.

Statistical analysis
Quantitative variables were described with means and standard deviations (SD). Paired t-test as appropriate were used to compare groups for continuous variables and the Chi- square test or Fisher’s exact test as appropriate was used to compare proportions. We used normalized log-transformed values for the correlation table. All analyses were done using the Windows-based SPSS statistical package (version 22.0, SPSS Inc, Chicago, IL) and p<0.05 was considered statistically significant.

Results
Table 1 illustrates the clinical and biochemical characteristics of the study individuals involved in the study. Metabolic surgery resulted in reduced body weight (p<0.001), BMI (p<0.001), waist circumference (p<0.05), systolic and diastolic blood pressure(p<0.001) in 6 and 12 months postoperative follow-up compared to the preoperative status. Improved glycemic variables included FPG (p<0.001), PPG (p<0.001) and HbA1c (p<0.001), total cholesterol (p<0.001) and triglyceride (p<0.05), VLDL (p<0.05); increased HDL cholesterol (p<0.001) in 6 and 12 months postoperative follow-up compared to preoperative. Interestingly, inflammatory marker hsCRP (p<0.05) was significantly reduced in 6 and 12 months postoperative follow-up compared to preoperative postoperative follow-up. Adiponectin was significantly increased post surgery (p<0.05).

Figure 1 shows that mtDNAcn (762±122 vs. 404 ± 55 vs. 208 ± 42, p<0.001) was significantly decreased at 6 months and this improvement persisted 12 months postoperatively compared to baseline. Figure 2. Shows data on relative telomere length (1.41±0.02 vs. 1.46 ± 0.03 vs. 1.48 ± 0.06 p<0.001) was significantly increased at 6 months and persisted 12 months postoperatively compared to baseline. This increase in Telomere length was suggestive of a decrease in oxidative stress and inflammation levels.

Pearson correlation analysis was performed between telomere length as well as mtDNAcn with anthropometric and biochemical parameters. Telomere length was positively correlated with weight (r=0.571, p=0.010) and BMI.
Table 2: Correlation of clinical and biochemical characteristics with pre-operative and 12-months change in telomere length and mitochondrial DNA in individuals with type 2 diabetes

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Telomere length (n=16)</th>
<th>mtDNA-CN(^N) (log transfer done) (n=16)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Correlation with baseline ((r))</td>
<td>Correlation with one year change ((r))</td>
</tr>
<tr>
<td>Age (years)</td>
<td>-0.356</td>
<td>-0.555</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>0.571</td>
<td>0.010*</td>
</tr>
<tr>
<td>BMI (kg/m(^2))</td>
<td>0.498</td>
<td>0.025*</td>
</tr>
<tr>
<td>Waist circumference (cm)</td>
<td>0.358</td>
<td>0.087*</td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>0.165</td>
<td>0.271*</td>
</tr>
<tr>
<td>Diastolic blood pressure (mmHg)</td>
<td>0.238</td>
<td>0.188*</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>0.303</td>
<td>0.127*</td>
</tr>
<tr>
<td>Fasting plasma glucose (mg/dl)</td>
<td>0.247</td>
<td>0.178*</td>
</tr>
<tr>
<td>Postprandial plasma glucose (mg/dl)</td>
<td>0.250</td>
<td>0.175*</td>
</tr>
<tr>
<td>hs-C-Reactive Protein (mg/l)</td>
<td>0.187</td>
<td>0.253*</td>
</tr>
<tr>
<td>Adiponectin (ng/ml)</td>
<td>0.064</td>
<td>0.407*</td>
</tr>
<tr>
<td>Serum cholesterol (mg/dl)</td>
<td>0.050</td>
<td>0.430*</td>
</tr>
<tr>
<td>Serum triglyceride (mg/dl)</td>
<td>-0.410</td>
<td>0.064*</td>
</tr>
<tr>
<td>HDL-Cholesterol (mg/dl)</td>
<td>-0.221</td>
<td>0.214*</td>
</tr>
<tr>
<td>LDL-Cholesterol (mg/dl)</td>
<td>0.374</td>
<td>0.085*</td>
</tr>
<tr>
<td>White blood cells (10(^3)/µL)</td>
<td>-0.096</td>
<td>0.377*</td>
</tr>
<tr>
<td>Hemoglobin (g/dL)</td>
<td>0.226</td>
<td>0.228*</td>
</tr>
</tbody>
</table>

\(r=0.498, p=0.025\) at preoperative and negatively correlated with age \((r=-0.555, p=0.013)\), weight \((r=-0.464, p=0.035)\), HbA1c \((r=-0.455, p=0.038)\) and hsCRP \((r=-0.691, p=0.002)\) with one year change. mtDNAcn negatively correlated with weight \((r=-0.450, p=0.040)\), waist circumference \((r=-0.688, p=0.002)\), and diastolic blood pressure \((r=-0.590, p=0.008)\) at 12 month postoperative follow-up (Table 2).

Discussion

Although metabolic surgery has been shown to offer beneficial primary outcome results in obese individuals / obese T2DM patients in terms of weight loss as well as reductions in glycemic and lipidemic parameters, there is paucity of information on the underlying mechanisms. In this context, the present study assumes significance and reports the following findings:

1) There was a significant increase in telomere length and decrease in mtDNA levels at 6 and 12 months post-surgery.
2) Inflammatory marker hsCRP levels were significantly reduced while there was an increase in the adiponectin levels at 6 and 12 months after surgery.
3) Interestingly, age, weight, HbA1c and hsCRP levels were negatively correlated with telomere length at 12 months follow-up in those underwent metabolic surgery.

Unlike the routine inflammatory and oxidative stress markers that change with short-term lifestyle, the levels of telomere length and mtDNA represent robust, long-term biomarkers. We earlier reported an association of telomere shortening in Asian Indian patients with T2DM. A recent meta-analysis showed a converse relationship between BMI and Telomere length in cross sectional studies. Nathan et. al reported an increase in telomere length following weight loss due to dietary modification and lengthening of telomere was shown associated with decrease in weight and fat mass. Interestingly, a recent Indian based GWAS study also revealed five genetic variants associated with telomere maintaining genes in T2DM.

Obesity is associated with number of metabolic alterations including increased oxidative stress and chronic low-grade inflammation. It is well conceived that adipose tissue promotes the process of aging and drives the development of chronic diseases, such as T2DM, non-alcoholic fatty liver disease (NAFLD), cancer, and cardiovascular diseases. Indeed, a recent, large meta-analysis using cross-sectional data from 146,114 people reported an inverse relationship between BMI and telomere length.

The increase in telomere length at 6 and 12 months post-metabolic surgery demonstrated in our study in obese-diabetic patients is a significant observation. Dersham et al showed an increase in telomere length after 3-5 years of post-gastric surgery. Jongbloed et al suggested that metabolic syndrome is a risk factor for accelerated aging of T cells and they have demonstrated an increase in the telomere length and decrease in T cell differentiation which was associated with percentage of body weight loss 6 months post bariatric surgery. Laimer et al demonstrated an increase in telomere length after profound and sustained weight loss 10 years post bariatric surgery and this study emphasized that bariatric surgery ameliorates metabolic abnormalities after profound weight loss and these changes could overrule the influence of age and protect the DNA from the damage. Brando et al also demonstrated an increase in telomere length following raise in fat free mass and decrease in waist circumference after 8 weeks of short term combined exercise.

In our study, metabolic surgery resulted in significant reduction in body weight, waist circumference, blood sugars, HbA1c and serum triglycerides. The post operative reduction in the availability of fuel (energy -glucose and TG) along with weight loss might have resulted in decrease in inflammatory markers like hsCRP and subsequent reduction in oxidative stress. There is a significant reduction in the circulating mtDNA copy number levels after metabolic surgery, which could reflect an underlying reduction of the mitochondrial oxidative stress levels.
While obesity has been shown to be associated with elevated urinary mtDNAcn levels, bariatric surgery has been demonstrated to reduce the levels of urinary mtDNAcn in obese individuals.24 In our earlier study, we showed that metabolic surgery resulted in significant improvement in beta cell function and insulin sensitivity along with reduction in anti-diabetes medications.25

Conclusion

To conclude, our study in India report an increase in telomere length and decrease in circulatory mtDNA copy number levels at 6 and 12 months post metabolic surgery in obese diabetic individuals. These robust biomarker alterations were more or less correlated to primary outcome benefits of metabolic surgery. One of the limitations of our study is the relatively small sample size as well as our estimations of telomere length and mtDNAcn levels which was done in serum samples. Future studies should focus on studying tissues — so as to demonstrate the underlying mechanisms of beneficial outcomes of metabolic surgery as well as to look at the clinical implications in the beneficial effect of telomere length and mtDNAcn as robust biomarkers.

Acknowledgements

This work is part of the PhD project of Dr. Sundaramoorthy Chandru undertaken at the University of Madras. We thank the participants for their cooperation.

Author Contributions

SC, PP, MB and VM, were involved in conception and design of this study. SC, PP, MB, RP, TAP, RMA, VM helped in the interpretation analysis and interpretation of data and revised all drafts of the article. VM and SC were involved in pre and post-operative assessment of individuals after metabolic surgery. RS were responsible for data analysis. All authors approved and read the manuscript.

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References

Validation of the OPtimal Treatment of Angina (OPTA) Questionnaire in Indian Patients with Chronic Stable Angina

Uday Jadhav1*, Tiny Nair2, PB Jayagopal3, Brian Pinto4, Sameer Srivastava5, Prasant Kr Sahoo6, Deepak Davidson7

Abstract

Background: A rising burden of coronary artery disease (CAD) in India is a major cause of concern, with angina being the leading manifestation. Hence a questionnaire to sensitize the clinicians about stable angina management and to assist in risk stratification is imperative.

Objective: To evaluate the content and face validity of a modified questionnaire adapted from the 7-item Seattle Angina Questionnaire (SAQ).

Materials and Methods: A panel of six experts in the field of evidence-based practice reviewed and rated the modified instrument for content clarity and relevance based on the 4-point ordinal scale. Face validity was assessed based on the trichotomous rating of “disagreed,” “agree” or “neutral.” Items on which ≥75% of patients “disagreed” were subjected to further review and revision.

Results: A total of six experts and 51 patients participated in the content and face validity, respectively. As no question received a score ≤2 by two or more experts for either content clarity or relevance, no modification in the questionnaire was required post content validation. During face validation, all patients agreed that the questions correctly measured the specific area of cardiovascular health status and response options correctly captured the answers provided. Demographic and baseline data of the patients were collected.

Conclusion: The newly developed 5-item questionnaire demonstrated content and face validity, suggesting it to be a potential instrument to improve management decision and care of angina patients in India.

Introduction

Coronary artery disease (CAD) is one of the leading cause of death globally.1 While data indicate a declining trend in the mortality from CAD in the developed countries, it is steadily increasing in the developing countries.2 Data indicate that this rate of increase is almost double in comparison to developed countries.3, 4

The epidemiological transition in India in the past two decades has been dramatic, with a shift from infectious disease condition to non-communicable disease burden. The CAD has emerged as the leading cause of death in all parts of India, including rural and urban areas, despite widespread heterogeneity in the prevalence of cardiovascular risk factors across different regions.5 Moreover, the rapid progression rate, the early age of disease onset, and high fatality rates ascribing to CAD epidemic in India are alarming. This increase in CAD prevalence in India could be attributed to industrialization, urbanization, and related lifestyle changes, leading to reduced physical activity, change in dietary habits, unhygienic and overcrowded living conditions, growing levels of stress, higher exposure to pollution and increased incidence of diabetes and hypertension. Hence the focus of CAD management should be to reduce premature cardiovascular death, prevent complications of stable ischemic heart disease that directly or indirectly impair patients’ functional well-being, maintain or restore a level of activity, functional capacity, and quality of life (QoL) that is satisfactory to the patient, and minimize costs of health care.

Angina is a common initial manifestation of CAD, with symptoms classified as a characteristic of typical (definite) angina, atypical (probable) angina, and non-specific chest pain. The Indian population displays a higher trend of presenting with atypical symptoms of angina, leading to missed diagnosis.6–9 Though early diagnosis of angina is important to reduce the future risk of more severe cardiac events, lack of awareness, inaccessibility to adequate health care services, economic constraints and other logistical difficulties may be the barriers in India for optimum healthcare.

Recognizing the need for a concerted effort to manage angina effectively led to the conception of the Optimal Treatment of Angina (OPTA) tool in 2018, which encompasses the entire spectrum from diagnosis and risk stratification to optimal medical management, in order to provide a more efficient use of the available antianginal armamentarium for more successful clinical outcomes.10 This was conceptualized by the eminent cardiologists of India, post intense discussions, comprehensive review of the literature and appraisals. The OPTA tool consists of: (i) A clinical checklist to enable the diagnosis of stable angina (ii) A questionnaire to assist in risk
Table 1: Summary of Expert Validation

<table>
<thead>
<tr>
<th>No</th>
<th>Questions</th>
<th>Number of Experts</th>
</tr>
</thead>
<tbody>
<tr>
<td>Experts assigning a score ≤2 for content clarity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Q1</td>
<td>Over the past 4 weeks, my day to day activities have been...</td>
<td></td>
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<tr>
<td></td>
<td>• Extremely limited</td>
<td></td>
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<tr>
<td></td>
<td>• Moderately limited</td>
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<tr>
<td></td>
<td>• Not limited at all</td>
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<td></td>
<td>0</td>
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<tr>
<td>Q2</td>
<td>Over the past 4 weeks, on average I have had chest pain/ chest tightness/ chest discomfort/ angina...</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• 4 or more times per week</td>
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<td>• 3 or less times per week</td>
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<td></td>
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<td></td>
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<tr>
<td>Q3</td>
<td>Over the past 4 weeks, on average, how many times have you had to take short acting nitrates for your chest pain, chest tightness or angina?</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• 4 or more times per week</td>
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<tr>
<td>Q4</td>
<td>Over the past 4 weeks, how much has your chest pain, chest tightness or angina limited your enjoyment of life?</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• It has extremely limited my enjoyment of life</td>
<td></td>
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<td></td>
<td>• It has moderately limited my enjoyment of life</td>
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<td></td>
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<td>Q5</td>
<td>If you had to spend the rest of your life with your chest pain, chest tightness or angina the way it is right now, how would you feel about this?</td>
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Experts assigning a score ≤2 for content relevance |

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<td></td>
<td>• Mostly satisfied</td>
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</tbody>
</table>

Clarity of the question

| Experts agreeing that the OPTA questionnaire appropriately assesses that the treatment received by the patients is optimum |
| Clarity of the question |
| Yes | 6 |
| No | 0 |

Relevance of the question

| Yes | 6 |
| No | 0 |

Methods

This cross-sectional study consisting of two phases (content validation by the experts and face validation by the patients) was conducted from September 2018 to January 2019. Phase 2 of the study was conducted at one centre in Mumbai (Dr. Uday Jadhav’s Clinic). Patients (≥18 years) with a confirmed history of chronic stable angina, who were on medical therapy for at least the past 6 months, and had reported ≥1 episode of angina were enrolled in the study. Patients with a history of coronary artery bypass grafting, acute coronary syndrome and/or percutaneous transluminal coronary angioplasty within the past 6 months or deemed unsuitable by the investigator were excluded from the study.

Questionnaire development and testing

The OPTA questionnaire was adapted from the 7-item Seattle Angina Questionnaire (SAQ). The OPTA questionnaire included five questions on the five areas of cardiovascular health status over the past four weeks: limitation on the activities because of angina, frequency of discomfort, frequency of need for emergency medication, effect on overall enjoyment of life, and views about living with symptoms of angina. The brevity of the questionnaire was planned considering the Indian setting.

Validation

Content Validation by the Experts

In phase 1 of the study, the experts evaluated the OPTA questionnaire on the basis of its suitability to determine whether the treatment obtained by patients for chronic stable angina was adequate. A panel of six independent experts (practising cardiologists with >10 years’ experience) in the field of evidence-based practice reviewed and rated the questionnaire independently for content clarity and relevance based on the 4-point ordinal scale. Clarity was rated as: 1=very confusing, 2=confusing, 3=clear, and 4=very clear. Relevance was rated as: 1=highly irrelevant, 2=irrelevant, 3=relevant, and 4=highly relevant. The questions scoring ≤2 by at least two experts for either clarity or content relevance were recommended for modification.

Face Validation by the Patients

In phase 2 of the study, all enrolled patients assessed whether the OPTA questionnaire could correctly measure the specific areas of cardiovascular health status, and whether the response options correctly captured the
**Table 2: Summary of Face Validation by Patients**

<table>
<thead>
<tr>
<th>No: Questions</th>
<th>Agree n (%)</th>
<th>Disagree n (%)</th>
<th>Neutral n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Q1 Over the past 4 weeks, my day to day activities have been…</td>
<td>51 (100)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>- Extremely limited</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Moderately limited</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Not limited at all</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Q2 Over the past 4 weeks, on average I have had chest pain/ chest tightness/ angina…</td>
<td>51 (100)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>- 4 or more times per week</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- 3 or less times per week</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Not at all</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Q3 Over the past 4 weeks, on average, how many times have you had to take short acting nitrates for your chest pain, chest tightness or angina?</td>
<td>51 (100)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>- I have taken nitroglycerin…</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- 4 or more times per week</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- 3 or less times per week</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Not at all</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Q4 Over the past 4 weeks, how much has your chest pain, chest tightness or angina limited your enjoyment of life?</td>
<td>51 (100)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>- It has extremely limited my enjoyment of life</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- It has moderately limited my enjoyment of life</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- It has not limited my enjoyment of life at all</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Q5 If you had to spend the rest of your life with your chest pain, chest tightness or angina the way it is right now, how would you feel about this?</td>
<td>51 (100)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>- Not satisfied at all</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Somewhat satisfied</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Mostly satisfied</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Q6 The OPTA questionnaire appropriately assesses that the treatment received by the patients for chronic stable angina is optimum</td>
<td>51 (100)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>No: Questions</td>
<td>Agree n (%)</td>
<td>Disagree n (%)</td>
<td>Neutral n (%)</td>
</tr>
<tr>
<td>Q1 Over the past 4 weeks, my day to day activities have been…</td>
<td>51 (100)</td>
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<td>0</td>
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<tr>
<td>- Extremely limited</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>- Moderately limited</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
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<td></td>
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<td></td>
</tr>
<tr>
<td>Q2 Over the past 4 weeks, on average I have had chest pain/ chest tightness/ angina…</td>
<td>51 (100)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>- 4 or more times per week</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>- 3 or less times per week</td>
<td></td>
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</tr>
<tr>
<td>- Not at all</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Q3 Over the past 4 weeks, on average, how many times have you had to take short acting nitrates for your chest pain, chest tightness or angina?</td>
<td>50 (98.0)</td>
<td>0</td>
<td>0</td>
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<tr>
<td>- I have taken nitroglycerin…</td>
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<td>- 4 or more times per week</td>
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<tr>
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<td></td>
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</tr>
<tr>
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<td></td>
<td></td>
</tr>
<tr>
<td>Q4 Over the past 4 weeks, how much has your chest pain, chest tightness or angina limited your enjoyment of life?</td>
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<td>0</td>
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<tr>
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<td>Q5 If you had to spend the rest of your life with your chest pain, chest tightness or angina the way it is right now, how would you feel about this?</td>
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</tr>
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<tr>
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</tr>
<tr>
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<td>51 (100)</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

**Statistical Analysis**

No formal statistical calculation of the sample size was performed for this study. The raw data from the responses of each participant were coded numerically. The data was analyzed using the Statistical Package for Social Sciences (version 17.0) (SPSS Inc., Chicago, IL, USA).

**Results**

**Demographic and Baseline Characteristics**

A total of seven experts across India in the field of evidence-based practice were enrolled to validate the content and relevance (phase 1), out of which six experts completed the expert validation process.

Of the 51 patients who participated in the face validation (phase 2), 40 were men and 11 were women, with age ranging between 37 to 79 years. The majority of the patients were graduate or postgraduate (45 [88.2%]).

**Content Validation**

Only one out of six experts gave a score of ≤2 for the content relevance of question-5. As no question received a score ≤2 by two or more experts for either content clarity or content relevance, no modification in the questionnaire was required. Hence the overall questionnaire was considered to be validated by the expert panel (Table 1).

**Face Validation**

All 51 patients agreed that the questions correctly measured the specific area of cardiovascular health status. One patient did not answer if the responding option of question-3 correctly captured the answer to the question. All other patients responded to all questions and agreed that the questions correctly measured the specific area of cardiovascular health status.

The study protocol was approved by the local independent ethics committee. The study was conducted in accordance with the principles of the Declaration of Helsinki, International Conference on Harmonization Good Clinical Practice (ICHGCP) guidelines, and Indian regulatory guidelines (Indian Council of Medical Research and Indian GCP guidelines). All patients provided written consent in the patient authorization form to participate in the study.
specific area of cardiovascular health status, assessed whether the treatment received by them for chronic stable angina was optimum and responding options correctly captured the responses (Table 2).

Discussion

This study establishes the content and face validity of a modified instrument designed to sensitize clinicians about stable angina management in view of the four important goals viz., disease control, symptom relief, exercise capacity building, and QoL improvement. The OPTA questionnaire was designed based on the 7item SAQ tool, with appropriate adaptations based on the Indian scenario. The 7item SAQ is a validated disease-specific health status instrument to facilitate the measurement of health status in patients with CAD, with high test-retest reliability, predictive power, and responsiveness.11 The modified instrument would enable clinicians to reach out to their patients to stratify the severity of the condition and accordingly plan the management.

In this study, a two-tier validation was performed; the first phase was expert validation for content clarity and relevance, which was followed by the face validation by patients. During content validation, the expert committee reviewed all versions of the editions and determined whether the adapted version achieved semantic, idiomatic, experiential, and conceptual equivalence.12-14 Any discrepancies were resolved, and a consensus was reached between all members of the expert committee on all items of the questionnaire. Nevertheless, as the content validation process is highly dependent on how well the expert panel assesses the extent to which the construct of interest is empirically validated, care has been taken to select relevant experts to ensure that the validity of the content is properly assessed. Post content validation, in the face validation phase, survey was rolled out to a subset of the intended population for subjective assessment of the questionnaire.

All the six experts agreed that the OPTA questionnaire could appropriately assess whether the treatment received by the patients for their chronic stable angina was optimum. Further, all the patients agreed that all the questions correctly measured the specific area of cardiovascular health status and that the response options correctly captured the answers provided to the corresponding question. As only one patient did not answer the appropriateness of question-3 to correctly capture the responses to the question, no revision was deemed necessary.

The SAQ angina frequency scale has been compared with daily angina diary documenting angina frequency and sublingual nitroglycerin and a significant correlation were reported both cross-sectionally and longitudinally.15 The OPTA questionnaire can thus be used as a substitute to such a daily diary. Responding to a questionnaire is more convenient than completing a daily diary, especially from the compliance perspective. The OPTA questionnaire can thus facilitate in the routine measurement of patient-reported outcomes which are imperative for assessing treatment effectiveness and QoL.

Our study should be viewed in light of the following potential limitations. The study was conducted in a single center in patients who were able to complete the English questionnaire. Most respondents were educated (graduates/postgraduates), resulting in limited generalizability to all patient sections. Further, longitudinal measurements are recommended to explore test-retest reliability and responsiveness to changes in the measure. Moreover, construct and criterion validation is warranted.

In conclusion, the validated OPTA questionnaire was found to be a clear, and relevant tool to measure the specific area of cardiovascular health status, to assess whether the treatment received by the patients for their chronic stable angina was optimum and to understand the clarity of the response options. The findings support the content and face validity of this 5-item OPTA questionnaire. This tool will be helpful for clinicians to assess the cardiac health status of patients under treatment for angina. To achieve a more patient-centered health care system, this questionnaire will enable clinicians to strategize management decisions based on the accurately documented patients’ perspectives of their health status, thereby tracking their health trajectories. Because of the ease of administration, compared with diaries, the questionnaire may be well-suited for studies with longer time frames of analysis, clinical care, and quality assessment/improvement efforts. The OPTA questionnaire thus appears to be a valid tool that can be used in clinical research and in the real world to assess therapies to reduce angina and improve quality of life.

Conflict of Interest

This study was funded by Abbott Healthcare Pvt. Ltd. The views expressed and stated in this publication are the views of the authors and not of Abbott India Ltd.

Acknowledgements

The authors would like to thank Dr. Nidhi Nair, an independent consultant, for providing support in manuscript writing.

Data Availability

The data sets supporting the results of this article are included within the article.

References

17. Nidhi Nair, an independent consultant, for providing support in manuscript writing.
Colonoscopic findings in Patients of Portal Hypertension Due to Different Etiologies and their Correlation

Vipin Mathur1, Gurdeep Kaur2, Rajesh Kumar Prajapat3*, Sanjay Parmar3, Poonam4

Abstract

Introduction: Recently, it is established that portal hypertension also produces vascular changes throughout the colon similar to lesion on Upper GI endoscopy. So we planned this study to see the spectrum and frequency of colonic lesions in patients with portal hypertension due to different etiologies, to assess whether the presence of portal hypertension related colonic lesions correlates with severity of liver disease as indicated by CTP and MELD scores and to study the relationship between upper GI lesions of portal hypertension and colonic lesions.

Material and Methods: This study was done over a period of one year. In this study, 100 patients of portal hypertension due to different etiologies were taken if they met the inclusion criteria.

Results: The frequency of portal hypertension related colonic lesions including rectal varices, rectopathy and portal hypertensive colopathy increases with increase in the severity of liver disease as ascertained by Child-turcotte-Pugh score. Portal hypertension related colonic lesions and hemorrhoids are more frequent in cirrhotic patients with higher MELD score. Rectal varices are more frequent among who had esophageal varices on upper GI endoscopy. There is significant increase in bleeding PR as frequency of hemorrhoids increases, whereas there was not any significant relationship between bleeding PR and rectal varices suggesting that cause of lower GI bleeding in present were haemorrhoids most likely.

Conclusion: Patients with portal hypertension due to any etiology have significantly higher frequency of colonic lesions as severity of liver disease increases indicated by worsening CTP and MELD scores. Inspite of large number of lower GI manifestations of Portal Hypertension seen in our patients none had significant life threatening lower GI bleeds. So it can be concluded that only upper GI manifestation of Portal Hypertension are clinically significant.

Introduction

The clinical course of patients with cirrhosis is often complicated by a number of important sequelae that are independent of the etiology of the underlying liver disease.1

Portal hypertension causes hemodynamic and mucosal changes in the entire gastrointestinal (GI) tract. Recently, it is established that portal hypertension also produces vascular changes throughout the colon. The portal hypertension related changes in the colon described as portal hypertensive colopathy (PHC), colonic varices, rectal varices, vascular ectasias in colon & rectum and haemorrhoids.1,2

These are also important cause of acute and chronic lower GI bleed in cirrhotic patients with portal hypertension.

Material and Methods

This cross sectional study was done from January 2016 to December 2017 at Department of Medicine and Department of Gastro-enterology, RNT Medical College and attached group of hospitals, Udaipur (Raj.).

A total of 100 patients diagnosed as cases of portal hypertension of any etiology undergoing upper GI endoscopy and colonoscopy were included in this study after approval from the institutional ethical committee and written & well informed consent from patient.

Inclusion criteria

1. Age > 12 years and ≤ 85 years.
2. Portal hypertension patient due to any cause.

Exclusion criteria

1. Age <12 years and >85 years.
2. Clinically unstable patients such as on vasopressure support, on ventilator support or in hepatic encephalopathy etc.
3. Inflammatory Bowel Disease patients.
4. Upper GI and colonic malignancy patients.

For assessment of severity, cirrhotic patients were divided into A, B and C classes according to Child Pugh criteria. They were also divided into 4 MELD groups (as per UNOS) as follows: Group 1 – MELD ≤10, Group 2 – MELD- 11-18, Group 3- 19-26, Group 4- MELD ≥27.

In upper GI endoscopy oesophageal varices were classified according to Modified Paquet classification6 into three grades.

The following lesions were identified in patients with portal hypertension of any etiology: Portal hypertensive colopathy: characterized by erythema of the colonic mucosa with or without mosaic pattern, vascular lesions including cherry-red spots, arterial like lesions, or angiodysplasia-like lesions (Figures 3 and 4) and rectopathy presenting similar to colopathy (Figure 5). Rectal varices were defined as dilated vessels noted 4 cms above the anal verge and which...
do not proplapse into proctoscope (Figure 5). Colonic varices (Figure 2) and Haemorrhoids; internal or external.

Results

In this study, 100 patients of Portal Hypertension due to any etiology were included (Figure 1). In the present study it was observed that the mean age of patients was 45.91 years. Among these patients 67% were males and 33% were females. The male to female ratio was almost 2:1.

Discussion

In our study, the mean age of patients was 45.91 ± 15.28 years. Of the 100 patients included in the study 67% were male and 33% were female and male to female ratio was almost 2:1. Of the 100 patients of cirrhosis included in the study by B Ramesh Kumar et al181% were male and 19% were female.

For all the patients in this study, CHILD-PUGH (CP) score was calculated and the patients were classified into Child-pugh class A, B, C. In this study 62% of the patients had Child Pugh Class B whereas 37% of the patients had Child Pugh Class C & only 1% of the patients had Child Pugh Class A. MELD score also calculated for all these patients and patients were categorized based on MELD score into 4 groups. In this study 62% of the patients had MELD score 11-18, whereas 16% patients had MELD score 19-26 and 12% of the patients had MELD score between ≤10. While only 10% patients

Table 1: Association of Lower GI Lesion with Child Pugh score and MELD score

<table>
<thead>
<tr>
<th>Findings</th>
<th>Present</th>
<th>Absent</th>
<th>P- value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Association of Child Pugh score with Hemorrhoids</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Class A</td>
<td>0</td>
<td>1</td>
<td>0.50</td>
</tr>
<tr>
<td>Class B</td>
<td>32</td>
<td>30</td>
<td></td>
</tr>
<tr>
<td>Class C</td>
<td>21</td>
<td>16</td>
<td></td>
</tr>
<tr>
<td>Association of Child Pugh score with rectal varices</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Class A</td>
<td>0</td>
<td>1</td>
<td>0.001</td>
</tr>
<tr>
<td>Class B</td>
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<td>37</td>
<td></td>
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<tr>
<td>Class C</td>
<td>32</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Association of Child Pugh score with rectopathy on Colonoscopy</td>
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<td></td>
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</tr>
<tr>
<td>Class A</td>
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<tr>
<td>Class B</td>
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</tr>
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<td>Class C</td>
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<td>17</td>
<td></td>
</tr>
<tr>
<td>Association of MELD score with Hemorrhoids</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤10</td>
<td>3</td>
<td>9</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>11-18</td>
<td>35</td>
<td>27</td>
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</tr>
<tr>
<td>19-26</td>
<td>6</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>&gt;27</td>
<td>9</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Association of MELD score with rectal varices</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤10</td>
<td>5</td>
<td>7</td>
<td>&lt;0.001</td>
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<tr>
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<td>29</td>
<td>33</td>
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</tr>
<tr>
<td>&gt;27</td>
<td>8</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Association of MELD score with rectopathy</td>
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<td></td>
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<tr>
<td>≤10</td>
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<td>Association of MELD score with PHC</td>
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<tr>
<td>19-26</td>
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<td>3</td>
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<tr>
<td>&gt;27</td>
<td>4</td>
<td>6</td>
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Table 2: Association of Esophageal Varices on Upper GI Endoscopy with Rectal Varices on Colonoscopy

<table>
<thead>
<tr>
<th>Esophageal varices</th>
<th>Rectal varices</th>
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<th>Absent</th>
<th>P value</th>
</tr>
</thead>
<tbody>
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<td></td>
<td>48</td>
<td>27</td>
<td>0.01(S)</td>
</tr>
<tr>
<td>No</td>
<td></td>
<td>9</td>
<td>16</td>
<td></td>
</tr>
</tbody>
</table>

Table 3: Association of Bleeding PR with Hemorrhoids on PR Proctoscopy and Rectal Varices on Colonoscopy

<table>
<thead>
<tr>
<th>Bleeding PR Haemorrhoids Rectal Varices</th>
<th>Present</th>
<th>Absent</th>
<th>Present</th>
<th>Absent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>20</td>
<td>0</td>
<td>15</td>
<td>5</td>
</tr>
<tr>
<td>No</td>
<td>33</td>
<td>47</td>
<td>42</td>
<td>38</td>
</tr>
<tr>
<td>P value</td>
<td>&lt;0.001 (HS)</td>
<td>0.07 (NS)</td>
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</tbody>
</table>
In the study by B Ramesh Kumar et al, haemorrhoids were found in 48% of cases. However, Jeong IB et al, Ghoshal UC et al, Zaman A et al, reported lower rates, 25%, 21.9%, 21% respectively. This discrepancy may be attributed to lack of clear grading system, different aetiologies of liver disease and variation in severity of liver disease of the cases included. Bleeding per rectum was noted in 20% of cases in the present study. All patients presenting with bleeding per rectum had haemorrhoids while only 75% patients had rectal varices. In our study on statistical analysis between bleeding PR and haemorrhoids P value was <.001, which was showing highly significant relationship between these two whereas statistical analysis between bleeding PR and rectal varices P value was .07, which was showing not significant relationship between these two (Table 3). In the present study cause of lower GI bleeding were haemorrhoids most likely. In the previous studies, B Ramesh Kumar et al, reported bleeding per rectum in 12% of cases, of which 3% presented with severe bleeding and all the patients who presented with severe bleeding per rectum had rectal varices. Also majority of the presenting with bleeding per rectum had haemorrhoids. Bresci et al, reported a lower GI bleeding rate of 6%. Salama ZA et al, reported a bleeding rate of 20%, mostly from haemorrhoids. Ghoshal UC et al, reported that detection of colorectal varices but not PHC was associated with haematochezia. In the study by Ganguly S et al, overt bleeding per rectum was seen in 4%of patients with colopathy and 8% of the patients with rectal varices. In the study by Ito K et. al, the primary indications for colonoscopy were faecal occult blood test positive in 34% and anaemia in 10%. So lower GI manifestations like rectal varices compared to their upper GI counterparts do not have much clinical significance as these are rare cause of lower GI bleed. This lower incidence of bleeding from rectal varices may be related to rectal varices having thicker walls and are less superficial than those in the lower esophagus.

In the present study, of the 57 patients with rectal varices, 56% were from Child–Pugh class C, 44% from Child–Pugh class B and 0% from Child–Pugh class A. On analysis there is a statistically significant (p=0.001) relation between the Child-Pugh score indicating severity of liver disease and presence of rectal varices (Table 1). Also 51% of the cases with rectopathy were from Child–Pugh class C, 49% from Child–Pugh class B and none of the cases from Child–Pugh class A had rectopathy and there is statistically significant (p=0.05) relation between the Child-Pugh score and presence of rectopathy (Table 2). Among 32 patients with PHC, 53% were from Child–Pugh class C, 47% from Child–Pugh class B and 0% from Child–Pugh class A. Of the cases with haemorrhoids, 60% were from Child–Pugh class B, 40% from Child–pugh class C and none of them were from Child–Pugh class A. In the study by B Ramesh Kumar et al, 63.5% of the cases with rectal varices were from Child–Pugh class C, 36.5% from Child–Pugh class B and none of the cases from Child–Pugh class A had rectal varices, among PHC 61% were from Child–Pugh class C, 33% from Child–Pugh class B and 6% from Child–Pugh class A. Of the cases with haemorrhoids, 60.4% were from Child–Pugh class C, 33.6% from Child–Pugh class B and 6.2% were from Child–Pugh class A. Gad YZ et al and Salama ZA et al, demonstrated increase in the prevalence of portal hypertension related colonic lesions with increasing severity of liver disease. The increase in the prevalence of portal hypertension related colonic lesions with advanced Child-Pugh class may be a result of increase in portal pressure due to increasing fibrosis coupled with worsening haemodynamic dysfunction associated with advanced liver disease (Table 1).

MELD score is the most accepted prognostic scoring system for allocation of organs for liver transplantation. It accurately predicts survival in patients with decompensated cirrhosis. When the cases with rectal varices were categorised based on MELD score, 14 % of cases with rectal varices had MELD score >27. There was statistically significant relation between presence of rectal varices and increasing MELD score (p < 0.001) (Table 1). Also, 20 % of cases with rectopathy had MELD score >27. The association between rectopathy and increasing MELD score was statistically significant (p < 0.001) (Table 1). Among patients with PHC, 12% had MELD score >27. The association between these two were
statistically significant (p < 0.001) (Table 1). Of the patients with haemorrhoids, 17% had MELD score > 27. There was high statistical significance between presence of haemorrhoids and MELD score (p<0.01) (Table 1). This relation between portal hypertension related colonic lesions and MELD score may be explained by worsening of fibrosis leading to increase in portal pressure and worsening haemodynamic dysfunction associated with high MELD score suggestive of advanced liver disease (Table 1). In the study by B Ramesh Kumar et al, a statistically significant relation of haemorrhoids and MELD score is observed in accordance with the previous studies. B Ramesh Kumar et al, Diaz-Sanchez et al, Ito K et al, Ghoshal UC et al, found no association between the presence of PHC and esophageal varices.

In this study it was observed that 62.8% patients with rectal varices had esophageal varices. There was a statistically significant relationship between presence of rectal varices and esophageal varices (p=0.01) (Table 2). In the study by B Ramesh Kumar et al, 54.5% patients with rectal varices had grade III esophageal varices. Hosking et al noted rectal varices in 19% of patients with cirrhosis without esophageal varices, 39% in patients with esophageal varices without history of bleeding, and 59% in patients with esophageal varices and history of bleeding. Similarly Gad YZ et al demonstrated a significant relation between the presence of esophageal varices and rectal varices.

In the present study when the association between the presence of rectopathy and esophageal varices was evaluated, there was no statistically significant relationship (p=0.407). Similarly association between Portal Hypertension Colopathy and esophageal varices was analysed, this relationship was statistically not significant (p=0.13). Association between presence of haemorrhoids and esophageal varices was also analysed, and there was no statistically significant relation (p=0.563). This finding is in accordance with the previous studies. B Ramesh Kumar et al, Diaz-Sanchez et al, Ito K et al, Ghoshal UC et al, found no association between the presence of PHC and esophageal varices.

On analysis there was no statistically significant association between portal hypertensive gastropathy and portal hypertension related colonic lesions (PHC, rectal varices and haemorrhoids), p>0.05. This finding is in accordance with studies by B Ramesh Kumar et al, Ito K et al and Diaz-Sanchez et al.

**Conclusion**

The frequency of portal hypertension related colonic lesions including rectal varices, rectopathy and portal hypertensive colopathy increases with increase in the severity of liver disease as ascertained by Child-turcotte-Pugh score. Portal hypertension related colonic lesions and haemorrhoids are more frequent in cirrhotic patients with higher MELD score (Table 2). Rectal varices are more frequent among those had esophageal varices on upper GI endoscopy (Table 2).

Inspite of large number of lower GI manifestations of Portal Hypertension seen in our patients none had significant life threatening lower GI bleeds. So it can be concluded that only upper GI manifestation of Portal Hypertension are clinically significant (Table 3).

**References**

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**COMPOSITION:**
- **Glycomet GP 0.5:** Each uncoated tablet contains metformin hydrochloride BP (as sustained release) 500 mg and glimepiride USP 1 mg.
- **Glycomet GP 2:** Each uncoated tablet contains metformin hydrochloride BP (as sustained release) 500 mg and glimepiride USP 2 mg.
- **Glycomet GP 1/850:** Each uncoated tablet contains metformin hydrochloride BP (as sustained release) 850 mg and glimepiride USP 2 mg.
- **Glycomet GP 3/850:** Each uncoated tablet contains metformin hydrochloride BP (as sustained release) 850 mg and glimepiride USP 3 mg.
- **Glycomet GP 0.5 FORTE:** Each uncoated tablet contains metformin hydrochloride BP (as sustained release) 1000 mg and glimepiride USP 1 mg.
- **Glycomet GP 1 FORTE:** Each uncoated tablet contains metformin hydrochloride BP (as sustained release) 1000 mg and glimepiride USP 2 mg.
- **Glycomet GP 2 FORTE:** Each uncoated tablet contains metformin hydrochloride BP (as sustained release) 1000 mg and glimepiride USP 4 mg.

**INDICATIONS:**
Glycomet GP is indicated for the management of patients with type 2 diabetes mellitus (T2DM) when diet, exercise and single agent (metformin hydrochloride or glimepiride alone) do not result in adequate glycemic control.

**DOSAGE AND ADMINISTRATION:**
Dosage of Glycomet GP should be individualized on the basis of effectiveness and tolerability while not exceeding the maximum recommended daily dose of glimepiride 8 mg and metformin 2000 mg. Initial dose: 1 tablet of Glycomet GP should be administered once daily during breakfast or the first main meal. Do not crush, chew or break tablets. Glycomet GP 0.5 FORTE and Glycomet GP 1 FORTE are gastroretentive and can be administered as a single dose. For Glycomet GP 2 FORTE, a divided dose (half tablet at each meal) is recommended. For patients who are unable to take the tablets whole, they can be divided after crushing the tablet in water. The tablet has a texture that is white and smooth to the touch.

**CONTRAINDICATIONS:**
- In patients hypersensitive to glimepiride, other sulfonylureas, other sulfonamides, metformin or any of the excipients of Glycomet GP.
- Acute renal failure or renal dysfunction, acute conditions with the potential to alter renal function (dehydration, severe infection, shock, cardiac/respiratory failure).

**WARNINGS:**
- Keep out of reach of children. Patient should be advised to report promptly exceptional stress situations (e.g. trauma, surgery, febrile infections) blood glucose regulation may deteriorate and a temporary change to insulin may be necessary to maintain good metabolic control. In case of lactic acidosis, patient should be hospitalized immediately.

**PRECAUTIONS:**
- In the initial weeks of treatment, the risk of hypoglycemia may be increased and necessitates especially careful monitoring. Serum creatinine levels should be determined before initiating treatment and regularly thereafter: at least annually in patients with normal renal function and prior to or at the time of any surgical procedure.
- Use of Glycomet GP should be discontinued 48 hours before any surgical procedure.

**ADVERSE REACTIONS:**
- For glimepiride: Hypoglycaemia; temporary visual impairment; gastrointestinal symptoms like nausea, vomiting, abdominal pain, diarrhoea may occur; increased liver enzymes, cholestasis and jaundice may occur; allergic reactions may occur occasionally.
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TH1 & TH2
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2. European Committee for Medicinal Products for Human Use. 30 September 2021.
Clinical Profile and Treatment Outcome in Scrub Typhus Patients in Central India

Yogendra V Bansod¹, Archana A Aher²*, Pragati Bhole³, Karthik Rengaraj⁴, Prasad Jadhav⁴

Abstract

**Background:** Scrub typhus is an acute febrile illness caused by Orientia tsutsugamushi. It is known from various parts of India. However Central India was naive to any epidemics of scrub typhus with occasional and sporadic occurrence now and then. This part of India witnessed an outbreak of scrub typhus in the months of August and September 2018. Therefore present research was carried out with an objective to study the clinical profile and treatment outcome in scrub typhus patients in central India.

**Method:** In this study, total 140 patients with an acute febrile illness diagnosed as scrub typhus by positive IgM antibodies against O. tsutsugamushi were enrolled, over a period of two months (August to October 2018). All relevant data were recorded and analyzed.

**Results:** Among 140 cases, 52.14% patients reported from urban area and 47.85% patients from rural area. The mean age of patients was 43.75±16.82 years, ranged from 12-83 years with female predominance (male:female=1:1.37). Fever (100%), cough (38.57%) breathlessness (27.85%), altered sensorium (9.28%) and headache (7.85%) were the predominant clinical features. Eschar was seen in 33 patients (23.57%). Renal (73; 52.14%) and hepatic dysfunction (68; 48.57%) was the commonest followed by respiratory dysfunction (59; 42.14%). All patients (except pregnant patients) were treated with oral or inj doxycycline. Seventeen patients (23.57 %). Renal (73; 52.14%) and hepatic dysfunction (68; 48.57%) was the commonest followed by respiratory dysfunction (59; 42.14%). All patients needed mechanical ventilation and five patients required dialysis. Total 24 (17.14%) patients died during the study period.

**Conclusion:** Scrub typhus has become a leading infectious disease in central India and an important cause of infectious fever. An increasing awareness of this disease coupled with prompt management will go a long way in reducing both morbidity and mortality from this disease.

Introduction

Scrub typhus is a re-emerging zoonotic bacterial infection in the region known as the ‘tsutsugamushi triangle’ of South and Southeast Asia, the Asian Pacific rim, and Northern Australia. India is an integral component of “tsutsugamushi triangle”. Scrub typhus, also known as mite borne typhus fever, tsutsugamushi disease, tropical typhus, is an acute infectious disease of variable severity that is caused by Orientia Tsutsugamushi and transmitted to humans by an arthropod vector of the Trombiculidae family. Human beings get infected accidentally when they encroach upon mite-infested rural and suburban areas.²

However, the diagnosis of Scrub Typhus is often not thought or missed because of close resemblance to other common diseases, low index of suspicion, non-specific signs and symptoms, absence of widely available sensitive and specific diagnostic tests. Delay in diagnosis and initiation of appropriate treatment can result in severe complications and death.³ Thus early diagnosis and case findings is important to control the spread of scrub typhus disease. Multiple outbreaks have been witnessed in the Sub-himalayan regions, Himachal Pradlesh, Rajasthan and Pondicherry. Central India was naive to any epidemics of scrub typhus with occasional and sporadic occurrence now and then. However this part of India witnessed an outbreak of scrub typhus in the months of August and September. Therefore present research was carried out with an objective to study the clinical profile and treatment outcome in scrub typhus patients in central India.

Materials and Methods

In this retrospective observational study, data of patients admitted from August 2018 to October 2018 of diagnosed scrub typhus cases with positive IgM was analyzed. Appropriate ethical approval was obtained from the Ethical Committee of the Government Medical College and Hospital, Nagpur. All demographic data, detailed history, organ involvement, any comorbid illnesses were recorded. Area of residence, detailed clinical examination, presence or absence of eschar was noted.

All patients of fever attending medicine OPD or casualty were subjected to investigations to establish the cause of fever. These included a peripheral blood smear for malarial parasites, complete blood count, and serology for dengue, leptospirosis, scrub typhus, enteric fever and retroviral infections. Out of these, patients who were positive for IgM scrub typhus antibodies and needed indoor admission were enrolled for the study. Test for serum IgM for scrub typhus was done in the microbiology department of our hospital. A chest X-ray, arterial blood gas analysis, electrocardiogram were ordered as and when required. A CT of the brain and cerebrospinal fluid (CSF) analysis was done when the need arises.

The diagnosis of scrub typhus was confirmed with positive IgM antibodies against O. tsutsugamushi and when required. All patients were treated with oral or inj doxycycline. Seventeen patients (23.57 %). Renal (73; 52.14%) and hepatic dysfunction (68; 48.57%) was the commonest followed by respiratory dysfunction (59; 42.14%). All patients needed mechanical ventilation and five patients required dialysis. Total 24 (17.14%) patients died during the study period.

Conclusion: Scrub typhus has become a leading infectious disease in central India and an important cause of infectious fever. An increasing awareness of this disease coupled with prompt management will go a long way in reducing both morbidity and mortality from this disease.
were done, if clinically indicated. Biochemical investigations including renal function and liver function tests were done and recorded. Patients with multi-organ dysfunction were managed with standard care, with ventilatory support or renal replacement therapy, as and when needed. All patients received oral or injection doxycycline along with other supportive care. ANC patients were given azithromycin. Final outcome were noted and cause of death was evaluated.

### Table 1: Baseline characteristics and co-morbidity of study population

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Number of Patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (Years)</td>
<td></td>
</tr>
<tr>
<td>12-29</td>
<td>35 (25.00%)</td>
</tr>
<tr>
<td>30-39</td>
<td>20 (14.28%)</td>
</tr>
<tr>
<td>40-49</td>
<td>28 (20.00%)</td>
</tr>
<tr>
<td>50-59</td>
<td>24 (17.14%)</td>
</tr>
<tr>
<td>60-69</td>
<td>23 (16.42%)</td>
</tr>
<tr>
<td>70-79</td>
<td>09 (6.42%)</td>
</tr>
<tr>
<td>&gt;80</td>
<td>01 (0.71%)</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>59 (42.14%)</td>
</tr>
<tr>
<td>Female</td>
<td>81 (57.85%)</td>
</tr>
<tr>
<td>Residence</td>
<td></td>
</tr>
<tr>
<td>Urban area</td>
<td>73 (52.14%)</td>
</tr>
<tr>
<td>Rural area</td>
<td>67 (47.85%)</td>
</tr>
<tr>
<td>Co-morbidity</td>
<td>No. of Patients (%)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>15 (10.71%)</td>
</tr>
<tr>
<td>Diabetes Mellitus</td>
<td>12 (8.57%)</td>
</tr>
<tr>
<td>Dengue</td>
<td>07 (5.00%)</td>
</tr>
<tr>
<td>PNC</td>
<td>06 (4.28%)</td>
</tr>
<tr>
<td>ANC</td>
<td>05 (3.57%)</td>
</tr>
<tr>
<td>Anemia</td>
<td>03 (2.14%)</td>
</tr>
<tr>
<td>Hyperthyroidism</td>
<td>04 (2.85%)</td>
</tr>
<tr>
<td>None</td>
<td>84 (60.00%)</td>
</tr>
</tbody>
</table>

### Table 2: Clinical features and Site of Eschar

<table>
<thead>
<tr>
<th>Sign and Symptoms</th>
<th>No. of Patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fever</td>
<td>140 (100%)</td>
</tr>
<tr>
<td>Cough</td>
<td>54 (38.57%)</td>
</tr>
<tr>
<td>Breathlessness</td>
<td>39 (27.85%)</td>
</tr>
<tr>
<td>Eschar</td>
<td>33 (23.57%)</td>
</tr>
<tr>
<td>ALT Sensorium</td>
<td>13 (9.28%)</td>
</tr>
<tr>
<td>Headache</td>
<td>11 (7.85%)</td>
</tr>
<tr>
<td>Abdominal Pain</td>
<td>9 (6.42%)</td>
</tr>
<tr>
<td>Jaundice</td>
<td>05 (3.57%)</td>
</tr>
<tr>
<td>Fever With Rash</td>
<td>02 (1.42%)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>02 (1.42%)</td>
</tr>
<tr>
<td>Burning Micturition</td>
<td>01 (0.71%)</td>
</tr>
<tr>
<td>Bodyache</td>
<td>01 (0.71%)</td>
</tr>
<tr>
<td>Oral Ulcers</td>
<td>01 (0.71%)</td>
</tr>
<tr>
<td>Chest Pain</td>
<td>01 (0.71%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Site of eschar on the body</th>
<th>No. of patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Head and face</td>
<td>0 (0.00%)</td>
</tr>
<tr>
<td>Neck</td>
<td>2 (1.42%)</td>
</tr>
<tr>
<td>Arm and axilla</td>
<td>12 (8.57%)</td>
</tr>
<tr>
<td>Thorax and breast</td>
<td>4 (2.85%)</td>
</tr>
<tr>
<td>Back</td>
<td>3 (2.14%)</td>
</tr>
<tr>
<td>Abdomen</td>
<td>6 (4.28%)</td>
</tr>
<tr>
<td>Groin and Buttok</td>
<td>4 (2.85%)</td>
</tr>
<tr>
<td>Thigh and leg</td>
<td>2 (1.42%)</td>
</tr>
</tbody>
</table>

### Observations and Results

During the period of August and September total 1000 patients of fever were investigated to establish the cause of fever. Out of these 400 were positive for IgM for scrub typhus. Out of these 400, 140 patients needed indoor admission. Data of these 140 patients were recorded.

In our study mean age of patients was 43.75±16.82 with female preponderance (M:F = 1:1.37). 52.14% patients reported from urban area and 47.85% patients from rural area. Most of the patients (84; 60%) did not have co-morbidity. Patients with comorbid illness and demographic characteristics are shown in Table 1.

The clinical features of scrub typhus patients at the time admission have been shown in Table 2. The most common clinical presentation was fever with chills which was present in all cases, and other presentation were cough (38.57%), breathlessness (27.85%), fever with altered sensorium (9.28%) and headache (7.85%). Majority of patients (54.28%) had onset of illness ranging from 5 to 15 days. Eschar was seen in 33 patients (23.57%). Various sites of eschar are shown in Table 2 and Figure 1.

Laboratory investigations are shown in Table 3. Low platelet counts and abnormal renal functions were frequently abnormal. 49.85% of patients had involvement of three or more organ systems. Renal (73; 52.14%) and hepatic dysfunction (68; 48.57%) was the commonest followed by respiratory dysfunction (59; 42.14%), (Table 4).

Twenty nine patients (20.71%) had multiorgan dysfunction involving CNS, Cardiovascular, pulmonary, renal and hepatic system during the course of hospitalization. Among the 59 patients with respiratory dysfunction, ARDS (41; 69.49%) was the commonest, followed by pleural effusion (37, 62.71%) and pulmonary infiltrates in chest X-ray (15, 25.42%).

All patients were treated with oral or inj doxycycline, pregnant patients were treated with azithromycin, and

### Table 3: Laboratory investigations

<table>
<thead>
<tr>
<th>Investigation</th>
<th>No. of Patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total leucocyte count &lt;4000/cmm</td>
<td>22 (15.71%)</td>
</tr>
<tr>
<td>Total leucocyte count &gt;11 000/cmm</td>
<td>41 (29.28%)</td>
</tr>
<tr>
<td>Anaemia</td>
<td>67 (47.85%)</td>
</tr>
<tr>
<td>Platelet count &lt;100 000/cmm</td>
<td>107 (76.42%)</td>
</tr>
<tr>
<td>Elevated transaminase levels</td>
<td>69 (49.28%)</td>
</tr>
<tr>
<td>Increased bilirubin</td>
<td>25 (17.83%)</td>
</tr>
<tr>
<td>Increased urea/creatinine</td>
<td>72 (51.42%)</td>
</tr>
</tbody>
</table>

### Table 4: Organ system dysfunction during the stay in hospital

<table>
<thead>
<tr>
<th>Organ/system</th>
<th>Frequency of dysfunction (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Respiratory</td>
<td>59 (42.14%)</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>41 (29.28%)</td>
</tr>
<tr>
<td>Renal</td>
<td>73 (52.14%)</td>
</tr>
<tr>
<td>Central nervous system</td>
<td>48 (34.28%)</td>
</tr>
<tr>
<td>Liver</td>
<td>68 (48.57%)</td>
</tr>
</tbody>
</table>
those with complications were treated with standard care. Seventeen patients needed mechanical ventilation and five patients required dialysis. Most of the patients (116; 82.85%) were discharged from the hospital and 24 (17.14%) patients were died within 1-15 days of admission. The average duration of hospital stay was 5.2 days.

Discussion

India is an integral component of “tsutsugamushi triangle” which depicts a part of the globe endemic to scrub typhus. Owing to frequent outbreaks witnessed in different parts of the country in the recent past, scrub typhus is thought to be the commonest occurring rickettsial infection in India and the mortality from untreated scrub typhus remains unknown. Central India witnessed an outbreak of scrub typhus in the months of August, September and October. Till now there are no reports of scrub typhus from our region. During the month of Aug to Oct we investigated 1000 patients presented for acute febrile illness, out of which 400 turned positive for scrub typhus. Out of positive cases, 140 patients needed admission. We hereby present data of these indoor patients. In current study in contrast to other studies, more number of patients was from urban area that didn’t have history of exposure to vegetation. When we surveyed the literature to know the source of infection in such patients, it was found that rodents carry the mites on their skin, which can transmit disease to the humans. And also when the rodents from the areas where the patients were hailing from were examined by a team from veterinary college, Nagpur, found the presence of mites on the bodies of rodents.

The majority of our patients were aged between 12 and 29 years similar to Sinha et al study. Female preponderance was seen which was comparable to Palanivel et al study, in which they reported male to female ratio of 1:1.3. In an outbreak report from Rajasthan India, Sinha et al reported scrub typhus in more number of females than males (66.7% Vs 33.3% respectively).

The clinical manifestations of this disease vary from minimal disease to severe fatal illness with multi-organ dysfunction. The commonest presenting symptoms were fever, cough and shortness of breath. Fever is almost universal in these cases and was seen in all cases. Fever can be of short (<7 days) or long (>7 days) duration. Rams et al. reported 28% and 72% cases with fever of short and long duration respectively. Thirteen patients presented with altered sensorium, similar to other studies. The presence of an eschar is a valuable clinical clue in the diagnosis of scrub typhus (though its frequency varies from 7-97%). A study done by Chanta et al shows that eschar, a pathognomonic sign of scrub typhus, were present in 75% of the presented patients and were usually painless and single, and a study done by Sudhakar et al shows all patient of diagnosed scrub typhus had eschar mark, differs from our study where only thirty three patients (23.57%) had eschar. So the suspicion of the disease could not be made on the basis of eschar mark only.

Scrub typhus is a cause of multi-organ dysfunction. Nearly half of our patients (49.85%) had three or more organ systems involved while 29 patients (20.71%) had evidence of dysfunction of five organs during the course of their hospital stay. Complications in scrub typhus develop after the first week of illness. Narvencar et al. found hepatic dysfunction to be the most common followed by ARDS, circulatory collapse and acute renal failure. We found renal dysfunction in 73 patients, followed by hepatic dysfunction 68 patients. However, the abnormalities in cell counts, liver and renal functions in our patients were consistent with those reported in other studies. Among patients who presented with any central nervous system manifestations, CSF examination was performed in all patients, CSF examination was acellular but with increased protein with normal sugar levels. However, Viswanathan et al had 17 patients with meningitis among 65 of their patients. This is possibly because they specifically searched for patients with scrub typhus and meningitis. Scrub typhus should be considered in the differential diagnosis of meningococcalis, especially when accompanied by renal failure or jaundice. Previous studies from India have reported meningococcalis in 9.5%-23.3% of patients. The mortality in patients with scrub typhus had wide variations and depends on the circulatory load of Orientia tsutsugamushi, early or late presentation and treatment modality. Deaths are attributable to delayed presentation or diagnosis, and development of MODS. Complications such as ARDS, renal failure and hepatic involvement are independent predictors of mortality. The mortality rate of 17.14% in our study was closely similar to the study from India by Kumar et al. (Mortality 17.2%). Initially, in our patients mortality was high. But subsequently we noticed eschar in one patient who was admitted as a case of acute febrile illness with multi organ failure (MODS). Later on we started suspecting scrub typhus in patients admitted as acute febrile illness with MODS. This created awareness in health department as well as in doctors who started investing patients for scrub typhus and using tablet doxycycline for the patients of fever. This resulted in decrease mortality in patients admitted later. As such it’s not a lethal disease. But when there is multi organ involvement, prognosis is bad.

Conclusion

Scrub typhus has become a leading infectious disease in central India and an important cause of infectious fever. Early presentation of disease with duration of fever <7 days has better prognosis. Multiorgan failure, renal, liver and respiratory dysfunctions are the important life threatening complications that lead to higher case fatality rates. Thus, in central India, an increasing awareness about the disease presentation, clinical features, laboratory findings and prompt management will help in reducing both morbidity and mortality from this infectious disease. Scrub typhus should be kept as one of the differential diagnoses of acute febrile illness.

References

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Melioidosis: A 5-year Review from a Single Institution in Pondicherry

Gadadhar Sharma¹, Stalin Viswanathan²

Abstract

Introduction: Forty-four percent of global cases are predicted to occur in the Indian sub-continent, but less than 2000 cases have been reported. Though the number of predicted cases in India is reported to be high, lesser numbers are being reported due to a lack of diagnostic capabilities and poor awareness of the disease.

Aims: We aimed to estimate the number of cases of melioidosis over a 5-year period, the proportion of non-survivors, and map the geographical regions of the patients.

Methods: Retrospectively, medical case records were reviewed with the search terms melioidosis and *Burkholderia pseudomallei*. Data on the geographical region, risk factors, clinical manifestations, and outcomes were collected and analysed.

Results: Thirty-four patients with melioidosis were found. 12/34 had died in the hospital. Case records of only 20 patients could be traced. Patients who died were older and had a longer duration of symptoms, had higher total leukocyte counts, higher platelet counts, and more severe hepatic and renal dysfunction compared to those who survived. Being a teetotaller, having received intensive care, and mechanical ventilation showed statistical significance between the two groups.

Conclusion: Three centres from Pondicherry have reported melioidosis; this study had the most significant reported number of cases from a single institution in Pondicherry. The mapping of our patients resulted in probable evidence of melioidosis in six other districts of Tamil Nadu. Since the Indian population is at high risk because of diabetes, and melioidosis can mimic tuberculosis, increased awareness among physicians is a must to diagnose and treat this disease with high mortality.

Introduction

Melioidosis, caused by *Burkholderia pseudomallei*, is common in tropical and sub-tropical climates, with an incidence risk rate of 5/100000 people per year. The Indian subcontinent is described to be endemic for melioidosis, but the disease is under-reported.³ Forty-four percent of global cases are predicted to occur in the Indian subcontinent; but less than 2000 cases have been reported.² A review of case reports described only 85 cases in India.³ Most reports from India are case studies, barring that of two centres- Christian Medical College(CMC), Vellore, and Manipal Academy of Higher Education(MAHE), Manipal and Mangalore, who have described significant numbers (>100).⁴ As of 2018, Karnataka and Tamil Nadu had reported 306 and 146 cases of melioidosis, respectively, contributed mainly by MAHE and CMC.⁵ The first case from Pondicherry was at our institution in 2002;² Six other cases have been reported.⁶⁻¹² Two other centres from Pondicherry have reported a
Table 1: Clinical features, laboratory investigations and treatment parameters

<table>
<thead>
<tr>
<th>Variables</th>
<th>Survivors (n=13)</th>
<th>Non-survivors (n=7)</th>
<th>(significant p value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Males (n=19)</td>
<td>13</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>47.5±2.3</td>
<td>50.8±3.6</td>
<td></td>
</tr>
<tr>
<td>Duration of symptoms (days)</td>
<td>49.0±27.0</td>
<td>64.7±14.9</td>
<td></td>
</tr>
<tr>
<td>Duration of stay (days)</td>
<td>28.2±2.7</td>
<td>18.7±7.1</td>
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</tr>
<tr>
<td>Respiratory symptoms(n)</td>
<td>6</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Hepatobiliary symptoms (n)</td>
<td>2</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>GIT symptoms(n)</td>
<td>9</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Urinary symptoms(n)</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Neurological symptoms(n)</td>
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<td>1</td>
<td></td>
</tr>
<tr>
<td>Musculoskeletal symptoms (n)</td>
<td>5</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Alcoholism(n)</td>
<td>2</td>
<td>4 (0.05)</td>
<td></td>
</tr>
<tr>
<td>Diabetes mellitus(n)</td>
<td>11</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Previous antibiotics(n)</td>
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<td>4</td>
<td></td>
</tr>
<tr>
<td>Pallor(n)</td>
<td>4</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Pulse rate (beats/min)</td>
<td>107.3±5.5</td>
<td>111.8±5.5</td>
<td></td>
</tr>
<tr>
<td>Systolic BP (mmHg)</td>
<td>103.0±3.8</td>
<td>108.0±3.9</td>
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</tr>
<tr>
<td>Respiratory signs(n)</td>
<td>7</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Musculoskeletal signs (n)</td>
<td>6</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Total leukocyte count(x10⁹/L)</td>
<td>11.5±1.4</td>
<td>12.5±2.8</td>
<td></td>
</tr>
<tr>
<td>Platelets (x10⁹/L)</td>
<td>178.8±28.3</td>
<td>328.9±76.2</td>
<td></td>
</tr>
<tr>
<td>Haemoglobin (g/dL)</td>
<td>9.3±0.7</td>
<td>9.0±0.8</td>
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</tr>
<tr>
<td>Sodium (mmol/L)</td>
<td>128.9±2.0</td>
<td>130.1±2.6</td>
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</tr>
<tr>
<td>Urea (mg/dL)</td>
<td>49.5±8.8</td>
<td>73.7±18.7</td>
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<td>Creatinine (mg/dL)</td>
<td>1.5±0.1</td>
<td>2.2±0.6</td>
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<td>Serum albumin(g/dL)</td>
<td>2.6±0.1</td>
<td>2.4±0.1</td>
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<tr>
<td>Aspartate transaminase (U/L)</td>
<td>55.0±38.18</td>
<td>201.7±466.7</td>
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<tr>
<td>Alanine transaminase (U/L)</td>
<td>25.5±7.7</td>
<td>119.0±117.5</td>
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</tr>
<tr>
<td>Alkaline transferase (U/L)</td>
<td>492.2±75.4</td>
<td>381.4±60.1</td>
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<td>Urine culture positivity (n)</td>
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<td></td>
</tr>
<tr>
<td>Blood culture positivity (n)</td>
<td>4</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Joint aspirate positivity (n)</td>
<td>4</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Endotracheal aspirate positivity (n)</td>
<td>1</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Mechanical ventilation (n)</td>
<td>2</td>
<td>6 (0.004)</td>
<td></td>
</tr>
<tr>
<td>Intensive care(n)</td>
<td>3</td>
<td>6 (0.007)</td>
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<tr>
<td>Ceftazidime, meropenem(n)</td>
<td>9</td>
<td>2</td>
<td></td>
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<tr>
<td>Ceftazidime alone (n)</td>
<td>2</td>
<td>0</td>
<td></td>
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<tr>
<td>Meropenem alone (n)</td>
<td>2</td>
<td>5</td>
<td></td>
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<tr>
<td>Arthrocentomy(n)</td>
<td>3</td>
<td>1</td>
<td></td>
</tr>
</tbody>
</table>

cumulative seven cases.

Large case series have been reported only from large academic centres or tertiary hospitals, where the awareness was high and laboratory facilities were available. Our institution is a catchment area for patients from Pondicherry, Tamil Nadu, Orissa, and West Bengal. The burden of cases from Pondicherry and its neighbouring districts is not known since most reports do not describe the place of origin of the patient. We decided to embark on a similar project to find the prevalence in Pondicherry and neighbouring districts of Tamil Nadu since only case reports had been described previously from our institution.

Materials and Methods

We aimed to estimate the period prevalence of melioidosis over five years among medical inpatients and estimate the proportion of non-survivors. Thirdly, we also attempted to map the geographical districts from where these patients hailed from. We performed a retrospective cross-sectional study of patients admitted between 01 January 2014 and 31 December 2018. After obtaining approval (JIP/IEC/2019/339), we searched computerized records of the Medical Records Department, the Admission and Discharge Registers of all the Medical Wardes for the five years using terms “melioidosis” and “Burkholderia pseudomallei”.

Melioidosis mimics such as pyrexia of unknown origin, abscesses of liver, splenic, kidney, lung, psoas, glutei, prostate, emphysematous pyelonephritis, and arthritis were also extracted. Case files with a proven diagnosis by the culture of blood or body fluids were considered. Using a mobile app, Epicollect, the following was captured: demographics, place of origin, risk factors, clinical presentation, examination, investigations, treatment, and outcomes.

Localized melioidosis was defined when the blood culture was negative and other foci of involvement, such as abscesses, and body fluids grew *Burkholderia pseudomallei*. Meningitis was diagnosed if the CSF showed a meningitic picture, and the organism was isolated in CSF or elsewhere. Septic shock was defined by the presence of persisting hypotension <90 mmHg SBP requiring vasopressors. Septicaemic melioidosis was considered if the blood culture grew *Burkholderia pseudomallei*.

Statistics

Data thus obtained was transferred to a spreadsheet and analysed using IBMSPSS for Windows version 22. Categorical data were studied using chi-square, while continuous variables were analysed using the T-test. Frequencies such as risk factors, clinical symptoms, signs, organ involvement, septic shock, and mortality were calculated. Means of the duration of illness and hospital stay and biochemical parameters were determined. Significance was considered when the P-value was less than 0.05.

Results

A list of 230 patients was obtained, with 34 having culture-proven melioidosis. Patients without melioidosis included: liver abscess (n=151), renal/perinephric abscess (n=15), splenic abscess (n=10), cerebral abscess (n=5), three each of gluteal and lung abscesses, two each of prostate, and psoas abscesses, one each of groin, perineal, intrapelvic, and multiple abscesses, and septic arthritis. Twelve of the 34 had died in hospital. Case records of only 20 patients (19M and 1F) could be traced in the MRD. Seven died during hospital stay (Table 1). Patients who died were older and had a longer duration of symptoms, had higher total leukocyte counts, higher platelet counts, and more severe hepatic and renal dysfunction compared to those who survived, but none of the parameters reached statistical significance. Being a teetotaller, having received intensive care, and mechanical ventilation showed...
Discussion

We focused on centres besides MAHE and CMC; a total of 301 cases were found. Twelve were excluded due to a doubtful diagnosis and one was a foreigner diagnosed post-mortem after he returned to Scotland, the first case reported in 1953. Other centres from South India that have described cases include Tamil Nadu (Chennai, Madurai, and Tiruchirapalli), Kerala (Thrissur, Thiruvananthapuram, Kochi, Kannur, Calicut, Thiruvalla, and Perinthalmanna), Karnataka (Mangalore, Bangalore, and Dharwad), Telangana (Hyderabad, Nalgonda, and Karimnagar), and Andhra Pradesh (Visakhapatnam).

In Karnataka, Dakshina Kannada and Udupi districts remain the biggest source of reports- five medical colleges contributed to them. Among a total of 29 cases, three non-MAHE colleges (K.S Hegde Medical Academy, Father Mueller Medical College, and AJ Institute of Medical Sciences) contributed to 26 cases. One other medical college and private super specialty hospital from Bangalore have contributed one case each. One case has also been reported from Dharwad. Seroprevalence among the adult population in Karnataka was found to be 29%.

In Tamil Nadu, Chennai was the only coastal district where cases were reported. Apollo Hospitals reported 32 culture-positive patients with melioidosis with their patients hailing from West Bengal, Tripura, Assam, and the Andamans and had a 75% cure rate. Between 2013 and 2019, Apollo Hospitals has described 49 cases. Two other private super-specialty hospitals and four medical college hospitals in Chennai have also reported cases. In Madurai, a medical college has reported eight cases of melioidosis, while a private hospital from Tiruchirapalli has reported one case of melioidosis septicemia.

We found that seven other districts from Tamil Nadu contributed to patients admitted in our institution-Villupuram, Cuddalore, Nagapattinam, Thanjavur, Ariyalur, Thiruvarur, and Namakkal. The first four of are coastal districts (Figure1). Soil samples collected from paddy fields of Cuddalore district had yielded B. pseudomallei isolates. Cuddalore contributed 8 cases to our study, and our institution is the nearest diagnostic centre 28 km away. Though coastal districts of Karnataka and Kerala have been shown to be areas of a high prevalence of melioidosis, as reported from Chennai, we found patients from interior districts of Tamil Nadu as well. Vellore is not a coastal district, but with the highest reportage of cases that includes patients from Tamil Nadu as well as other states of the east coast.

Except for Pathanamthitta, all the other seven districts in Kerala where melioidosis was reported are coastal. Among 82 cases reported from Kerala, Thiruvananthapuram has reported more than 41% (n=34) of the total. All these cases from Kerala have been reported from 10 medical college hospitals.

Four medical colleges from Telangana have reported cases of melioidosis, with Nizam’s Institute reporting the majority. Meanwhile, in Andhra Pradesh, the sole report is from Apollo Hospital, Vishakapatnam. Behera et al. have described a large cohort of 47 cases from Odisha over a 2-year period; 4/47 and 2/47 hailed from West Bengal and Uttar Pradesh, respectively. AIIMS, Bhubaneshwar has described 50 cases in four reports. In New Delhi, private hospitals began reporting melioidosis from 2013 onwards. In all these instances, it was observed that medical colleges and specialty private hospitals with laboratory backup were at the forefront of reporting melioidosis, indicating a widespread need for laboratory facilities in areas needing surveillance. We found 49 other non-MAHE/CMC centres that have reported melioidosis: Tamil Nadu (n=9), Kerala (n=10), Karnataka (n=6), Pondicherry (n=3), Telangana (n=4), Andhra Pradesh (n=1) and Maharashtra (n=4), West Bengal (n=4), Odisha (n=1), New Delhi (n=5), Assam (n=1), Madhya Pradesh (n=1), Uttar Pradesh (n=1), and Rajasthan (n=1).

Eighty percent of our patients were diabetics in contrast to that of 43.7% from Chennai, 67.5% from Thrissur, and 94.5% from Mangalore. Thirty-three percent of our patients died while 25%, 24.3% and 41% were the numbers from the above three studies. Only 6/20 patients had a history of alcoholism in our study compared to higher percentages in other studies. Tuberculosis has been associated with
Melioidosis coinfection in one of our patients as borne out in other reports. Thirty-five percent of our patients had musculoskeletal manifestations compared to 18% in Chennai, 16 5.4% in Thrissur19 and 29.4% in Mangalore.20

Limitations

Since it was a retrospective study, many case records could not be retrieved (n=14/34). This was mainly due to technical reasons. In some instances, details of whether the disease was localized or disseminated could not be ascertained. Soil studies are available from only one district that corresponded to 40% of our patients. Getting one patient from each district cannot be generalized to the entire district as to its prevalence or risk of the disease. There is a referral bias because our hospital is the nearest government tertiary care centre for most of these patients and nine patients (9/20) had been previously treated in other hospitals with intravenous antibiotics.

Conclusions

Our institution is a catchment area for patients from Pondicherry, Tamil Nadu, Orissa, and West Bengal. Three centres in Pondicherry have reported melioidosis, with this study having the largest reported number of cases from a single institution in Pondicherry. The mapping of our patients resulted in probable evidence of melioidosis in six other districts of Tamil Nadu. More population and soil studies in such areas are needed before the recommendation of surveillance centres in these districts. Melioidosis is being reported only from medical college hospitals and super-specialty centres. Since the Indian population is at high risk because of diabetes, and melioidosis can mimic tuberculosis and its protein manifestations, it behaves that awareness among physicians is a must to diagnose and treat this disease with high mortality.

Funding

This was done under the aegis of the ICMR-STS 2019 project (Proposal Number 2019-08647).

Key messages

- Melioidosis in India appears to be under-reported for want of awareness and lab facilities.
- Just about 45 centres in India have reported/treated melioidosis.
- Patients need to be mapped to their origins, rather than the place of treatment.

References

# Journal of The Association of Physicians of India

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**September 2021**

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## Key Parameters of Combination

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<th>Allegra-M (Fexofenadine + Montelukast)</th>
<th>Levocetirizine + Montelukast</th>
<th>Bilastine + Montelukast</th>
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<td>Bioequivalence published data&lt;sup&gt;1,4&lt;/sup&gt;</td>
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<td>Synergistic effect&lt;sup&gt;1,3,4&lt;/sup&gt;</td>
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<td>9.6%</td>
<td>23.2%</td>
<td>No HTH data</td>
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</table>

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**References:**
2. This dissolution study compares Allegra M, Allegra, Singulair and one Fexofenadine + Montelukast fixed dose combination available as a monolayered tablet in India. Data on File, 2012 (b)

**API Link:**

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**Allegra-M**

The only bioequivalent **FEXOFENADINE & MONTELUKAST** combination published in the IJPS<sup>1,2</sup>

* Indian Journal of Pharmaceutical Sciences

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**THE SUPERIOR SYNERGISTIC COMBINATION**

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*Indian Journal of Pharmaceutical Sciences*
Management of Hyperglycemia in COVID-19 and Post-COVID-19 Syndrome - Proposed Guidelines for India

Arun Nanditha¹, Arun Raghavan¹, Anoop Misra², Banshi Saboo³, Awadhesh Kumar Singh⁴, Shashank R Joshi⁵, Sanjay Agarwal⁶, Nikhil Tandon⁷, Mangesh Tiwaskar⁸, Sosale R Aravind⁹, Ambady Ramachandran¹⁰

Abstract
SARS-CoV-2 virus spread rapidly all over the globe in 2020 and the second wave has taken our nation, India by storm. The pandemic has posed unique challenges in people with metabolic disorders, including diabetes, hypertension, obesity, pulmonary, cardiovascular, kidney and non-alcoholic fatty liver disease. Uncontrolled diabetes, in conjunction with endocrine, inflammatory and metabolic effects of the infection itself has made management of hyperglycemia in COVID-19 infection particularly challenging. Furthermore, the post-COVID-19 syndrome has also emerged as a sequela in COVID-19 survivors, increasing the risk of death, complications and adding further burden on the health care system. With more than a year of experience, we have gained substantial insight; and now provide practical recommendations on the management of hyperglycemia in COVID-19 as well as post COVID-19 syndrome.

Introduction
The pandemic has proven to be a huge challenge to the healthcare system, especially in India. It has become evident that diabetes is one of the most important risk factors for increased morbidity and mortality in patients with COVID-19 infection.¹ Optimal management of hyperglycemia in patients with COVID-19 infection and well as post COVID-19 is extremely important to reduce this risk. It is observed that there is considerable heterogeneity in the effect of COVID-19 on glucose metabolism, ranging from mild to severe hyperglycemia with or without ketoacidosis. The severity is mainly attributed to steroid therapy, cytokine storm, acute stress, autoimmune damage to the β-cells and COVID-19 induced pancreatitis.² Moreover, the resurgence of COVID-19 in India has brought newer challenges in the management of hyperglycaemia. In comparison to the first, the second wave caused predominantly by the SARS-CoV-2 variants reported a surge in the number of cases affecting the younger population, patients presenting with shortness of breath, requiring oxygen supplementation and/or mechanical ventilation.³,⁴ Of all co-morbid conditions that have been associated with the severity of the COVID-19 infection, diabetes takes the centre stage due to its increased prevalence among our population. Studies have shown that uncontrolled hyperglycaemia per se causes increased mortality among patients with COVID-19 infection.⁵,⁶

Even under normal circumstances, clinical decision making in the management of diabetes is complex, more so during the pandemic due to increased severity of the infection among diabetes patients in comparison to persons without diabetes. Limited access to diabetes care in the hospitals has caused a setback in the optimal glycaemic management resulting in hyperglycaemia and poor treatment outcomes for COVID-19 infection. The immune-escape of the “double” and “triple” SARS-CoV-2 variants poses a great concern on the emergence of re-infections especially among diabetes patients. Moreover, there are emerging data on the direct detrimental effect of the virus on the pancreatic β-cells, predisposing COVID-19 patients to an increased risk of new-onset diabetes.⁴,⁵,⁶

Beyond this, there are many uncertainties with COVID-19 infection. Hence an expert committee was formed to address many of these unanswered questions, and develop a consensus guideline on the management of hyperglycaemia for people with COVID-19 for use in both primary and specialist care, and to further address issues pertaining to post COVID-19 sequelae as well.

The expert committee which reviewed and finalized this document comprised of eminent diabetologists and endocrinologists who have contributed extensively to public health research in diabetes in India. The members have individually published important scientific data relating to the management of COVID-19 in India. The guideline was developed through practical expertise in the clinical management of diabetes and COVID-19. A systematic literature search of published studies and articles was performed using PubMed SEARCH.

¹Director, Consultant Diabetologist, India Diabetes Research Foundation and Dr. A. Ramachandran’s Diabetes Hospitals, Chennai, Tamil Nadu; ²Chairman, Fortis-C-DOC Centre of Excellence for Diabetes, Metabolic Diseases and Endocrinology, Chairman, National Diabetes, Obesity and Cholesterol Foundation (N-DOC); ³President, Diabetes Foundation (India) (DFI), New Delhi; ⁴Director – Aegle Clinic for Diabetes Care, Ahmedabad, Gujarat; ⁵Senior Consultant Endocrinologist, G D Hospital & Diabetes Institute, Kolkata, West Bengal; ⁶Senior Consultant Endocrinologist, Lilavati Hospital and Research Centre, Mumbai, Maharashtra; ⁷Director – Aegle Clinic for Diabetes Care, Head of Dept. Medicine & Diabetes, Ruby Hall Clinic. Senior Consultant Diabetes & Medicine, Jehangir Hospital, Pune, Maharashtra; ⁸Professor & Head, Department of Endocrinology & Metabolism, All India Institute of Medical Sciences, New Delhi; ⁹Consultant Physician & Diabetologist, Shilpa Medical Research Centre, Mumbai, Maharashtra; ¹⁰Director, Diacon Hospital, Bangalore, Karnataka; ¹¹President, India Diabetes Research Foundation, Chairman, Dr. A. Ramachandran’s Diabetes Hospitals, Chennai, Tamil Nadu; *Corresponding Author

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The following recommendations were proposed with the intention to guide clinicians to manage hyperglycaemia in COVID-19 infection and post-COVID-19 syndrome more effectively.

**Hyperglycaemia in COVID-19 Infection – Clinical Scenarios and Pathophysiology**

In order to treat hyperglycaemia is COVID-19 infection, it is important to differentiate the various types of clinical presentations/scenarios.

1. Pre-existing known case of diabetes with COVID-19 infection
2. Undetected diabetes identified during COVID-19 infection
3. Prediabetes, converted to type 2 diabetes, due to COVID-19 infection/stress
4. Steroid/stress induced hyperglycaemia
5. New onset diabetes due to COVID-19 infection

A classification has been brought out on the heterogeneous hyperglycaemic states based on the presentation of hyperglycaemia in individuals with or without known diabetes in varying degrees of COVID-19 infection. Among the groups described, patients with diabetes or prediabetes treated with corticosteroids for moderate to severe COVID-19 infection experience acute rise in blood glucose levels, and require high doses of insulin. Even without steroid therapy, infection and acute stress is said to increase blood glucose levels. Many patients with COVID-19 infection, develop ketoacidosis, and hyperglycaemic hyperosmolar state (HHS), resulting in worsening of outcomes. In an analysis by Li et al., the prevalence of ketoacidosis was 6-4% in patients with COVID-19 without diabetes as compared to 11-6% in patients with COVID-19 with diabetes, resulting in a higher mortality rate (33-3%).

Even individuals with no prior history of diabetes or pre-diabetes may present with ketoacidosis suggesting acute insulinopenia due to the severity of COVID-19 infection and pneumonia.

In a study that compared adults diagnosed with new onset diabetes during the time of the pandemic and prior showed that individuals newly diagnosed with diabetes with a history of COVID-19 infection had significantly higher blood glucose values and HbA1c compared to those without a similar history. However, no differences in symptomatology or other biochemical characteristics were noted between the two groups.

As discussed, although, acute stress and infection with the cytokine storm may itself be a trigger to result in hyperglycaemia and ketosis, the direct effect of SARS-CoV-2 virus on the pancreatic β-cells may be considered. It is proposed that affinity of the SARS-CoV-2 spike protein towards angiotensin converting enzyme 2 receptor expressed on the pancreatic β-cells among other tissues facilitates its entry causing direct viral tissue damage. This may result in an acute loss of insulin secretory capacity, which could lead to a rapid metabolic deterioration resulting in diabetic ketoacidosis or HHS. This SARS-CoV-2 ‘tropism’ may result in β-cell destruction of the pancreas, leading to of new onset diabetes in previously normoglycemic patients with COVID-19 infection. Even in the absence of new-onset diabetes, varying degrees of metabolic dysregulation in patients with COVID-19 may occur due to immune cell infiltration, necroptotic cell death and SARS-CoV-2 viral infection of the pancreatic beta-cells.

**Challenges in Management of Hyperglycaemia in COVID-19 Infection**

There are various challenges in patients with COVID-19 infection that may need to be addressed or overcome to achieve glycemic control.

These may include:

1. Lack of / inability to frequently monitor blood glucose due to restricted contact between nurses/healthcare worker and the patient
2. Lack of / non – availability of diabetes care expert in many hospital settings thus hyperglycemia is given less importance to management.
3. Concomitant use of steroid therapy, and the infection/virus itself that contributes to hyperglycemia and makes the correction of blood glucose more challenging.
4. Virtual consultation – Insulin initiation becomes challenging

**Hyperglycaemia and COVID-19 – Clinical Implications**

- Diabetes has been identified as the major risk factor for worsening of outcomes in patients with COVID-19 infection. A study in UK that included more than 5500 patients with COVID-19 reported that poor glycemic control, as indicated by increased HbA1c values prior to hospital admission, was associated with a high risk of in-hospital mortality. The in-hospital death was greater in patients with HbA1c of ≥7.5% (Hazard Ratio (HR) 3.36, 95% CI 2.18-2.56) than in those with lower HbA1c values (HR 1.50, 95% CI 1.4-1.6).

In line with this observation, findings from various other studies also suggest that at-admission hyperglycaemia is strongly associated with mortality and complications among known and new-onset diabetes. At-admission hyperglycaemia was defined as increased blood glucose levels measured at the time of hospital admission or on the immediate next day of admission on fasting. In another study, with 1122 patients with COVID-19 admitted to hospital in the USA, the mortality rate was four times higher in those with diabetes or hyperglycaemia during the hospital stay (28.8%) than those with normoglycaemia (6.2%). In a study conducted in South India, by Arun et al., among 800 patients with COVID-19 infection, treated in the intensive care unit, the mortality rate was two times higher in patients with diabetes (10.2%) as compared to the non-diabetic patients (5.9%), p = 0.021. Furthermore, mortality was more than three times higher in patients with uncontrolled diabetes (HbA1c >8%) (59.1%) as compared to patients with a HbA1c of <6.5% (22.7%). An analysis by Singh et al. showed that among patients with diabetes and COVID-19 infection, there were significant increases in acute respiratory distress syndrome (14.8% vs. 7.2%, p = 0.01) acute kidney injury (3.2% vs. 0.4%, p = 0.04) and acute heart injury (6.8% vs. 1.6%, p = 0.01) among poorly-controlled diabetes patients (n=528, blood glucose >180mg/dl) compared to patients with well-controlled diabetes.
to improve outcomes in patients with COVID-19 infection. The purpose of this review is to stress the importance of blood glucose as the fifth parameter among the vital signs in monitoring patients with COVID-19 infection.17

Management of Blood Glucose in COVID-19 Infection

A. Patients with pre-existing diabetes and COVID-19 infection

In patients with pre-existing diabetes with COVID-19 infection, the first step is to check blood glucose levels and HbA1c at baseline.18

- In Mild to Moderate COVID-19 infection / Home isolation

The flow chart (Figure 1) provides recommendations on the management of hyperglycaemia and self-monitoring of blood glucose for diabetes patients with mild infection and are in home quarantine. In mild to moderate cases, with satisfactory blood glucose control (HbA1c (<7%, Fasting Plasma Glucose (FPG) <130mg/dl, Post Prandial Glucose (PPG) <180mg/dl) there is no compelling need to change therapy. However, close and frequent home monitoring of blood glucose is recommended, with up-titration of therapy if required through the course of infection. In patients with unsatisfactory glucose levels (HbA1c ≥7%, FPG ≥130mg/dl, PPG ≥180mg/dl) there is no compelling need to change therapy. However, close and frequent home monitoring of blood glucose is recommended, with up-titration of therapy if required through the course of infection. In patients with unsatisfactory glucose levels (HbA1c ≥7%, FPG ≥130mg/dl, PPG ≥180mg/dl), treatment intensification is recommended in order to achieve target blood glucose levels. The choice of glucose lowering agents can be made with clinicians’ discretion.

- In Moderately-Severe COVID-19 infection

This is defined as having fever and at least one sign/symptom of respiratory disease and requirement for hospitalization.19 The flowchart (Figure 2) provides recommendations for patients with moderate to severe COVID-19 infection who require hospitalization. Glucose monitoring must be given high priority, so as to reduce mortality and complication risk. As discussed earlier, the use of high-dose steroids makes glucose control in these patients more challenging. Specific recommendations have also been given by the Ministry of Health and Family Welfare on the management of diabetes at patient care facility for COVID-19.20

B. Management of Hyperglycaemia in previously non-diabetic patients

![Flowchart: Mild COVID-19](image1)

![Flowchart: Moderate to Severe COVID-19 infection](image2)
with COVID-19 infection

In all patients with COVID-19 infection, it is advised to check blood glucose and HbA1c as part of routine blood work up. Table 1 provides recommendations for treatment of hyperglycaemia in patients not known to have diabetes previously.

### Glucose Lowering Agents in COVID-19 Infection

Over the last year and more, we have learnt that the oral glucose lowering agents cause no negative effects or worsening in the course of SARS-CoV-2 infection. In patients with mild to moderate infection, there is no compelling need to withhold or stop antidiabetic medication if the patients eating and drinking adequately. Patients with severe infection who require hospitalization may need modification in ongoing antidiabetic therapy and insulin initiation. The decision must be made based on the patient’s clinical status, including hydration status, nutritional status, risk of hypoglycemia and renal status.

The use of oral antidiabetic agents however does have specific considerations in COVID-19 infection as shown in Table 2.

### Metformin

Metformin has been implicated to have anti-viral effects in the past, against infections including Hepatitis B, Hepatitis C, and even in HIV, through mechanisms not clearly known. Additionally, metformin may also exhibit anti-inflammatory, anti-oxidative and immune-modulatory effects. These beneficial effects that the drug offers may in fact improve host response to COVID-19 infection. There are several clinical studies that have assessed outcomes in patients on Metformin with COVID infection. The most recent Coronavirus Disease and Diabetes Outcome (CORONADO) study in patients with diabetes and COVID-19 infection, showed significant improvement in outcomes in metformin users versus non-users, including a significant 37% risk reduction in mortality observed in metformin users (OR 0.63; 95% CI 0.52-0.77; p < 0.001). Several other retrospective analyses have shown significant improvement in outcomes with the use of metformin in patients with diabetes and COVID-19 infection.

Although there is evidence suggesting a favourable effect of metformin in COVID-19 infection, the drug must be discontinued in patients with acute renal injury, sepsis or respiratory distress.

### Dipeptidyl-Peptidase 4 Inhibitors (DPP4i)

Experimental studies suggest that DPP4i may also have anti-inflammatory effects. Another theory is that the soluble DPP-4 might act as a co-receptor for a subset of corona viruses, hence may interfere with their binding and hypothetically reduce the viral load.

There are several retrospective studies that assessed the effects of DPP4 inhibitors in COVID-19 infection. The results of most of these analyses suggest that these agents do not have a negative impact on the prognosis of the infection. In the prospective CORONADO study, the rates of discharge from hospital were significantly higher in DPP-4i users (22%) as compared to the non-users. However, there was no difference in mortality rates between patients using DPP4i versus non-users. A large retrospective study, SIDIACO-RETRO, studied the effect of sitagliptin in patients with type 2 diabetes and COVID-19 infection (n=334). The results showed a significant relative risk reduction (56%) in mortality in patients with type 2 diabetes and COVID-19 using sitagliptin, as compared to standard-of-care. The DPP4i have advantages of being well tolerated with low risk of hypoglycemia and can be safely used through wide range of estimated Glomerular Filtration Rate (eGFR), with dose adjustment. In patients with mild to moderate COVID-19 infection, the DPP4i can be safely continued. However, in severe infection, the decision must be made based on the patient’s clinical status (Figure 2).

### Sodium Glucose Cotransporter -2 (SGLT2) Inhibitors

There exists a hypothesis that the SGLT2 inhibitors can decrease intracellular pH and increase lactate concentrations which could reduce viral load in COVID-19 infection. SGLT-2i may also have anti-inflammatory properties and reduce oxidative stress, which may in turn provide a positive impact in COVID-19 infection. There have been some studies to assess the effects of this group of agents in patients with COVID-19 infection. A study by Kim et al., suggested no difference in death rates or severity of illness in SGLT2i users versus non users with COVID-19 infection. Similarly, preliminary results from the Dapagliflozin in Respiratory Failure in Patients with COVID-19 [DARE] study shows no worsening of outcomes in patients with respiratory failure with COVID-19 infection. Furthermore, Dapagliflozin was well tolerated by the patients, with numerically fewer adverse events than placebo. However, it is strongly recommended to use these group of drugs with caution during acute infection due to the risk of dehydration, electrolyte imbalance and euglycaemic diabetic ketoacidosis.

### GLP-1 Receptor Agonists

GLP-1 Receptor agonists may worsen nausea and due to their gastrointestinal side effects, must be discontinued in patients with severe COVID-19 infection, due to the risk of aspiration. Experimental models suggest that both GLP-1 receptor agonists may have some anti-inflammatory effects. Although there are some case reports of GLP-1 therapy in patients with COVID-19 infection describing improved outcomes, these agents have not been widely studied in COVID-19 infection. The CORONADO study, did however report that in patients with COVID-19 infection, there was no detrimental effects or worsening in outcomes, among GLP -1 RA users (254/2794) compared to non-users.

### Sulphonylureas

Caution must be sought with the
use of sulphonylureas due to the risk of hypoglycemia, especially if the patient is not eating well during acute infection. Some retrospective studies with sulphonylureas in patients with COVID-19 infection have reported no harm or detrimental effects. Similarly, reports from the CORONADO study also found neither detrimental nor beneficial effects on outcomes in the combined group of sulphonylureas and glinides. However, it is strongly recommended to judiciously use sulphonylureas, due to their high risk of hypoglycemia.

**Pioglitazone**

There exists some evidence from experimental and human studies that pioglitazone may have anti-inflammatory properties, including reduction in levels of inflammatory markers like Interlukin (IL) -6, IL-8 and tumor necrosis factor alpha (TNF-α). However, there is little known about its effects in patients with COVID-19 infection, including the CORONADO study where effects of pioglitazone were not reported. It is recommended to avoid the use of pioglitazone in patients with severe COVID-19 infection due to its risk of fluid retention.

**Insulin**

Insulin is the safest option, especially in patients who are critically ill and will benefit from intravenous insulin use. Insulin requirements may also be very high due to the hyper-inflammatory state during COVID-19 infection as discussed earlier. In patients without proper food intake, and are previously on oral agents conversion to subcutaneous insulin may be required. The disadvantage of insulin use is the risk of hypoglycemia, which can be largely reduced with frequent and close monitoring of blood glucose.

However, some studies conducted in other countries have reported treatment with insulin to be associated with lower chance of early hospital discharges and higher mortality. But the findings are likely to be due to confounding by severity of infection, other comorbidities and compliance to diabetes management prior to admission.

The following Table 2 discusses the advantages and disadvantages of antidiabetic agents used in the treatment of hyperglycemia in patients with COVID-19 infection.

Table 2: Antidiabetic treatment during COVID-19

<table>
<thead>
<tr>
<th>Agent</th>
<th>Advantages</th>
<th>Disadvantages</th>
<th>Clinical outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metformin</td>
<td>No risk of hypoglycaemia</td>
<td>Risk of lactic acidosis</td>
<td>Risk reduction in mortality by 57% among metformin vs. non-metformin users (OR 0.63; 95% CI 0.52-0.77; p &lt; 0.001)</td>
</tr>
<tr>
<td>DPP-4 inhibitors</td>
<td>No risk of hypoglycaemia. Available for a wide renal function range. Potential anti-inflammatory action. Potential modification of SARS-CoV-2 binding to DPP-4</td>
<td>Risk of hypoglycaemia. Decrease in mortality compared to non-users (HR 0.44; 95% CI 0.29-0.66; p &lt; 0.0001) with sitagliptin vs. insulin therapy.</td>
<td>Decrease in all-cause mortality (HR 0.44; 95% CI 0.29-0.66; p &lt; 0.0001) with sitagliptin vs. insulin therapy.</td>
</tr>
<tr>
<td>SGLT2 inhibitors</td>
<td>No risk of hypoglycaemia. Avoid initiation in acute infection</td>
<td>Risk of hypoglycaemia. Decreased risk of mechanical ventilation (Adjusted RR 0.03; 95% CI, 0.00-0.70; p = 0.03)</td>
<td>Decreased risk of mechanical ventilation (Adjusted RR 0.03; 95% CI, 0.00-0.70; p = 0.03)</td>
</tr>
<tr>
<td>GLP-1 receptor agonists</td>
<td>No risk of hypoglycaemia. Potential anti-inflammatory action. Avoid initiation in acute infection</td>
<td>Risk of gastrointestinal side effects. Studies report no detrimental or beneficial effect compared to non-users.</td>
<td>Studies report no detrimental or beneficial effect compared to non-users.</td>
</tr>
<tr>
<td>Sulfonylureas</td>
<td>Not applicable</td>
<td>Risk of hypoglycaemia if oral intake is administered with other glucose-lowering agents. Risk of fluid retention. Risk of hypoglycaemia.</td>
<td>No confirmatory reports available</td>
</tr>
<tr>
<td>Pioglitazone</td>
<td>Anti-inflammatory action. Preferred agent of choice. Recommended in hospitalized/critical patients.</td>
<td>Possible need for high doses.</td>
<td>Increase in mortality compared to non-users (27.2% versus 3.5%; adjusted HR, 5.38 [2.75-10.54])</td>
</tr>
<tr>
<td>Insulin</td>
<td>Intravenous administration</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Table 2: Antidiabetic treatment during COVID-19**

- **Advantages**
  - No risk of hypoglycaemia
  - No risk of hypoglycaemia.
  - No risk of hypoglycaemia.
  - No risk of hypoglycaemia.
  - No risk of hypoglycaemia.
  - Anti-inflammatory action
  - Recommended in hospitalized/critical patients.

- **Disadvantages**
  - Risk of lactic acidosis
  - Risk of hypoglycaemia. Decrease in mortality compared to non-users (HR 0.44; 95% CI 0.29-0.66; p < 0.0001) with sitagliptin vs. insulin therapy. Decrease in mortality in DPP-4i users, compared to the non-users (HR 0.13; 95% CI, 0.02-0.92; p=0.04). Higher rate of discharge from hospital (22%) compared to non-users (OR 1.22; 95% CI,1.02-1.47; p<0.03) Decreased risk of mechanical ventilation (Adjusted RR 0.03; 95% CI, 0.00-0.70; p = 0.03)
  - Risk of hypoglycaemia. Decreased risk of mechanical ventilation (Adjusted RR 0.03; 95% CI, 0.00-0.70; p = 0.03)
  - Risk of hypoglycaemia.
  - Risk of fluid retention.
  - Risk of hypoglycaemia.
  - Possible need for high doses.

- **Clinical outcomes**
  - Risk reduction in mortality by 57% among metformin vs. non-metformin users (OR 0.63; 95% CI 0.52-0.77; p < 0.001)
  - Decrease in all-cause mortality (HR 0.44; 95% CI 0.29-0.66; p < 0.0001) with sitagliptin vs. insulin therapy.
  - Decrease in mortality in DPP-4i users, compared to the non-users (HR 0.13; 95% CI, 0.02-0.92; p=0.04).
  - Higher rate of discharge from hospital (22%) compared to non-users (OR 1.22; 95% CI,1.02-1.47; p<0.03)
  - Decreased risk of mechanical ventilation (Adjusted RR 0.03; 95% CI, 0.00-0.70; p = 0.03)
  - Decreased risk of mechanical ventilation (Adjusted RR 0.03; 95% CI, 0.00-0.70; p = 0.03)
  - Studies report no detrimental or beneficial effect compared to non-users.
  - No confirmatory reports available
  - Increase in mortality compared to non-users (27.2% versus 3.5%; adjusted HR, 5.38 [2.75-10.54])

- **Intravenous administration**
  - Not applicable
  - Decrease in all-cause mortality (HR 0.44; 95% CI 0.29-0.66; p < 0.0001) with sitagliptin vs. insulin therapy.
  - Decrease in mortality in DPP-4i users, compared to the non-users (HR 0.13; 95% CI, 0.02-0.92; p=0.04).
  - Higher rate of discharge from hospital (22%) compared to non-users (OR 1.22; 95% CI,1.02-1.47; p<0.03)

**Follow up visits**

- In patients with new onset hyperglycemia
  - Repeat HbA1c after 3 months.
  - Continue insulin, until clarity on type of diabetes
  - After one month / after discontinuation of steroid check for Serum insulin levels/ C-peptide levels, to r/o insulin deficiency/ assess pancreatic β-cell function
  - In patients with pre-existing diabetes or unmasked diabetes

**Discharge advice**

- Self Monitoring of Blood Glucose – patients must be encouraged to closely monitor blood glucose levels at home.
- Challenges include: - Continued steroid therapy and changes in dietary habits, including loss of/ increased appetite, loss of taste etc.
- Rehabilitation care team must include dietitian and patient educator.
- Advise on resuming exercise gradually, based on patient’s status.
After discontinuation of steroid/1 month/ patient eats adequately, stabilize Glucose lowering therapy

In patients not requiring insulin, Insulin therapy can be switched to oral agents

**Post COVID Sequela / Syndrome**

In many patients recovery from COVID-19 infection is followed by the post infective stage, which poses many challenges for the patient and treating clinician. Reports suggest residual effects of SARS-CoV-2 infection, such as fatigue, dyspnea, chest pain, cognitive disturbances, arthralgia and decline in quality of life.\(^6,36,37\) Manifestation of post-infectious seizures has also been reported indicating the importance of monitoring for neurologic diseases particularly in patients with preexisting co morbidities such as diabetes and hypertension.\(^38\)

As shown in Figure 3, there are three phases in COVID-19 infection (1) acute symptomatic which includes symptoms and abnormalities presentlor up to 4 weeks (2) ongoing symptomatic with signs and symptoms of COVID-19 from 4 to 12 weeks and (3) post-COVID-19 syndrome includes persistent symptoms and/or delayed or long-term complications over 12 weeks from the onset of acute infection and not attributable to alternative diagnoses.\(^37,39,40\)

During the post-COVID phase many patients continue to be on steroid therapy for a significant period even after discharge from hospital, which contributes to uncontrolled blood glucose levels. This has also been a concern in increasing the risk of opportunistic infections like mucormycosis.\(^16,36\) Thus, maintenance of good glycemic control during the post – COVID-19 phase is of utmost importance for optimal recovery.

**Etiopathogenesis / Risk Factors for Post COVID-19 Syndrome**

Little is known about the etiopathogenesis of the debilitating symptoms that persist in the post COVID-19 infective phase beyond 3 or 4 weeks from the onset of acute symptoms. The replication-competent of SARS-CoV-2 has not been isolated after 3 weeks. However, development of sequelae or long-term complications of SARS-CoV-2 infection may occur months together affecting various organs and systems.\(^39\) There are also very little data on the risk factors or the high risk groups for post COVID-19 syndrome. One study reported a higher risk of long COVID-19 in women, in persons aged >70 years, patients requiring hospitalization during the acute infection, and presence of asthma, without differences between countries or socioeconomic groups. Also, the number of symptoms during the acute

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**Fig. 3: Timeline to Post COVID-19 sequela – Frequency of signs and symptoms**

- Detailed history and background (history on COVID-19 infection, including treatment details)
- Clinical examination, including systemic examination, with specific attention to oropharynx and cardio-respiratory system.
- Investigations – Basic blood workup
  - Other tests include – Coagulation profile, D-dimer, C-reactive protein, electrolytes, Thyroid Stimulating Hormone
  - Muscle enzymes
  - Chest x-ray/ CT thorax
  - Electrocardiogram, Echocardiogram

**Confirmation of Post – COVID-19 syndrome**

- Other causes of presenting symptoms ruled out

**In patients with Diabetes / New onset hyperglycemia**

- Specific focus on blood glucose control
- Stabilize glucose, with priority on lower risk of hypoglycemia
- Lab tests to assess pancreatic \(\beta\)-cell function
- Patient education

**In all patients**

- Specific diet advice, with nutrition team
- Advise on resuming exercise/physical activity, according to patient status
- Physiotherapy and exercises to be included to manage sarcopenia
- Appropriate symptomatic/ supportive therapy, including pain relief etc
- Psychological assessment and counseling
- Appropriate/ timely referral to concerned specialist for further management

**Fig. 4: Flowchart – Clinical assessment of patient with post COVID-19 syndrome**

- After discontinuation of steroid/1 month/ patient eats adequately, stabilize Glucose lowering therapy
- In patients not requiring insulin, Insulin therapy can be switched to oral agents

- Fig. 3: Timeline to Post COVID-19 sequela – Frequency of signs and symptoms
- Fig. 4: Flowchart – Clinical assessment of patient with post COVID-19 syndrome
COVID-19 infection and diabetes may have an association. Patients’ with ≥5 symptoms during the acute infection had higher risk of long-term symptoms.1 Post-COVID-19 manifestations due to continued inflammation and immune-mediated responses such as arthritis, myositis, pancreatitis, others relating to skin, neurological, endocrine and autoimmune may occur occasionally.42 It is important to be aware of these symptoms as early treatment is crucial in most cases.

Management of Post COVID Syndrome

The management of post COVID-19 syndrome requires a holistic approach with a multidisciplinary team. The diagnosis of post COVID-19 syndrome is primarily a diagnosis of exclusion. The main objective of the clinical approach in management of post COVID-19 syndrome must be to make a systematic and thorough clinical assessment, in order to rule out other causes for the patients presenting symptoms (Figure 4).

Conclusion

The second wave of the COVID-19 pandemic has taken a toll on the healthcare system with thousands of lives affected every day. The healthy, young and the productive were more among those afflicted. The number risk of long-term symptoms.41 Post-COVID-19 syndrome must be to make a worldwide observational study in England. Lancet Diabetes Endocrinol 2021; 9:293-303. doi: 10.1016/S2213-8572(21)00094-4.


Clinical Rheumatology

by Author Dr. Rohini Handa
Publisher: Springer Nature, Singapore PTE Ltd.
1st Indian Reprint 2021, pages 260

It was a pleasure to read “Clinical Rheumatology” by Dr Rohini Handa. I had readily agreed to review the book, because it provided me with a meaningful activity during the unending lockdowns, and an opportunity to read a rheumatology book end to end. The last book on rheumatology that I had read completely was the 1st edition of Kelly’s, way back in 1981!

Clinical Rheumatology by Dr Handa is a 260-page single author book. This ensures uniformity of language and presentation. Dr Handa writes in a lucid, easy to understand style, and states and explains concepts clearly with the aid of figures, tables and flowcharts. These add to the readability of the book. The references are as recent as of 2020.

The general pattern of disease specific chapters is first an introduction (that often includes history), followed by the clinical description, investigations, and therapeutics of the disease, ending with an additional section as needed. The contents reflect the transformation that has taken place in rheumatology because of the newer diagnostics and effective therapeutics. These are allocated more space (gone are the days when rheumatology was mostly restricted to clinical signs and symptoms). Therapeutics is the tour-de-force of the book. Up-to-date, Dr. Handa provides a balanced approach to therapy. Clinical features are described concisely, enough to provide diagnostic information (possibly because of space constraints) and the book avoids being pedantic. To me, this is somewhat at the expense of practical points such as in A.S., the eye with iritis recovers fully, or that hand deformities of SLE are reversible, and joint erosion is not a feature as seen in R.A. I am sure these will be taken care of in the subsequent editions. However, this does not diminish the high quality of each chapter; chapters on gout, spondyloarthritides and connective tissue diseases – concepts and approach, deserve special mention.

The initial two chapters are devoted to beside approach to musculoskeletal complaints and laboratory investigations in rheumatology. There is also a table of radiological findings in some common rheumatological diseases. Ultrasound, CT and MRI findings are described under individual diseases. Unlike the usual pattern, low back pain, osteoarthritis, gout and other crystal arthritides are described first. Rest of the diseases are essentially in the usual sequence. Rare, esoteric diseases are not described beyond the scope of the book. The book also does not include some basic topics like immunology.

Disease specific chapters are followed by a set of useful, practical chapters on joint aspiration and infection; pregnancy, lactation and contraception; immunisation in autoimmune diseases, and a topical chapter on COVID-19 (I hope this will not be necessary in subsequent editions!) The chapters on pregnancy, lactation and immunization in autoimmune diseases address day to day problems faced especially so in today’s pandemic. The book does not provide an index. Also I hope subsequent editions will have chapters on physiotherapy and surgical aspects. The book ends with a chapter listing useful web-sites.

Dr Handa’s book will be most useful to medical practitioners who face rheumatology problems, and to students in training. Even rheumatologists will find some useful information, as I did.

To summarize, the book ‘Clinical Rheumatology’ is a welcome addition to the existing rheumatology literature, and I have no hesitation in recommending it to anyone who is interested in knowing more about the subject.

Dr. V.R. Joshi
Director Research (Emeritus), P.D. Hinduja Hospital, Mumbai
16th August 2021
Roadmap for the Management of Acute Undifferentiated Febrile Illness: An Expert Discussion and Review of Available Guidelines

Shashank Joshi¹, Gifty Immanuel²*, S Arulrhaj³, Mangesh Tiwaskar⁴, Agam Vora⁵, Srinivas Samavedam⁶

Abstract
Acute undifferentiated febrile illnesses (AUFIs) are associated with specific characterizations like fever of less than two weeks duration with no organ-specific symptoms at onset. These range from mild and self-limiting disease to progressive, life-threatening illness. Acute undifferentiated febrile illnesses are classified into malaria and non-malarial illnesses on the basis of microscopy or malaria-diagnostic tests. Various challenges, such as comorbidities, geriatrics, pregnancy, and immune-compromised profile of the patient, impede the treatment regimen. Identifying the root cause of undifferentiated fever becomes critical and involves correct diagnostic tests along with empirical treatment initiation. Doxycycline, being a broad-spectrum antibiotic, confers activity against many Gram-positive, Gram-negative, and “atypical” bacteria. Apart from antimicrobial activity, Doxycycline demonstrates the potential to inhibit dengue virus replication and exhibits anti-inflammatory activity by down-regulating proinflammatory cytokine levels. As coronavirus disease 2019 (COVID-19) spreads, the clinical management of associated cytokine storm remains unanswered. Considering the probable beneficial effect of doxycycline, it has been recommended by the national and international experts for the empirical management of COVID-19.

Introduction
Acute undifferentiated febrile illnesses (AUFIs), also known as “short febrile illness” or “acute fever”, are the common causes of visiting healthcare centers of Southeast Asia, including India.¹,² The febrile illness conditions are characterized by fever of less than two weeks without organ-specific clinical features.¹,² The severity of AUFIs ranges from mild to self-limiting to life-threatening.³ Some of the common causes of AUFIs include dengue, scrub typhus, murine typhus, leptospirosis, and enteric fever, which continue to contribute significantly to the febrile disease burden. The occurrence of AUFIs is common in tropical countries like India.¹³ Malaria and dengue are the most prevalent febrile illness-associated forms of fever in India.⁴

In a multicenter study in India, approximately 17% of AUFI cases were diagnosed as malaria, out of which 54% had *P. falciparum.⁴* India is estimated to contribute to 34% of the total global burden of dengue.⁵ Around 35% of bloodstream infections in AUFIs are caused by *Salmonella typhi* or *S. paratyphi*.¹ The incidence of scrub typhus, an underreported endemic in various parts of India, ranges from 10% to 47.5%.⁶,⁷ The incidence of leptospirosis in India ranges from 3% to 7%.⁶,⁷ In 2006, an outbreak of chikungunya affected 13 states of India with more than 1.39 million suspected cases.⁸ Another one-year, retro-prospective, observational study of patients (>18 years of age) presenting with undifferentiated febrile illness (5–14 days) revealed dengue as a predominant diagnosis with an incidence of 37.54% followed by enteric fever (16.5%), scrub typhus (14.42%), bacterial sepsis (10.3%), malaria (6.8%), hepatitis A (1.9%), hepatitis E (1.4%), leptospirosis (0.14%), and mixed infections (1.9%).⁷ The frequency of AUFIs is also associated with seasonal variation.¹ Like malaria, arboviral infections, scrub typhus, leptospirosis, and melioidosis peak during the rainy season. However, in many tropical areas, malaria occurs round the year.³ Seasonal dynamics of enteric fever are variable, with peaks after rainfall observed in northern latitudes.³,⁹ Chikungunya virus (CHIKV), an acute febrile illness caused by an arthropod-borne alphavirus characterized by high-grade fever and arthropalgia, also peaks during post-monsoon period.¹⁰,¹¹ All these conditions can be manifested by a plethora of microbes (bacterial, viral, rickettsial, or protozoal organisms) along with overlapping etiologies.¹,² Non-specific/overlapping clinical symptoms along with a scarcity of available appropriate diagnostic facility often results in an indiscriminate/irrational use of antibiotics and antimalarials.¹,² Due to limited awareness and knowledge about local etiology of AUFIs, coupled with overlapping clinical presentation and unavailability of accurate diagnostic testing, AUFIs treatment faces both diagnostic and therapeutic roadblocks.¹,² To address all these shortcomings, an expert meeting was convened entitled “Optimizing Fever Management in Current Pandemic” by the Association of Physicians India (API). A literature review was conducted to identify the relevant articles on AUFIs, from online databases such as Medline, PubMed, Google Scholar, etc.

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Acute febrile illness

Acute localized infections
Respiratory, urinary tract, gastrointestinal, etc

Acute undifferentiated febrile illness
(AUFI)

Malaria

Non-malarial AUFI
(smear or RDT negative)

Viral

Arboviral infections
Dengue
Chikungunya
Zika
Japanese encephalitis

Bacterial

Influenza
(Occasionally if respiratory symptoms not prominent)

Bacteremia
Enteric fever, Other bacteria such as E. coli, S. aureus

Zoonotic infections
Spirochetal (such as leptospirosis, relapsing fever)
Rickettsial (scrub typhus, murine typhus, spotted fever)

Parasitic

Hepatic amebiasis
Acute schistosomiasis
Acute trypanosomiasis

Fig. 1: Malaria versus non-malaria febrile illness laboratory testing algorithm

Classification of AUFI

Acute undifferentiated febrile illnesses are classified into malarial and non-malarial illnesses. Malaria remains a crucial, but treatable cause of AUFI in the tropics and has secured top rank in the list of differential diagnosis of acute fevers. Therefore, patients with negative malaria test are subjected to diagnosis of non-malarial AUFI. Owing to overlapping clinical etiologies and features, the development of a disease algorithm is imperative for proper differentiation between the febrile conditions based on the underlying etiology/root cause.

Table 1: Five prominent disease groups responsible for AUFI.

<table>
<thead>
<tr>
<th>Name of disease group/disease</th>
<th>Responsible pathogens included disease per group</th>
<th>Incidence of each condition in AUFI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Malaria</td>
<td>Include all malaria due to Plasmodium falciparum, P. vivax, P. ovale, P. malariae, P. knowlesi</td>
<td>All types: 5% to 50% cases</td>
</tr>
<tr>
<td>Arboviral infections</td>
<td>Dengue, chikungunya, Japanese encephalitis, Zika, yellow fever</td>
<td>Dengue: 4%–19%</td>
</tr>
<tr>
<td>Enteric fever</td>
<td>Occurs due to Salmonella enterica serovar typhi and paratyphi A, B, C</td>
<td>7%–30%</td>
</tr>
<tr>
<td>Spirochete infection</td>
<td>Leptospirosis and tick-borne or louse-borne relapsing fever</td>
<td>Leptospirosis: 3%–10%</td>
</tr>
<tr>
<td>Rickettsial infections</td>
<td>Scrub typhus, murine typhus, spotted fever</td>
<td>Scrub typhus, murine typhus, spotted fever 4%–49%</td>
</tr>
</tbody>
</table>

Etiological Pattern and Profile of Febrile Patients

The etiological and demographic profile of each patient in addition to essential laboratory investigations is recorded as the patient profile. This includes immune response, pregnancy, presence of comorbidities, geriatric patients, etc. Patient profile plays a significant role in planning or executing a management plan in patients with AUFI. For example, pregnant women with a compromised immune system are associated with an increased severity of malarial febrile illness. Symptomatic dengue infection during pregnancy is associated with an increased risk of fetal death. Also, diabetic individuals or chronic kidney disease patients are at a higher risk of melioidosis.

Pathogenesis of AUFI: Role of Cytokine Storm

An elevated body temperature (less than two weeks) could indicate possibility of AUFI by various pathogens. Once a pathogen enters host physiology, it induces the activation of mediators referred to as endogenous pyrogens (EP) that synthesize and secrete cytokines. These, in turn, signal a febrile response using the English language. Published reports were extracted for AUFI-specific population, pathogens, clinical information, epidemiology, diagnosis, and treatment of febrile illnesses. The objective herein is to review the diagnosis, management, and challenges associated with AUFI, highlighting the importance of chartering updated guidelines and treatment algorithms.
Dengue virus (DENV), a single-stranded RNA virus, is transmitted by mosquito vectors, *Aedes aegypti* and *Aedes albopictus*. The introduction of dengue virus by mosquito bites activates the innate immune system, which, in turn, stimulates production and activation of proinflammatory cytokines. Dendritic cells (DCs) and macrophages are the primary targets of dengue virus infections. Dengue viruses induce cytokine production by binding to C-type lectin domain family 5 member A (CLECSA). This interaction between DENV and host cells causes the secretion of proinflammatory, antiviral, and immunoregulatory cytokines. Dengue virus-infected macrophages and endothelial cells release IL-8, IL-6, C-X-C motif chemokine ligand 10 (CXCL10), CXCL11, and chemokine ligand 5 (also known as RANTES). Dengue fever presents itself as a high fever, retro-orbital pain, myalgia, leukopenia, thrombocytopenia, and hemorrhagic signs.

**Current Limitations/Challenges of AUFIs Management**

The management of AUFIs is often limited by poor infrastructure, absence/lack of technical knowledge, presence of non-specific symptoms that hinders timely diagnosis, and lack of comprehensive guideline recommendations from the local governing bodies in addition to inadequate diagnostic facilities. Out of these, the absence of specificity in symptoms of various febrile illnesses challenges the diagnosis and increases the inconsiderate use of antibiotics. Only diseases with defined localization to tissues have structural and effective treatment guidelines. However, those with overlapping etiologies/non-specific clinical signs and symptoms along with non-availability of accurate diagnostic modalities make treatment difficult. Despite being highly recommended tests, RTDs may demonstrate suboptimal accuracy, leading to exhibit false-positive results, and thus, may fail to prove their quality. Rapid diagnostic tests are also temperature sensitive and eventually lose their diagnostic ability when stored at room temperatures.

Despite advancements in laboratory infrastructure like use of high-throughput sequencers to identify pathogens from serum samples, their utility is only restricted to capital cities. Therefore, expansive geographic representation and epidemiological data for each pathogen to assess heterogeneity are mandated to increase antimicrobial resistance surveillance and improve patient diagnosis.

**Diagnosis of AUFIs**

**Laboratory Diagnosis of AUFIs**

To diagnose the root cause of AUFIs, a stepwise approach with laboratory tests is required. Firstly, epidemiologic information based on host factors such as comorbidities, immune-suppression, geriatrics, and pregnancy along with local disease prevalence, seasonality (malaria, leptospirosis, scrub typhus), and animal and vector exposure is collected. Secondly, the evaluation of clinical symptoms (excluding localized infections) and triaging by analyzing the disease severity is completed. Several aspects like time of disease onset and characteristic features of any organ involvement are taken into consideration at this stage. Thirdly, first-line and, if required, confirmatory diagnostic tests are conducted to rule out malaria and influenza. Evaluation of non-malarial AUFIs along with complete blood count (CBC) and biochemical tests for pathogen identification is performed. Additionally, host biomarkers of bacterial infections like C-reactive protein (CRP), procalcitonin, etc. could also be checked to differentiate between bacterial and non-bacterial infections in febrile patients.

**Conformatory Tests for Specific AUFI Pathogens**

Pathogen-specific confirmatory tests like RDTs for malaria help clinicians confirm the probable diagnosis and initiate treatment. They are the current gold standard for malaria confirmatory test and cost-effective and provide results within minutes. For malaria, the current gold standard for malarial RDTs confirms parasite antigens like histidine-rich protein 2 (HRP-2) and plasmodium lactate dehydrogenase (pLDH), in blood with 95% sensitivity and specificity for *P. Falciparum*. Rapid diagnostic tests for dengue-specific immunoglobulin M (IgM) antibody and nonstructural protein 1 (NS1) antigen in blood are performed for detection of dengue. The confirmatory tests include serological and culture testing for the presence of RNA in specimen sample with a sensitivity of 60%–100%. Rapid diagnostic tests for enteric fever can detect antibody against Salmonella species in a single serum. Widal test confirms sensitivity of up to 40% to 87% in blood and 80% of enteric specimens in the marrow.

Rapid diagnostic tests and enzyme-linked immunosorbent assay (ELISA) specific for IgM help diagnose scrub typhus but have variable testing sensitivity. Serology remains the cornerstone diagnostic modality for identifying scrub typhus infection. The Weil–Felix OX-K agglutination reaction is the oldest test available for this infection, which is cost-effective and easy to perform, with availability of results overnight. Confirmatory tests also help validate positive microscopic agglutination and nucleic acid amplification of Leptospira in blood samples. New pathogen-specific point-of-care tests (POCT) for common infections, such as dengue or scrub typhus, could offer some improvement in fever management but are limited due to high cost. Moreover, their utility is subjected to climate change and varied epidemiological trends.

**Management of AUFIs: Significance of Empirical Antimicrobial Therapy**

Early presumptive antibacterial therapy is imperative for suspected bacterial AUFIs, presenting with characteristic clinical features. These empirical therapies are preeminent if diagnostic confirmatory testing is awaited or not available. In cases of rapidly progressive infections, like rickettsioses and leptospirosis, delayed therapy may increase disease severity as well as mortality.

**Empirical Doxycycline in AUFIs Management: Revisiting the Old Antibiotic for New Uses**

Doxycycline, being a broad-
**Role of Doxycycline against Dengue Virus/Fever**

In an *in vitro* study, conducted to assess the potential activity of doxycycline against dengue virus replication, doxycycline demonstrated inhibitory action against dengue virus replication by reducing viral protease activity and entry in the host cell.

In a hospital-based, observational, interventional, study, conducted on 24 serology-proven dengue patients (adults and children), doxycycline therapy demonstrated a significant reduction in organ-specific complications of dengue fever. Thrombocytopenia was one-third less, plasma leakage was reduced, and no pancreatic, renal, or cardiac involvement was observed in doxycycline-treated group of dengue patients vs. patients in control group.

**Role of Doxycycline in Leptospirosis and Scrub Typhus Cases**

Oral doxycycline is the standard treatment of choice for defervescence of both leptospirosis and scrub typhus cases. In a study, conducted on patients presented with uncomplicated AUIF (without an obvious focus of infection or malaria or typical dengue infection), empirical doxycycline therapy was found to be effective.

Empirical doxycycline was associated with the shortest duration of fever (average 2.24 days) and highest cure rate at the end of the first week, vs. no antibiotic-treated group who exhibited not only the longest average duration of fever of 5.35 days (95%CI 5.32–5.39), but also worst cure rate. In another open, multicenter, randomized controlled trial, conducted on 296 adult patients presenting with acute fever (<15 days), doxycycline demonstrated comparable efficacy and fever clearance times to that of azithromycin and was found to be an affordable and effective choice for the treatment of both leptospirosis and scrub typhus. However, doxycycline is an effective empiric therapy for both leptospirosis and scrub typhus for most cases due to its low cost and shortest duration of fever.

**COVID-19: A Pandemic that Wreaks a Global Havoc**

Coronavirus disease 2019, the current global pandemic, is distinguished by increased cytokine levels like interleukins (IL)-2, IL-7, granulocyte colony-stimulating factor, interferon-γ-inducible protein 10, monocoye chemoattractant protein 1, macrophage inflammatory protein 1-α, and tumor necrosis factor-α. Figure 3 represents the mechanisms of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)-associated cytokine storm and associated damages. Infection with SARS-CoV-2 can stimulate a hyperinflammatory immune response wherein epithelial-cell-mediated production of reactive oxygen species (ROS) can cause cell death. Reactive oxygen species can also stimulate the synthesis of...
during the COVID-19 pandemic even priced, unavailable in low resource like tocilizumab, are relatively high steroids, or immunomodulating drugs, also enhance the risk of transmission. May delay viral clearance that could lead to clinically relevant conditions, such as acute respiratory distress syndrome (ARDS), sepsis, multiorgan dysfunction syndrome, and potentially death. Owing to the association of cytokine storm with severe COVID-19 complications, management with the potential of combating cytokine storm is warranted. 34

**Shortcomings/ Limitations of Other Therapies as Empirical Treatment for COVID 19**

Real-time reverse transcription-polymerase chain reaction (RT-PCR) assays are the primary molecular test of choice for COVID-19 diagnosis at both pre- and post-analytical disease stage. 35 The use of anti-inflammatory agents like corticosteroids and non-steroidal anti-inflammatory drugs (NSAIDs) may delay viral clearance that could lead to further complications and also enhance the risk of transmission. Immunosuppressive agents, such as steroids, or immunomodulating drugs, such as anti-IL6 monoclonal antibodies like tocilizumab, are relatively high priced, unavailable in low resource settings, and may be in short supply during the COVID-19 pandemic even in developed countries. 34 Though hydroxychloroquine and azithromycin combination is being used in COVID-19, major safety concern with regard to drug–drug interactions and cardiotoxicity, including fatal arrhythmia, has limited its use. 36

Doxycycline (a semisynthetic derivative of tetracycline) offers to be an effective alternative to azithromycin. In fact, in addition to its well-defined antibiotic effects (bacteriostatic action by inhibition of bacterial protein synthesis), in vitro studies have shown doxycycline to exert anti-inflammatory effects at low (20–40 mg per day) and high (100 or 200 mg per day) doses with inhibitory action on metalloproteases and modulating effects of proinflammatory cytokines IL-6, IL-8, and tumor necrosis factor-alpha. 35 Also, low dose of doxycycline demonstrated higher efficacy, versus high dose, in preventing proinflammatory cytokines (such as IL-6). Doxycycline potentially alleviates the lung sequela and ensures coverage against atypical bacterial pneumonia, such as *Mycoplasma pneurniae* and *Legionella pneumophila*. 36

A retrospective analysis was conducted to evaluate the clinical outcomes of early doxycycline intervention in high-risk COVID-19 patients with moderate-to–severe symptoms in long-term care facilities. Doxycycline demonstrated a clinical recovery rate of 85%, which was determined by resolution of fever (average 3.7 days, p=0.0001), resolution of shortness of breath (average 4.2 days), and improvement of pulse oximetry (POX) (average 84% before treatment and average 95% after treatment [84.7 ± 7% vs. 95 ± 2.6%, p=0.0001]). Treatment with doxycycline for high-risk patients with moderate-to–severe COVID-19 infections was associated with early clinical recovery, decreased hospitalization, and reduced mortality. 34

### Key Expert Opinions

- Doxycycline is a potential broad-spectrum empirical therapy for the treatment of AUFIs (antiviral action i.e. inhibits dengue virus replication; matrix metalloprotease inhibitor; anti-angiogenesis action; controls COVID-19-associated secondary bacterial infections and prevents cytokine storm risk).
- Asymptomatic or mild COVID-19 recovers with body's own immune defense (80% cases). Low doxycycline doses might be a promising prophylactic and therapeutic strategy for the early phase of COVID-19.
- If COVID-19 presents with comorbidities, azithromycin or doxycycline alone should be initiated. Oxygen plus supportive therapy is an optimal therapy for COVID-19 patients.
- Patients’ neutrophil/lymphocyte (N/L) ratio helps differentiate COVID-19 patients from other febrile illnesses.
- Any disease presenting with myalgia, cough, and fever must first rule-out COVID-19.
- COVID-19 is also a thrombo-inflammatory disease, and thus, coagulation regulation becomes important.
- Complete blood count (CBC) helps identify N/L ratio, lymphopenia, thrombocytopenia, neutrophil–to–monocyte ratio (NMR), and macrophage activation syndrome (MAS). The CBC i.e. the levels of neutrophil, lymphocyte, and ferritin help predict disease severity.
- The Radiological society has given 7 patterns of radiological pictures for pneumonic COVID-19 patients (administer steroid and anti-coagulants). Repeat chest CT to check lung viral clearance to 10%.

### Empirical Doxycycline Therapy in AUF I Including COVID-19: Through the Lens of Different Guidelines

#### Indian Guidelines

Empirical treatment with doxycycline for patients with undifferentiated fever and negative rapid diagnostic tests for malaria and dengue is an option for the clinician (ICMR). Doxycycline is an antimicrobial choice for treatment of rickettsial infections and second-line treatment therapy for *Falciparum malaria*. 39 In high endemic zones, short-term chemophrophylaxis of doxycycline (100 mg daily in adults and 1.5 mg per kg for children over eight years old) is recommended. For tuberculosis-endemic zones in India, initiating doxycycline for suspected scrub typhus cases could be a reasonable choice. Doxycycline is also the preferred drug for patients who have comorbidities and are critically ill owing to community-acquired pneumonia (CAP). As per the recommendations of Association of Physicians of India, empirical treatment with doxycycline is a clinically apt strategy for reducing morbidity and mortality in patients with non-malarial AUF I.

#### Recommendations by International Regulatory Bodies

The World Health Organization recommends doxycycline for non-specific fevers. 40 As per the National Institute for Health and Care Excellence (NICE) guideline, as initial treatment, doxycycline should be the first choice of oral antibiotics for managing adult COVID-19 patients with suspected or confirmed pneumonia. Doxycycline is preferred because it covers a broader spectrum as compared to amoxicillin, particularly against *Mycoplasma pneumoniae* and *Staphylococcus aureus*, which are more likely to be secondary bacterial causes of pneumonia during the COVID-19 pandemic. 41 A guidance published by the Massachusetts General Hospital has favored the use of empiric antibiotic treatment regimen for COVID-19 (associated with a smaller number of superinfections). For empiric COVID-19 regimen, oral administration of 100-mg doxycycline twice a day for five days is recommended along with 1-g ceftriaxone intravenous daily. 42

### Proposed Algorithm to Illustrate Diagnosis and Management of AUF I in India

Considering the pathogen epidemiology, prevalent clinical regimen, and heterogeneity across India, we devised a management algorithm for AUF I (Figure 4). 13 The first step is to assess the history of fever,
Table 1: Five prominent disease groups responsible for AUFIs.\textsuperscript{1,3} followed by systemic inflammatory response syndrome (SIRS) or sepsis. This is important because malaria, dengue, and ARDS share an overlapping pathophysiology, including elevated body temperatures. Next, clinical features are examined to help localize diagnose-specific syndrome of AUF.

If the fever lasts for less than 3 days and RDTs show negative results, antipyretics (paracetamol) should be prescribed alone (Figure 4).\textsuperscript{1,3}

![Fig. 4: Diagnostic and management algorithm for AUFI](image-url)
Conclusion
In order to dissect and correctly diagnose febrile illnesses, it is imperative to understand various etiologies responsible for AUFI. The expert opinions herein recommended to formulate a broader diagnostic approach to identify a wide range of infectious agents and re-purposing the existing drugs for empirical treatment. Future studies to determine the benefits and cost-effectiveness of using doxycycline against acute undifferentiated fever are needed. Funding to develop accurate and low-cost, high-sensitive diagnostic pathogen-specific confirmatory tests for rural India is warranted. An algorithm-based approach, early empiric treatment initiation, and biomarker assays for diagnosing and managing AUFI will improve positive outcomes, reduce hospital cost, and burden on healthcare. Also, adequate follow-up of the standardized clinical guidelines established by government consensus is a prerequisite to thwart local prevalence and spread of AUFIs.

Author contributions
All authors have contributed equally towards analysis of data, intellectual inputs and approval of final draft.

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References
A Case of Crouzon Syndrome

Shiji PV¹, Raveendran AV¹, Shajith Sadanandan¹, Sreekumar S¹

This 45 year old lady presented to our OP with features suggestive of upper respiratory tract investigations when we made a clinical diagnosis of Crouzon Syndrome due to the characteristic clinical features (Figures 1, 2, 3).

Crouzon Syndrome is a condition resulting from premature fusion of the sutures of the skull and deformity of the skull. Characteristics include:¹

- Craniosynostosis: skull is prematurely fused and unable to grow normally.
- Bulging wide-set eyes due to shallow eye sockets (ocular proptosis)
- A small underdeveloped upper jaw, due to hypoplasia of maxilla, mandibular development is normal.
- Downward slanting eyelids
- Hypertelorism due to differential bone growth.
- Curved, parrot-like nose
- High, narrow, arched palate

There is no racial or sex predilection. Deformity of bone can be diagnosed soon after birth. Other factors reveal

Pathophysiology

- Crouzon syndrome is caused by mutations in the fibroblast growth factor 2 receptor-2 (FGFR2) gene but exhibits locus heterogeneity with causal mutations in FGFR2 (Crouzon syndrome) and FGFR3 (Crouzon syndrome with acanthosis nigricans) in different affected individuals.³
- Premature synostosis of the coronal, the sagittal, and, occasionally, the lambdoidal sutures begins in the first year of life and is completed by the second or third year. The order and rate of suture fusion determine the degree of deformity and disability. Once a suture becomes fused, growth perpendicular to that suture becomes restricted, and the fused bones act as a single bony structure. Compensatory growth occurs at the remaining open sutures to allow continued brain growth. However, multiple sutural synostoses frequently extend to premature fusion of the skull base sutures, causing midfacial hypoplasia, shallow orbits, a foreshortened nasal dorsum, maxillary hypoplasia, and occasional upper airway obstruction.⁴

Differential Diagnosis⁵

- Beare-Stevenson syndrome
- Apert syndrome / acrocephalosyndactyilia
- Marie-Sainton syndrome
- Greig syndrome
- Jackson-Weiss syndrome
- Saethre-Chotzen syndrome

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Refractory Autoimmune Hematological Presentations of Undiagnosed Tuberculosis

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Abstract
Four patients who presented with autoimmune cytopenias as the sole manifestation of undiagnosed tuberculosis are described here. These were refractory to conventional immunosuppressive therapy and responded dramatically to treatment of the infection. The potential association between tuberculosis and immune hematological conditions is highlighted. Literature is reviewed with respect to possible pathogenetic mechanisms. Clinicians need to be aware of this type of unusual presentation of tuberculosis and must consider this chronic bacterial infection as a potential cause for refractory cytopenias.

Introduction
Autoimmune hematological disorders include immune thrombocytopenic purpura (ITP), autoimmune hemolytic anemia (AIHA), a combination of the two (Evans syndrome), autoimmune neutropenia (AIN), acquired hemophilia and thrombotic thrombocytopenic purpura (TTP). Many of these conditions are idiopathic and respond well to immunosuppressive therapy. Occasionally they may be causally related to infections, usually a recent viral illness. Tuberculosis (TB) has been reported to be associated with some cases of AIHA.1,2 Here we report on a series of patients with previously undiagnosed TB, who presented with varying autoimmune hematological manifestations. Their cytopenias did not respond to immunosuppression, whereas complete resolution was noted after identification and treatment of underlying tuberculosis.

Case Report
Case 1 (Cold AIHA)
A previously fit and well 60-year-old lady was referred with anemia, reticulocytosis and jaundice (Hb 7.4 g/dL, WBC 4800/mm3, neutrophils 3100/mm3, platelets 284000/mm3, reticulocyte count 19%, total bilirubin 4.3 mg/dL, unconjugated bilirubin 3.9 mg/dL). Examination revealed splenomegaly 3 cm below left costal margin. Peripheral smear showed numerous microspherocytes, red cell agglutination and polychromasia. Direct Coombs’ test (DCT) was positive and cold reacting auto-antibodies were detected. Lactate dehydrogenase (LDH) level was elevated at 680 U/L (normal range 170-230). Bone marrow aspiration and biopsy showed hypercellular marrow with erythroid hyperplasia and no features of lymphoid infiltration. She was managed with red cell transfusions and immunosuppressive therapy using prednisolone 1 mg/kg/day and later danazol 5 mg/kg/day, to which she did not respond. A PET CT scan was performed to rule out underlying lymphoproliferative etiology. Mediastinal and abdominal lymphadenopathy were noted along with splenomegaly. Transbronchial biopsy of mediastinal lymph node showed granulomatous lymphadenitis with acid fast bacilli (AFB) and caseous...
necrosis, consistent with TB (Figure 1a). Anti-TB treatment (ATT) was commenced with isoniazid, rifampicin, pyrazinamide and ethambutol. After a week of ATT, she was started on rituximab 375 mg/m²/week for 4 doses. Her anemia and jaundice gradually resolved and she has remained transfusion independent since then, with a negative DCT. She completed 9 months of ATT and remains asymptomatic.

**Case 2 (Evans syndrome)**

A 62-year-old lady was referred with anemia and thrombocytopenia, which were refractory to prednisolone, intravenous immunoglobulin (IVIG) and azathoprine. Her diagnostic work up confirmed Evan’s syndrome (Hb 6 g/dL, WBC 12100/mm³, neutrophils 8720/mm³, platelets 50000/mm³, nucleated RBCs 3%, reticulocyte count 16.6%, total bilirubin 13.46 mg/dL, unconjugated bilirubin 10.57 mg/dL). DCT was positive and IgG type warm autoantibodies were identified. Bone marrow biopsy was hypercellular with erythroid hyperplasia and increased megakaryocytes, with no lymphoid infiltrates. Due to cough, mild hemoptysis and crepitations, a chest radiograph was done and showed bilateral reticulonodular opacities. Due to cough, increased megakaryocytes, with no dysplastic features, consistent with ITP. She was treated with 5 doses of intravenous pulse methyl prednisolone 1000 mg daily, despite which bleeding manifestations continued and platelet count remained low (5000/mm³). Second line treatment with IVIG 1 gram/kg was administered. She still had no response and developed productive cough with hemoptysis. Further investigations revealed a cavitating lesion in the right lung (Figure 1b) and AFB were detected on bronchoalveolar lavage (BAL). Following 4-drug anti-TB treatment (ATT) with isoniazid, rifampicin, pyrazinamide and ethambutol, her platelet count improved to 35000/mm³ within a week. Prednisolone at a dose of 1 mg/kg/day was reintroduced and platelet count normalized (183000/mm³) by the 20th day of ATT.

**Case 4 (Autoimmune neutropenia)**

A 51-year-old male presented with a 4-week history of weight loss, daily fevers and night sweats. He had anemia and neutropenia (Hb 8.6 g/dL, WBC 1300/mm³, neutrophils 700/mm³, platelets 249000/mm³). DCT was negative and bilirubin level was normal. Bone marrow morphology and immunohistochemistry showed 40% infiltration by lymphoplasmacytic cells and adequate myeloid precursors. Serum electrophoresis showed raised IgM levels and borderline low levels of IgG, IgA and light chains. A diagnosis of Waldenstrom’s macroglobulinemia (lymphoplasmacytic lymphoma) was made and a CT scan of thorax, abdomen and pelvis were done for staging. This showed enlarged mediastinal, paratracheal and retroperitoneal lymph nodes with necrotic centres (Figure 1c). As the patient had not yet received any chemotherapy, this necrotic radiological appearance of the nodes was unexplained. Hence he underwent transbronchial biopsy of mediastinal lymph node, which revealed granulomata of TB with caseation and AFB (Figure 1d). After 4 weeks of ATT, his leukopenia and neutropenia resolved but anemia persisted (Hb 9.2 g/dL, WBC 5200/mm³, neutrophils 2900/mm³, platelets 214000/mm³). ATT was continued for 6 months and was followed by treatment of lymphoma with 4 cycles of bendamustine and rituximab chemotherapy. He is currently off treatment for 2 years and is in complete remission with normal Hb, WBC count and IgM levels. His initial neutropenia was most probably an immune response to TB and the anemia was non-immune, as a result of bone marrow infiltration by lymphoma.

**Discussion**

Autoimmunity is believed to originate from disequilibrium in the body’s immunological surveillance mechanism. Biologically it is quite plausible that infections can result in such an imbalance, triggering autoimmune disorders. In some immunohematological conditions such as acute ITP in children, as many as 50% may have a history of viral illness 2-3 weeks prior to the onset of symptoms of thrombocytopenia. This is less so in adults and especially in other autoimmune blood disorders such as AIHA and AIN.

Previous studies have explored the potential link between *Mycobacterium tuberculosis* and autoimmune pathogenesis in the host. This has variably been attributed to molecular mimicry, T-cell cross reacting epitopes and a high level of peptide sharing between bacterial and human proteomes. Cameron, through early random observations on 8 patients, had postulated that ‘in some predisposed individuals, widespread TB may provoke blood dyscrasias by alterations in host immunological responses’. However, other early studies did not support this observation. A large retrospective analysis of 130 consecutive patients with pancytopenia resulting from leukemia, pernicious anemia or aplastic anemia was reported by Coburn *et al* from London. This study had concluded that although 4.6% of these patients had concurrent active TB, it was a result of reactivation of latent infection related to the pancytopenia and defective cell mediated immunity. No convincing association with autoimmune hematological disease was found.

Recent reports have rekindled the interest in Cameron’s hypothesis on the probable association between TB and immune blood disorders, notably AIHA, Warm, cold and mixed antibody type hemolysis have been reported. Our case series provides more evidence for this link with AIHA and also describes other autoimmune cytopenias such as ITP and AIN as manifestations of TB.
such situations, prompt identification and treatment of TB is of utmost importance. This is not only because of the possibility of disseminated and life threatening spread of TB with immunosuppressive treatment, but also because the autoimmune hematological manifestation can remain refractory unless the underlying TB is cleared.

In this case series, it is obvious that TB did play a role in the pathogenesis of autoimmune hematological abnormalities. The first three patients had a total lack of response to initial lines of immunosuppression. Complete resolution of cytopenias was noted shortly after commencement of ATT followed by additional immunosuppressive therapy. The fourth patient had AIN which resolved promptly with ATT, even before definitive chemotherapy for lymphoma was commenced.

Clinicians should be aware of this potential association of TB with autoimmune hematological manifestations. A high index of suspicion for underlying TB is warranted in patients with AIHA, ITP, Evans syndrome or AIN especially when the disease remains refractory to conventional immunosuppressive drugs. Investigations such as chest radiograph, mantoux test, biopsy of enlarged lymph nodes, or a TB quantiferon test by ELISA can potentially inform management in such situations.

References


Gaisbock’s Syndrome: A Case Study

Sanjiv Rao1, Mallikarjun Kalashetty2, D Venkateswarlu3

Abstract

A 73-year-old hypertensive was found to have new-onset polycythemia during his routine health check up. A workup revealed no evidence of polycythemia rubra vera or a secondary cause of his polycythemia (his erythropoietin level was normal, he had no splenomegaly, and a test for JAK2 v617F mutation was negative). Over the next year of follow up, his hematological profile returned to normal levels. We conclude that this patient had Gaisbock’s syndrome, a relative polycythemia that occurs when there is clinically evident contraction of the intravascular fluid space (plasma volume) in smokers and people who received diuretics.

Introduction

First described in 1905, Gaisbock’s syndrome refers to a symptom complex associated with polycythemia that cannot be attributed to polycythemia rubra vera or to a secondary erythrocytosis that has occurred in response to hypoxemia. Risk factors for the development of Gaisbock’s syndrome include male sex, hypertension, smoking, diuretic therapy, obesity, and emotional or physical stress. The polycythemia has been attributed to decreases in plasma volume, and may be associated with increases in blood viscosity and peripheral vascular resistance

Table 1: Patient’s hematologic parameters

<table>
<thead>
<tr>
<th></th>
<th>PCV (mL/dL)</th>
<th>Hemoglobin (g/dL)</th>
<th>RBC count (million/uL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>On presentation</td>
<td>61.7</td>
<td>21.2</td>
<td>6.8</td>
</tr>
<tr>
<td>After phlebotomy</td>
<td>59.7</td>
<td>20.2</td>
<td>6.6</td>
</tr>
<tr>
<td>After 6 weeks of follow up</td>
<td>49.0</td>
<td>16.5</td>
<td>5.6</td>
</tr>
<tr>
<td>After one year</td>
<td>43.5</td>
<td>14.6</td>
<td>5.1</td>
</tr>
</tbody>
</table>

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hematocrit in regular health check up. His past medical history was notable for hypertension. He was taking hydrochlorothiazide and telmisartan and was on no other medication. He was a chronic smoker and had no history of sleep apnea.

Physical examination revealed a temperature of 98.6°F, a blood pressure of 110/70 mmHg, a regular pulse rate of 78 beats/minute, a respiratory rate of 19 breaths/minute and a BMI of 26.50 kg/m2. He had glossitis, palmar erythema and his tongue was dark red. He had no lymphadenopathy, and the examination of his heart, lungs and abdomen was unremarkable. His skin turgor was normal.

His complete blood count revealed elevations in his hematocrit (packed cell volume, PCV), hemoglobin, and red blood cell count (Table 1). Other red blood cell parameters (mean corpuscular volume, mean corpuscular hemoglobin, and mean corpuscular hemoglobin concentration) were within normal limits. His erythropoietin level was normal and testing for a JAK2 V617F mutation was negative. His vitamin B12 was found to be low (96.6 pg/ml) and serum uric acid was high (8.2 mg/dl). ABG showed hypoxemia with pO2 (33.9 mmHg). Other blood studies, including blood urea nitrogen, creatinine, electrolytes, liver chemistries and thyroid stimulating hormone were within normal limits. An ultrasound abdomen was normal with no evidence of splenomegaly and a chest x-ray was unremarkable. Doppler of renal vessels didn’t show any evidence of renal artery stenosis bilaterally. The bone marrow biopsy didn’t show the panmyelosis characteristic. The bone marrow biopsy didn’t show the pannymyelosis expected in classic polycythemia vera. Therapeutic venesection (400ml) was done. The repeat hematological profile showed reductions in haemoglobin, RBC count and hematocrit. Over the next several weeks, his hematologic parameters incrementally returned to normal (Table 1).

**Discussion**

Polycythemia is a disease state in which there is increased hemoglobin level (>16.5 g/dL in men or >16.0 g/dL in women), hematocrit (>49 percent in men or >48 percent in women), or other evidence of increased red cell volume. It may occur as a result of overproduction of red blood cells in the setting of a myeloproliferative disorder, such as polycythemia vera, or in lung diseases and conditions such as sleep apnea that cause sustained or intermittent levels of hypoxia with consequent increases in erythropoietin-mediated erythropoiesis. Our patient had normal erythropoietin, an absence of splenomegaly, and a negative test for a JAK2 V617F mutation, which mediates strongly against a primary or secondary cause of his polycythemia. Although we were unable to measure his plasma volume and red cell mass, his hematologic and clinical parameters and his course are in keeping with Gaisbock’s syndrome, in which the polycythemia is ascribed to a contraction in the plasma volume. Our patient had four risk factors for Gaisbock’s syndrome - hypertension, male sex, smoking and diuretic therapy; of these, hypertension appears to be the most significant contributor to the polycythemia of Gaisbock’s syndrome. In this regard, Emamian and associates studied 9,808 individuals with essential hypertension and found that they had spurious elevations in their hematocrits, hemoglobin levels, red cell counts, and mean corpuscular hemoglobin values. Their finding is in keeping with the fact that plasma volumes are usually (but not always) decreased in patients with hypertension and that, as a group, hypertensives have low plasma to interstitial fluid volume ratios, indicating that extracellular fluid distribution between the intravascular and interstitial compartments is shifted toward the latter. This shift is thought to be related to altered capillary filtration pressure due to increased venous resistance. Patients with a history of Gaisbock’s syndrome should be monitored closely for the possibility of recurrence. Messinezy and Pearson found that the PCV returns to normal in one-third of patients with relative polycythemia, in one-third the PCV stays elevated, and in the remaining third the PCV is intermittently elevated. Management should include tight control of hypertension, avoidance of diuretic therapy, smoking cessation, and in obese individuals and institution of a vigorous weight loss regimen. Venesection is rarely necessary, but should be considered if PCV levels are sufficiently elevated to place the patient at risk of thrombotic events (i.e., > 54 mL/dL) or if the patient is experiencing symptoms of cardiovascular ischemia.

**Conclusion**

We have documented a case of Gaisbock’s syndrome in an elderly man with hypertension. His polycythemia resolved over a 6 week period and reached to normal values over a year. Gaisbock’s syndrome is best categorized under the heading of a relative polycythemia, components of which are commonly seen in persons with essential hypertension.

This case has been presented for the following reasons:

i. Rarity in presentation. This is the first reported case in India to the best of our knowledge.

ii. This can be confused with polycythemia rubra vera and smoker’s polycythemia and one must be aware of this condition as the treatment regimens are different.

iii. This case was followed for a full year and it showed complete resolution of this condition.

**References**


Current Role of Dapagliflozin in Clinical Practice

Abdul Hamid Zargar¹, Abhijit Anil Trailokya², Suraj Ghag³, Roshan Pawar³, Amol Aiwale³, Ashish Zalke⁴

Abstract
Dapagliflozin is the first in a novel class of glucose-lowering agents known as sodium-glucose co-transporter-2 (SGLT2) inhibitors which was approved by USFDA in management of type 2 diabetes mellitus (T2DM) as an adjunct to diet and exercise to improve glycemic control in adults initially, followed by to reduce the risk of hospitalization for heart failure (HHF) in adults with T2DM and established cardiovascular disease or multiple cardiovascular risk factors. Most recently, it is approved to reduce the risk of cardiovascular death and in adults with heart failure (HF) with reduced ejection fraction (NYHA class II-IV). Dapagliflozin has been studied in a wide range of patients with diabetes and plethora of evidence has confirmed its efficacy as a monotherapy as well as an add-on to the oral therapies and insulin, when compared to placebo. Additional advantages include weight reduction which has been consistently demonstrated in Phase III studies and good tolerability. Also there is a demonstrable reduction in systolic blood pressure in patients treated with SGLT2 inhibitors. DECLARE TIMI 58 study clearly demonstrated that Dapagliflozin was non inferior in reducing major adverse cardiovascular events (MACE) in patients with T2DM and high CV risk compared with placebo. 27% risk reduction in heart failure hospitalisation was noted along without increased risk of amputation. DAPA HF evaluated the efficacy and safety of the dapagliflozin in patients with HF and reduced ejection fraction, irrespective of the presence or absence of diabetes. Patients with symptomatic HF due to reduced ejection fraction treated with dapagliflozin had positive outcomes with reduction in cardiovascular deaths and HF events. The DAPA-CKD trial which was conducted to assess the efficacy and safety of dapagliflozin in patients with chronic kidney disease (CKD), with or without type 2 diabetes found that it significantly lowered the risk of a sustained decline in the estimated GFR of at least 50%, end-stage kidney disease, or death from renal or cardiovascular causes in patients with CKD, regardless of absence of diabetes. Ongoing trials like DELIVER, DAPA ACT HF-TIMI 68, DICTATE-AHF, HF readmission study, DAPA MI Study, Effectiveness of Dapagliflozin for Weight Loss, will throw more light on the precise effects of dapagliflozin in several clinical scenarios. To conclude - Dapagliflozin was well studied not only in T2DM but also in HF and CKD patients with positive results and good safety profile.

Introduction
Over the past quarter-century, the burden of diabetes has steadily increased in India and across the globe. India is a major contributor to the global burden. United Nations has identified diabetes as one of the four priority non-communicable diseases targeted for action due to its growing disease burden. The epidemiology of type 2 diabetes mellitus (T2DM) is changing with the shift of youth to urban and rural areas. Age-specific prevalence of diabetes in India has also increased with increasing age over the last 25 years. In addition, the prevalence of T2DM in both urban and rural India has increased 10-fold in this duration. This steep increase in the prevalence of diabetes in India can be attributed to urbanisation, change from traditional healthier diets to those high in refined carbohydrates and fat, and decreased physical activity. The pathophysiology of T2DM explored from the triumvire of β-cell–, muscle-, and liver-related defects to the “ominous octet”.

T2DM is a metabolic disorder characterized by hyperglycemia and results into an increased risk of micro- and macrovascular complications. Current therapies for T2DM include oral agents with diverse mechanisms of action such as insulin-sensitizing agents, agents that promote insulin secretion, agents that act on the incretin pathway to stimulate insulin secretion while also exerting additional metabolic effects i.e. glucagon-like peptide1 receptor analogs (GLP-1 RA) and dipeptidyl-peptidase-4 inhibitors (DPP4I), and insulin.

A patient-centred approach should be used to direct the choice of pharmacologic agents. Considerations include effects on cardiovascular and renal comorbidities, efficacy, hypoglycaemia risk, impact on weight, cost, the risk of side effects, and patient preferences. Among patients with T2DM who have established or indicators of high-risk of atherosclerotic cardiovascular disease, established kidney disease, or heart failure, a sodium-glucose transporter 2 (SGLT2) inhibitor or GLP-1 RA with established cardiovascular disease benefit is recommended as part of the glucose-lowering regimen independent of A1C and in consideration of patientspecific factors. The selection of glucose-lowering agent must be made carefully, particularly when a various class of OAD (oral antidiabetic drugs) are available for the treatment of T2DM.

SGLT2 inhibitors*8
SGLT2 inhibitors (SGLT2I) have a novel mechanism of action when
SGLT2 inhibitors act by inhibiting SGLT2 in the kidney and SGLT1 is also expressed in the gastrointestinal tract where it has a role in the absorption of glucose with high capacity, low affinity SGLT2. The other 10–20% is reabsorbed by the low capacity but high-affinity SGLT1 in the distal portion of the proximal tubule. This is achieved by co-transporting glucose with sodium via Na+/K+-adenosine triphosphatase (ATP) pumps. SGLT2 is selectively expressed in the kidney and SGLT1 is also expressed in the gastrointestinal tract where it has a role in the absorption of glucose and galactose. In healthy persons, essentially all glucose is reabsorbed and the urine is free from glucose. SGLT2is act by inhibiting SGLT2 in the kidneys, reducing the reabsorption of glucose in the proximal convoluted tubule and increasing glucose excretion in the urine.

Weight loss with SGLT2

Obesity is associated with diabetes mellitus, metabolic syndrome, insulin resistance, and increased cardiovascular risk. Weight gain is associated with insulin therapy, sulfonylureas, and thiazolidinediones.

Weight reduction has been a consistently demonstrated in the Phase III studies of all available SGLT2 inhibitors. Mean change in weight at 24 weeks for placebo vs. dapagliflozin as initial therapy were −2.2 & −3.3 kg, respectively. Initial weight loss may be due to the osmotic diuretic effect of treatment. Nevertheless, sustained weight loss over the subsequent weeks is a consequence of caloric loss due to glycosuria. The glucose excreted in the urine associates to net loss of 200–300 calories/day. Dapagliflozin also significantly reduces waist circumference (−1.52 cm) when compared to placebo.

Effects of SGLT Inhibitors on Blood Pressure

In patients treated with SGLT2 inhibitors, there is a noticeable reduction in systolic blood pressure (SBP). Chronic osmotic diuresis due to glycosuria results an increase in 24-h urine volumes of 107–400 mL, which has a positive effect on blood pressure reduction.

Dapagliflozin causes a reduction in SBP of 2–9 mmHg without an increase in the heart rate or increase in syncopal episodes. In a pooled analysis of 12 studies, treatment with 10 mg of dapagliflozin daily resulted in a reduction in SBP of 4.4 mm Hg and a reduction in diastolic blood pressure (DBP) of 0.5 mm Hg compared to placebo group at 24 weeks.

SGLT2 inhibitors have many benefits over alternative therapeutic options and act independently of pancreatic β cell function, which deteriorates over time, and therefore there should be no loss of potency with long-term use. Moreover, SGLT2 inhibition does not interfere with either endogenous insulin or glucose production in response to hypoglycemia and therefore does not increase its risk.

SGLT2 inhibitors have been developed to satisfy the efficacy and safety criteria of the United States Food and Drug Administration (USFDA) and European Medicines Agency (EMA). In addition, ipragliflozin, luseogliflozin, & tofogliflozin are available for clinical use in Japan.

Dapagliflozin

Dapagliflozin, the most studied SGLT2 inhibitor, have been developed to satisfy the efficacy and safety criteria of the USFDA and EMA.

Dapagliflozin Approval Status

On January 8, 2014 USFDA approved dapagliflozin to treat type 2 diabetes which was followed by approval to reduce the risk of hospitalization for HF in adult patients with type 2 diabetes and established CV disease or multiple CV risk factors in October 2019. The approval was based on the results of DECLARE-TIMI 58 trial. In May 6, 2020 dapagliflozin was approved in the US for the Treatment of Heart Failure in Patients with Heart Failure with Reduced Ejection Fraction.

In India DCGI provided approvals for the following Indications

In adult aged 18 years and older with Type-II diabetic mellitus to improve glycemic control: As mono-therapy when diet and exercise alone do not provide adequate glycemic control in patients for whom use of metformin is considered inappropriate due to intolerance (Dapagliflozin 5 and 10 mg) – on 25.02.15 and Dapagliflozin is indicated in adults for the treatment of heart failure with reduced ejection fraction (Dapagliflozin 10 mg) - on 03-07-2020.

Dosage and Administration

Renal function assessment is necessary before initiating and periodically thereafter. The suggested starting dose is 5 mg once daily, taken in the morning, with or without food to improve glycemic control. The dose can be increased to 10 mg once daily in patients tolerating 5 mg who require additional glycemic control. To reduce the risk of hospitalization for heart failure, the recommended dose is 10 mg once daily. Dapagliflozin is not recommended when the eGFR is less than 45 mL/min/1.73 m2.

For patients who undergo planned surgery, temporarily discontinuing Dapagliflozin for at least 3 days prior to surgery is recommended.

There are no data from the use of dapagliflozin in pregnant women. When pregnancy is detected, dapagliflozin should be discontinued. Dapagliflozin should not be used while breastfeeding.

Patients with history of serious hypersensitivity reaction to Dapagliflozin and Severe renal impairment (eGFR less than 30 mL/min/1.73 m2), end-stage renal disease, or dialysis Dapagliflozin is contraindicated (Table 1).

Pharmacology

Dapagliflozin is a very potent and reversible SGLT2 inhibitor. It is
Reductions in HbA1c were seen across mean change from baseline at Week statistically significant improvements metformin, Sitagliptin, glimepiride, monotherapy and in combination with receptor agonist (exenatide extended- and in combination with a GLP-1 compared to a sulfonylurea (glipizide), without other oral antidiabetic therapy), + sulfonylurea, or insulin (with or (with or without metformin), metformin and −0.67 % with 5 mg, −0.7 % with 10 mg. 102-week extension study
The glycemic control benefit was persistent in patients who completed the 102-week extension study (mean HbA1c changes of +0.02, −0.48, −0.58, and −0.78 % with placebo, 2.5, 5, and 10 mg dapagliflozin)
Similar improvements have been reported with dapagliflozin added on to sulfonylurea (glipizide) and a dipeptidyl peptidase-4 (DPP-4) inhibitor (Sitagliptin).

Dapagliflozin in combination with Metformin (modified-release)
Two 24-week randomized trials (n = 598, n = 638) showed that the benefits of both agents (Dapagliflozin & Metformin) were better than the individual components on HbA1c reduction (combined results showed reduction in HbA1c for dapagliflozin plus metformin XR −2.05 %, dapagliflozin alone −1.19 %, and metformin alone −1.35 %). The second study using 10 mg of dapagliflozin showed non-inferiority to metformin.

Adverse Effects and Safety
SGLT2 inhibitors are well tolerated when given as monotherapy or used in combination with other oral hypoglycemic agents (OHA) or insulin therapy.

Hypotension, Ketoacidosis, Acute Kidney Injury, Urosepsis and Pyelonephritis, Hypoglycemia with Concomitant Use with Insulin and Insulin Secretagogues, Necrotizing Fasciitis of the Perineum (Fournier’s Gangrene), Genital Mycotic Infections are the important adverse event seen with Dapagliflozin.

A. Hypoglycemia
SGLT2 associated with relatively low hypoglycemic risk due to its insulin independent action. There were no major events of hypoglycemia documented when SGLT2 inhibitors were used as monotherapy in the Phase III development studies even meta-analysis has concluded that the hypoglycemic risk was similar to that associated with other agents. The hypoglycemia risk is increased when used in combination with sulfonylurea or insulin therapy, in the conditions like chronic kidney disease (CKD) and when treating elderly patients. The prescribing advice with these combinations is to use a lower dose of insulin secretagogue or insulin to reduce the risk of hypoglycemia when used in combination with an SGLT2 inhibitors like dapagliflozin.

The combination of dapagliflozin as add-on to metformin is associated with a lesser incidence of hypoglycemic events compared to glipizide in combination with metformin (4.8 % for placebo vs. 7.1–7.9 % over the dose ranges of dapagliflozin).

B. Genital Infections
Diabetes is associated with an increased risk of genital and urinary tract (UTI) and genital infections, due to hyperglycemia and subsequent glycosuria. Numerous placebo controlled trials have stated that genital and urinary tract infections were more common with dapagliflozin when compared to placebo (genital infection 4.1–5.7 % vs. 0.9 %; UTI 3.6–5.7 % vs. 3.7 %). Similar findings were reported from other SGLT2Is. For dapagliflozin, canagliflozin, and empagliflozin, the frequency of genital and urinary infections were increased in females, and patients usually experienced one single episode that was mild to moderate in intensity and responded to standard treatment.

C. Volume Depletion
Roughly 375 mL of additional urine is produced daily in patients on 10 mg of Dapagliflozin daily. Safety analysis of dapagliflozin from 12 double-blind placebo controlled trials revealed that volume depletion events occurred 0.6–1.2 % with dapagliflozin, compared to 0.4 % with placebo. This indicates a slightly elevated risk and emphasizes the importance of maintaining oral

Table 2: Pharmacokinetics characters

<table>
<thead>
<tr>
<th>Character</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Absorption</td>
<td>Rapidly absorbed after oral administration, with peak plasma concentrations usually reached within 2 h (fasted state)</td>
</tr>
<tr>
<td>Distribution</td>
<td>Mean steady state volume of distribution of dapagliflozin is 118 L and it is 91% protein bound</td>
</tr>
<tr>
<td>Metabolism</td>
<td>Largely metabolized by UGT1A9 (an enzyme in the liver and kidneys) to its major inactive metabolite 3-O-glucuronide; the major and other metabolites of dapagliflozin do not contribute to its glucose-lowering effects.</td>
</tr>
<tr>
<td>Excretion</td>
<td>Dapagliflozin and its metabolites are largely excreted in the urine, with 75% of a dose recovered in the urine (&lt;2% as unchanged parent drug) and 21% in the faeces (&lt;15% as unchanged parent drug).</td>
</tr>
<tr>
<td>Half life</td>
<td>Mean plasma terminal elimination half-life is 12.9 h.</td>
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</table>

1400 times more selective for SGLT2 than SGLT1. In patients with T2DM Dapagliflozin increased the amount of glucose excreted in the urine and improved both fasting (FPG) and post-prandial plasma glucose levels. Urinary glucose excretion was seen after the first dose of dapagliflozin, was continuous during the 24 h dosing interval and maintained over the course of therapy.

Pharmacokinetics of dapagliflozin is not affected significantly because of age, gender, race, and body weight and thus, no dose adjustment is recommended (Table 2).

Overview of Clinical Studies of Dapagliflozin for Type 2 Diabetes (Table 3)

Dapagliflozin has been studied as monotherapy, and in combination with drugs like metformin, pioglitazone, sulfonylurea (glimepiride), sitagliptin (with or without metformin), metformin + sulfonylurea, or insulin (with or without other oral antidiabetic therapy), compared to a sulfonylurea (glipizide), and in combination with a GLP-1 receptor agonist (exenatide extended-release) add-on to metformin.

Treatment with Dapagliflozin as monotherapy and in combination with metformin, Sitagliptin, glimepiride, pioglitazone, or insulin produced statistically significant improvements in mean change from baseline at Week 24 in HbA1c compared to control. Reductions in HbA1c were seen across subgroups including gender, race, age, duration of disease, and baseline body mass index (BMI).
**Table 3: Evidence from cardiovascular/renal outcome trials of Dapagliflozin**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Cardiovascular Outcome Trials (Number of participants)</th>
<th>Associated CV or renal risk factors</th>
<th>Primary outcomes (HR, 95% CI,p-value)</th>
<th>Other significant outcomes</th>
<th>Number needed to treat (NNT, CI)</th>
<th>Data for Asians (HR, 95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dapagliflozin</td>
<td>DECLARE vs Placebo (N=47,160)</td>
<td>Established CVD (41%) or at high-risk without CVD (59%)</td>
<td>3-p MACE: Established CV safety (0.93, 0.84-1.03, p=0.17a, p=0.001b)</td>
<td>Reductions in: Renal composite outcome - 24% hHF or CV mortality - 17%</td>
<td>N=13.42%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>TIMI-58 (N=17,160)</td>
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<tr>
<td>DAPA-HF</td>
<td>NYHA class II, III, or IV HF and EF ≤40%</td>
<td>Composite of worsening HF or CV mortality: 26% reduction (0.74, 0.65-0.85; p=0.001)</td>
<td>25% reduction in CV mortality or hHF 18% improvement in KCCQ total symptom score</td>
<td>To prevent one primary event (21, 15-38)</td>
<td>N=23.52%</td>
<td>Primary outcome (0.64, 0.48-0.86)</td>
</tr>
<tr>
<td>DAPA-CKD</td>
<td>Adults with or without type 2 diabetes, with eGFR 25-75 ml/min/1.73m² and urinary albumin-to-creatinine ratio of 200-5000</td>
<td>Composite of decline in eGFR of ≤50%, ESRD, or death from renal or CV causes: 39% reduction (0.61, 0.51-0.72; p=0.001)</td>
<td>Reductions in: Composite of decline in eGFR of ≤50%, ESRD, or death from renal causes - 44% All-cause mortality - 31%</td>
<td>To prevent one primary event (19, 15-27)</td>
<td>N=34.08%</td>
<td>Primary outcome (0.66, 0.4-0.93)</td>
</tr>
</tbody>
</table>

**Table 4: Various guideline recommendation of SGLT2I**

- **American Diabetes Association (ADA) 2021 Guidelines**
  - ADA 2021 recommends that, if the A1C target is not achieved after approximately 3 months on metformin, it can be combined with any one of the preferred 6 treatments options like sulfonylurea, a thiazolidinedione, DPP-4 inhibitor, SGLT2 inhibitor, GLP-1 RA, or basal insulin. The selection of drug depends on drug-specific effects and patient factors.

- **Pharmacological management of South Asians with Type 2 Diabetes: Consensus Recommendations from the South Asian Health Foundation**
  - Class of Medicine – SGLT2I
  - **Recommendations**
  - Dapagliflozin is approved by USFDA to reduce the risk of hHF in adults with type 2 diabetes and established CVD or multiple CV risk factors
  - First line therapy in drug naïve people with type 2 diabetes and ASCVD or high/very high CV risk (for drugs with proven CVD benefit)

- **Considerations in South Asian population**
  - Vital therapeutic preference to delay or prevent complications due to high CV risk of CVD among South Asians
  - Preferable for South Asians owing to lower BMI cut off for obesity
  - Suitable for use during fasting on account of high hypoglycaemia risk profile; however, volume depletion may be a concern
  - Insulin independent mechanism of action may be favourable as South Asians are generally more insulin resistant

- **2019 ACC/AHA guideline on primary prevention of cardiovascular disease**
  - SGLT2I or GLP 1 RA as an early add on to metformin in patient with T2DM and CV risk factor for primary prevention of CVD

- **2019 ESC Guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASD**
  - For the first time we have evidence from several CVOTs that indicates CV benefits for the use of SGLT2s and GLP1RA in patients with CVD and at very high/very high CV risk

- **KDIGO 2020 - Clinical Practice Guideline For Diabetes Management In Chronic Kidney Disease**
  - Glycemic management for patients with T2D and CKD should include lifestyle therapy, first-line treatment with metformin and a sodium–glucose cotransporter-2 inhibitor (SGLT2I), & additional drug therapy as needed for glycemic control

**fluid intake**

The frequency of hypovolemic events in dapagliflozin treated groups was increased in the elderly population (>75 years of age), in those with moderate renal impairment or those treated with concomitant loop diuretics. Other studies have demonstrated clinically significant increases in hematocrit, serum urea, and creatinine, with no increase in the rates of renal impairment, hypotension, or dehydration.

The estimated glomerular filtration rate declined initially at treatment initiation but was shown to return to baseline by 24 weeks, and this was maintained to 102 weeks.

**D. Ketoacidosis**

There have been concerns about the risk of euglycemic ketoacidosis with SGLT2 inhibitors, resulting in both the FDA and EMA issuing warnings.

Sodium-glucose co-transporter 2 (SGLT2) inhibitors should be used with attention in patients with increased risk of diabetic ketoacidosis (DKA).

Patients who be at higher risk of DKA include patients with a low beta-cell function reserve (e.g. type 1 diabetes patients, type 2 diabetes patients with low C-peptide or latent autoimmune diabetes in adults (LADA) or patients with a history of pancreatitis), patients with conditions that lead to limited food intake or severe dehydration, patients for whom insulin doses are reduced and patients with increased insulin requirements due to acute medical illness, surgery or alcohol abuse.

Before introducing dapagliflozin, factors in the patient history that may predispose to ketoacidosis should be considered. Treatment should be stopped in patients who are hospitalised for major surgical procedures or acute serious medical illnesses. Monitoring of ketones is recommended in these patients. Treatment with dapagliflozin may be resumed when the ketone values are normal and the patient’s condition has stabilized.

**Recent Guidelines on Management of Diabetes**

Cardiovascular outcome trials in patients with type 2 diabetes at high cardiovascular risk resulted in our understanding of the effectiveness of SGLT2 inhibitors to...
reduce cardiorenal events. Different guidelines have published the updated recommendations for the management of these patients (Table 4).

**Place in therapy**

Dapagliflozin is a reversible, potent and selective sodium-glucose cotransporter-2 inhibitor (SGLT2i) indicated worldwide for the treatment of type 2 diabetes (T2D) and recently got approval for management of heart failure with reduced ejection fraction. For the treatment of T2DM the recommended starting dose is 5 mg once daily, taken in the morning, with or without food and dose can be increased to 10 mg once daily in patients tolerating dapagliflozin who require added glycemic control. For the Treatment of Heart Failure (HF) in Patients with Heart Failure with Reduced Ejection Fraction (HFrEF) the recommended dosage is 10mg once a day. In various well-designed clinical studies, Dapagliflozin as monotherapy and combination therapy with other anti-hyperglycaemic agents provided effective glycaemic control and reduced bodyweight and blood pressure (BP) across a wide-ranging spectrum of patients.

Dapagliflozin reduced the rate of cardiovascular (CV) death or hospitalization for heart failure (HHF), did not adversely affect major adverse CV events (MACE) and probably reduced advancement of renal disease relative to placebo in patients with proven atherosclerotic CV disease (CVD) or multiple risk factors for CVD. Dapagliflozin was generally well-tolerated, with a negligible risk of hypoglycaemia; diabetic ketoacidosis (DKA), although rare, and genital infections were common with dapagliflozin than placebo. There are various ongoing trials like DELIVER, DAPA ACT HF-TIMI 68, DICTATE-AHF, HF readmission study, DAPA MI Study Effectiveness of Dapagliflozin for Weight Loss and will get to see the results soon.

To conclude Dapagliflozin provides an important option for the management of a broad patient population, regardless of the history of CVD due to its promising anti-hyperglycaemic, cardioprotective and possibly renoprotective properties and generally favourable tolerability profile.

**References**

Probiotics & Prebiotics

Jayant Pai-Dhungat

Use of probiotics can be traced back to the use of cheese and fermented milk products by ancient Greeks and Romans. However, importance of Dahi (Indian yogurt) or curd- in Indian diet dates back to prehistoric times. Indians have always regarded Dahi, lassi, raita, shrikhand, etc as being integral part of their diet. Dahi is one indigenous ingredient, which has united north and south India.

Probiotics have received renewed attention in the 21st century from product manufacturers and consumers which has made probiotics a huge industry. This has led to stricter requirements for scientific research to substantiate the benefits claimed. The word was coined in 1965 and later redefined as “live microorganisms which when administered in adequate amounts confer a health benefit on the host.” They are available as yogurt, sour milk products. A large number of organisms are being used in clinical practice for a variety of indications. The most widely used and thoroughly researched organisms like L. acidophilus, L. Bulgaricus, Saccharomyces, are available in convenient formulations.

Prebiotics: the term was introduced in 1995 to describe food supplements which are non-digestible by the host but, are able to exert beneficial effects by selective stimulation of microorganism growth in large bowel. They include foods like bananas, onions, garlic, skin of apples, chicory root, beans, and many others. The list may be long, from asparagus to yams.

Modern hypothesis regarding the positive role played by certain bacteria was first introduced by Stamen Gigorov and Elie Metchnikoff in the beginning of 20th Century.

Stamen Gigorov (1878 -1945) was a Bulgarian physician and microbiologist. He graduated in medical science from Geneva, Switzerland at the age of 27. Gigorov isolated Lactobacillus bulgaricus from Bulgarian yogurt for the first time in microbiological laboratory of his mentor Professor Masso’sl at Geneva In 1905.

Elie Metchnikoff (1845-1916) Russian microbiologist, Nobel Prize winner (1908) and Professor at the Pasteur Institute in Paris. Metchnikoff devoted the last decade of his life to investigate means of increasing human longevity. He was interested in Dr. Gigorov’s discoveries in 1905 and went on to discover that more centurions lived in Bulgaria than other European countries. He linked this to Bulgaria’s most traditional food – yogurt. He proposed the hypothesis that the aging process results from the activity of putrefactive (proteolytic) microbes producing toxic substances in the bowels like, phenols, ammonia, and are responsible for what he called “intestinal-autointoxication”. He suggested that it would be possible to modify the gut microbiota by replacing harmful microbes with beneficial ones (1907). Metchnikoff himself introduced in his diet, sour milk fermented with the bacteria he called “Bulgarian Bacilli” and believed that his health benefited.

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Expert Opinion on Usage of Pidotimod in Adult Patients with Chronic Obstructive Pulmonary Disease: An Indian Perspective

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Abstract

India has a disproportionately high burden of acute and chronic pulmonary diseases. In India, 65 million suffer from non-communicable respiratory diseases. The outbreak of the novel coronavirus disease 2019 (COVID-19) had worsened the situation. Patients affected with COVID-19 with a previous history of comorbidities, such as COPD and chronic lung diseases, had the worst prognosis, resulting in adverse outcomes, such as acute respiratory distress syndrome (ARDS) and pneumonia. Immune modulation strategies have since gained a lot of traction amongst practitioners. Modulation of the immune system with Pidotimod along with standard-of-care (SOC) treatment has proven efficacious in the past two decades in patients with recurrent respiratory tract infections (RRTIs), bronchitis, COPD, and pneumonia. In this article, we have reviewed the current unmet needs in the management of COPD in India and evaluated the usage of Pidotimod in adult COPD patients based on expert panel discussion.

Introduction

India has a disproportionately high burden of acute and chronic pulmonary diseases. In India, 65 million population suffer from non-communicable respiratory diseases, out of which chronic obstructive pulmonary disease (COPD) and asthma account for 42 million cases; and this number is projected to grow by 20% by 2030.¹ The outbreak of the novel coronavirus disease 2019 (COVID-19) had worsened the situation. Patients affected with COVID-19 with a previous history of comorbidities, such as COPD and chronic lung diseases, had the worst prognosis, resulting in adverse outcomes, such as acute respiratory distress syndrome (ARDS) and pneumonia.²,³ The Global Initiative for Chronic Obstructive Lung Disease (GOLD) recognized patients with COPD as the worst affected by the COVID-19 pandemic.³ Uncontrolled immune response to severe acute respiratory syndrome coronavirus (SARS-CoV-2) infection may cause multi organ failure, and detrimental systemic effects on several physiological systems were observed.⁴ Up regulation of the immune system is important, especially in patients with comorbidities in challenging times like COVID-19.

Current treatment guidelines for COPD rely to a greater extent on the use of bronchodilators and anti-inflammatory therapeutics, particularly corticosteroids, as well as infection control with antimicrobial agents whenever necessary.⁵ Treatment with corticosteroids increase the risk of upper and lower respiratory tract infections (RTIs), particularly in patients with COPD while overuse of antimicrobial agents may increase morbidity and antimicrobial resistance.⁶ Next-generation monoclonal therapies have shown promising results in COPD and asthmatic patients; however, the long-term use of these therapies remains expensive and beyond the reach of developing countries like India.⁷ The use of immunomodulatory therapies has shown to reduce severity of symptoms, exacerbations, hospitalizations, and drug consumption (antibiotics) in patients with asthma, COPD, allergic rhinitis (AR) and chronic rhinosinusitis (CRS).⁸ Modulation of the immune system with Pidotimod along with standard-of-care (SOC) treatment has proven efficacy in the past two decades in patients with recurrent respiratory tract infections (RRTIs), bronchitis, COPD, and pneumonia.⁹ In this article, we have reviewed the current unmet needs in the management of COPD in India and evaluated the usage of Pidotimod in adult COPD patients based on expert panel discussions.

Methodology

A total of four advisory board meetings were convened between September 7 and 10, 2020 on a virtual platform to generate insights from experts, on the role of Pidotimod in adult patients with COPD in India. The members of the panel were selected to best represent the breadth of knowledge and clinical experience in the field from all over India. The key purpose of the meetings was to: (i) evaluate the usage of Pidotimod in times of COVID-19 in patients with comorbidities; (ii) generate insights on the role of Pidotimod in adult patients with a risk or established history of COPD; and (iii) determine COPD patient subgroups who would experience maximum benefits from Pidotimod as adjuvant therapy.

A literature review was carried out based on data from the PubMed Database to identify relevant articles between January 2001 and October 2020 using keywords such as COPD, Pidotimod, and COVID-19.
as "India", "adults", "burden", "chronic obstructive pulmonary disease", "coronavirus disease", "immunostimulants", "Pidotimod", "guidelines", and "management". Key articles were shortlisted and circulated among the expert panel members before the advisory board meetings as pre reading material. During advisory board meetings, in addition to interactive discussion, a qualitative question-and-answer-based format was used to facilitate discussion.

After the group discussion, key expert opinions were formulated based on the opinions and agreement of the majority. The key highlights of the expert panel discussion for each of these topics were recorded and are summarized in this manuscript.

Results and Discussion

Evaluation of usage of pidotimod in times of COVID-19 in adults with immune dysfunction

The outbreak of COVID-19 has created a worldwide health crisis and had a deep influence on our day-to-day lives. The immune response is unquestionably one of the crucial determiners of the susceptibility and severity of COVID-19 disease. The clinical spectrum of COVID-19 varied from asymptomatic or paucisymptomatic forms to severe clinical conditions characterized by viral pneumonia with respiratory failure that necessitates mechanical ventilation or support in an intensive care unit (ICU), to multi organ dysfunction and death. A study reported that around 82.1% of COVID-19 cases displayed low circulating T lymphocyte counts (CD4+ and CD8+ type), especially in patients requiring ICU care, and surviving T cells appeared functionally exhausted. Since an effective immune response against viral infections depends on the activation of cytotoxic T cells, boosting the numbers and function of T cells in adult patients was crucial in times like COVID-19.

Immune dysfunction in patients with COPD and diabetes: The immune system acts as a victim and also an aggressor in patients with COPD. A study published by Xie S et al. demonstrated that the decline in adaptive immune response to bacterial infections in patients with COPD could be attributed to the net effect of augmented function of immunosuppressive cells (regulatory T cells [Treg] and myeloid-derived suppressor cells) and decreased function of effector T cell (Teff). In addition, imbalance of CD4+/CD8+ ratio and imbalanced shifts in Treg/Th1/Th2/Th17 CD4+ T cells and Treg/Tc1/Tc2/ Tc17 CD8+ T cells play critical roles in the defective immune responses in patients with COPD. The defective immune responses later contribute to recurrent respiratory infections, worsening the inflammatory lung microenvironment and disease severity. Patients with diabetes are at an increased risk of predisposition to respiratory tract infections (viral or bacterial origin) due to metabolic derangements and suppressed innate and humoral immunity. The level of glycated hemoglobin (HbA1c) >9% in patients with diabetes has been linked to a 60% increased risk of hospitalization and pneumonia-related severity during bacterial infections. Evolving data in diabetic cohorts with COVID-19 suggest that diabetes is associated with severe or critical COVID-19 symptoms with the prevalence varying from 14% to 32% in different studies. In a study published by Wang D et al., 72% patients affected with COVID-19, with comorbidities including diabetes, required admission in the ICU, compared to 37% of patients without comorbidities.

Role of pidotimod in patients with immune deficiencies and pulmonary disorders: Various classes of immunomodulators (bacterial lysates, enzyme therapies, and herbal remedies) have been studied in the past few decades in patients with pulmonary disorders. OM-85, a lysate of 21 common bacterial respiratory pathogens, has demonstrated clinical efficacy in preventing respiratory tract infections (RTIs) in several clinical studies, as well as exacerbations of various respiratory conditions, such as COPD, asthma, AR, and CRS. However, OM-85 BV is not available in India. The only allopathic immunostimulant available in India is Pidotimod. Pidotimod is a synthetic dipeptide molecule (L-pyroglutamyl-1-thiazolidine-4-carboxylic acid) endowed with immunomodulatory activity that can ameliorate both innate and adaptive immune responses. Pidotimod was approved in 2011 by the Drug Controller General India for the treatment of RTIs in primary and secondary immune deficiencies with alteration of maturation in T cells in adults. It has shown to stimulate various components of immune system, including regulation of cell-mediated immune responses. Several in vivo and in vitro studies have shown the usefulness of Pidotimod in reducing the need for antibiotics in airway infections, increasing the level of immunoglobulins (IgA, IgM, IgG), and improving Th1/Th2 balance. Pidotimod has shown to promote maturation of dendritic cells, promote phagocytosis and chemotaxis, up regulate expression of toll-like receptors-2 (TLR-2), and increase natural killer (NK) cells activity (Figure 1). The pharmacokinetic study of Pidotimod showed that the drug was absorbed rapidly by oral administration. The bio-availability

![Fig. 1: Immunomodulatory activity of Pidotimod](image-url)

*Fig. 1: Immunomodulatory activity of Pidotimod. NK: Natural killer; TLR: Toll-like receptor; Ig: Immunoglobulin; TH: T helper*
of human oral administration was 43%–45%, and the elimination half-life was 4 hours.15 In a study published by Ucciferri C et al., Pidotimod was used in paucisymptomatic COVID-19 patients without any evidence of concurrent pneumonia.16 The study concluded that Pidotimod was well tolerated and associated with a rapid reduction of systemic symptoms, especially fever.16

Experts’ Discussion

Usage of Pidotimod in times like COVID-19 in adult patients with comorbidities: The experts opined that in the COVID times, young adults with multiple comorbidities (such as COPD, diabetes, hypertension, liver problems, and cardiovascular disease [CVD]) and immunocompromised elderly individuals (aged 60 and above) are at an increased risk of severe illness from COVID-19 due to reduced immunity. Experts opined that COPD patients have a higher chance of developing severe pneumonia and poor outcomes in conditions like COVID-19.

Usage of Pidotimod in patients of COVID-19

The experts shared their opinions about administration of Pidotimod in COVID-19 patients. They suggested that the administration of Pidotimod in COVID-19 patients with mild-to-moderate symptoms of the disease, along with standard-of-care (SOC) treatment, could help in the rapid reduction of systemic symptoms and in preventing adverse outcomes. Experts mentioned that the administration of Pidotimod in COVID-19 patients with high C-reactive protein (CRP) levels for 15 days led to symptomatic improvement and reduction in CRP levels. They suggested that prophylactic use of Pidotimod would be beneficial in adults and/or children in close contact with COVID-19 patients on a day-to-day basis (such as family members, police officials, and healthcare professionals).

Experts’ Opinions

- Stimulation of innate and adaptive immune response by Pidotimod could help in reducing disease severity in the acute phase, and prophylactic use can effectively reduce infectious disease recurrence in patients with COPD in challenging times like COVID-19.
- Experts opined that pidotimod adjuvant therapy should be promoted in vulnerable COPD patient groups who experience frequent acute exacerbations and severe COPD symptoms.

Insights on the Role of Pidotimod in Adult Patients with Risk or Established History of COPD

Burden and Prevalence of COPD in India: As per the 2016 Global Burden of Disease study, COPD is the second leading cause of disease burden in India after ischemic heart disease.17 The crude prevalence rate of COPD in India has increased by 29.2% from 1990 to 2016.18 Of the disability-adjusted life-years (DALYs) due to COPD in India in 2016, 53.7% were attributable to air pollution, 25.4% to active tobacco use, and 16.5% to occupational risks.19 Studies on long-term mortality have shown one-year mortality of 22%–43% and two-year mortality of 36%–49% after hospitalization due to acute exacerbations (AEs) of COPD.18 The reported average frequency of AEs in COPD patients varies from 0.68 per patient-year to as high as 7.5 per patient-year depending on clinical phenotypes of COPD patients.19 These exacerbations are responsible for rapid deterioration in lung function, high healthcare resources utilization, and deterioration of both short- and long-term quality of life.20

Experts’ Discussion

The experts opined that there are different clinical phenotypes of COPD patients in India: (i) frequent exacerbator (with the occurrence of ≥2 exacerbations per year); (ii) stable mild-to–moderate COPD patients (with the occurrence of 0 or 1 exacerbations per year); (iii) severe COPD category with comorbidities, such as diabetes (with the occurrence of 3–4 exacerbations per year). The majority of the clinical experts mentioned that in their clinical practice, the average frequency of exacerbations in COPD patients is 2–3 attacks per patient-year. Bacterial infections are the predominant cause of acute exacerbation of chronic bronchitis (AECB) attacks in COPD patients. However, all exacerbations might not be infectious; some might be due to seasonal variations or due to allergies. The experts commented that COPD exacerbations and hospitalizations are more frequent in winter and rainy seasons as compared with summer seasons. Smoking is a predominant factor in COPD exacerbations. There is a high prevalence of COPD exacerbations, requiring admission to a hospital unit, in those patients who do not adhere to prescribed treatment regimens regularly and continue to smoke.

Challenges in the management of COPD in India: The key goal in the management of COPD is the prevention of exacerbations. The 2020 GOLD recommendations place a major focus on the role of exacerbations in determining initial treatment options with the updated ABCD disease risk-stratification tool (Figure 2).21,22 The GOLD ABCD tool combines symptom severity, using either the COPD assessment test (CAT) score or the Modified Medical Research Council (mMRC) scale, together with exacerbation risk, determined by either spirometry-defined airflow limitation or exacerbation history of
the patient to guide individualized pharmacotherapy.\textsuperscript{21,22}

For group A patients, a short- or long-acting bronchodilator is recommended based on its effects on the patient’s breathlessness.\textsuperscript{21,22} The initial therapy for group B COPD patients should consist of a long-acting bronchodilator (long-acting muscarinic antagonist [LAMA] or long-acting beta-agonist [LABA]).\textsuperscript{21,22} For patients classified in group C, initial therapy should consist of a LAMA as it is superior to LABAs regarding COPD exacerbation prevention.\textsuperscript{21,22} In group D patients, with more severe symptoms of COPD (CAT>20), such as greater dyspnea and/or exercise intolerance, a LAMA–LABA combination can be chosen as initial treatment. In group D patients with an eosinophil count >300 cells/μL or those with a history of asthma and COPD, a LABA–ICS combination is preferred as the initial treatment choice.\textsuperscript{21,22} Preventive measures recommended by GOLD guidelines include vaccinations and smoking cessation.\textsuperscript{21,22}

Adherence to prescribed medication among individuals with COPD is suboptimal in India, which negatively impacts survival and healthcare costs. Poor awareness of the nature of COPD and confusion about prescribed medication regimes are the major reasons reported in studies for poor medication adherence among patients with COPD.\textsuperscript{23} Spirometry is currently the gold-standard diagnostic test for COPD. In India, spirometry is a poorly utilized tool, especially in primary care settings and patients cannot afford regular use of spirometry regularly leading to underdiagnosis of COPD.\textsuperscript{24} The economic burden of COPD is high in India. Around 40%–57% of direct medical COPD costs are a result of AE-related hospitalization.\textsuperscript{25}

**Experts' Discussion**

The experts opined that understanding about COPD is poorer compared to asthma in India. There is no local name for COPD in India and the disease is often confused with asthma due to lack of awareness. Non-adherence to prescribed medications is high among low-income groups due to high medication costs. Deliberate discontinuation or reduction in the use of therapy during periods of symptom remission is high among patients with COPD. The experts mentioned that COPD patients are far more resistant to smoking cessation treatment than smokers without COPD due to stronger physical dependence on nicotine. Frequent exacerbations in this subgroup of COPD patients deteriorate patient’s health-related quality of life (HRQoL) and accentuate healthcare costs.

The current pharmacological treatment of COPD aims for symptomatic relief and reducing the severity and frequency of exacerbations. To date, none of the existing medications for COPD care have convincingly shown to modify the long-term decline in lung function.

**Experts' Opinions on Ways to Tackle Unmet Needs in the Medical Management of COPD in India**

- Early recognition of COPD symptoms, the proper use of medications, and nationwide patient awareness programs with special emphasis on cessation of smoking could help reduce the COPD burden in India.

- Awareness about COPD symptoms among the general public can be created through social media and health awareness campaigns.

- Creating awareness about regular use of spirometry (after every three months), especially among primary care physicians and educating them about how to perform and interpret spirometry, can reduce under diagnosis of COPD patients in India.

- The current treatment options for COPD target in reducing the duration and severity of exacerbations and not the up regulation of the innate and adaptive immune response.

**Efficacy and Safety of Pidotimod in Adult Patients with Exacerbations of COPD**

Table 1 summarizes clinical studies of Pidotimod in the management of COPD. In an early mechanistic study, Pidotimod (800mg twice a day [BD] for 30 days) was found to increase T-cell blastogenesis in patients with COPD, highlighting a potential route for enhanced immune response.\textsuperscript{2,26} During the study, it was observed that the effects on T-cells appear after 15 days of Pidotimod therapy and last for approximately 5 weeks after the end of therapy.\textsuperscript{2,26} A study published by Chen et al. investigated the role of Pidotimod in elderly COPD patients who were immune-deficient and had acute exacerbations.\textsuperscript{27} Pidotimod was administered 800 mg twice a day (BD) for the first 15 days as a loading dose followed by 800 mg once-daily (OD) for the next 15 days as a maintenance dose. On the tenth day, clinical symptoms, such as cough, amount of expectoration, and pulmonary wet rates, improved significantly after treatment with Pidotimod.\textsuperscript{27} Another study published by Cogo et al. evaluated the role of Pidotimod in severe (GOLD stage III level) COPD patients.\textsuperscript{28} The COPD patients were randomized and subjected to influenza vaccination with or without Pidotimod. The treated group was administered Pidotimod 800 mg OD for 15 days/month for two months.\textsuperscript{28} The incidence of minor exacerbations in the Pidotimod treatment group resulted in fewer physician visits, reduced disease progression, and improved HRQoL in patients with severe COPD symptoms.\textsuperscript{28} A prospective study published by Goyal A et al., evaluated the safety, efficacy, and cost-effectiveness of Pidotimod in adult Indian patients with COPD (≥2 exacerbations that required antibiotics therapy or ≥2 exacerbations requiring hospitalization in last 12 months) as an add-on drug in maintenance therapy of acute exacerbations.\textsuperscript{29} Pidotimod was administered 800mg BD for 8 days and continued at 800 mg OD until the completion of 2 months of therapy.\textsuperscript{29} At the end of 12 months, no episodes of either exacerbations or antibiotic prescription were reported in patients. Pidotimod was well tolerated by Indian patients, and around 97.3% of patients completed the treatment without safety concerns.\textsuperscript{29}

**Experts' Discussion**

Determination of patient subgroup that can reap maximum benefits from Pidotimod adjuvant therapy: Experts opined that Pidotimod adjuvant therapy along with standard of care medications would be beneficial in COPD patients as it plays an important role in modulating the balance of Th1/Th2 cytokines. The stimulation of innate and adaptive immune response by Pidotimod could help in reducing disease severity in the acute phase, and its prophylactic use can effectively reduce infectious recurrence in CB and COPD patients. Experts suggested that COPD patient subgroups that can experience maximum benefit from Pidotimod adjuvant therapy are: (i) group C and group D patients with recurrent exacerbation of chronic bronchitis (CB; 2–4 exacerbations/year); (ii) group A and group B patients (0–1 exacerbations/year) with comorbidities, such as diabetes; (iii)
**Table 1: Clinical studies of Pidotimod in management of COPD**

<table>
<thead>
<tr>
<th>Author and Year</th>
<th>Study Design</th>
<th>Key Findings</th>
</tr>
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<tbody>
<tr>
<td>Benetti et al., 1994&lt;sup&gt;1,2&lt;/sup&gt;</td>
<td>Multicenter, placebo-controlled, parallel-group study in 52 patients affected with COPD.</td>
<td>Significant increase of Stimulation index was observed in Pidotimod treatment group on day 15 and day 30.</td>
</tr>
<tr>
<td>Chen et al., 2010&lt;sup&gt;27&lt;/sup&gt;</td>
<td>Randomized trial. A total of 70 elderly patients with acute exacerbations of COPD were randomized recruited as: Pidotimod treatment group (N=35); control group (N=35); and additional health control group of 20 elderly people.</td>
<td>Levels of CD14, CD15Bb, and HLA-DR improved after 30 days of treatment with Pidotimod in COPD patients.</td>
</tr>
<tr>
<td>Cogo R et al., 2014&lt;sup&gt;14&lt;/sup&gt;</td>
<td>Randomized trial. 85 patients affected by COPD (GOLD III) subjected to influenza vaccination in November, 2012.</td>
<td>Among the 16 patients from the Pidotimod group, 1 more exacerbations were registered, compared to the 29 patients in the control group.</td>
</tr>
<tr>
<td>Goyal et al., 2018&lt;sup&gt;19&lt;/sup&gt;</td>
<td>Prospective, open-label, single-arm, single-center study. Inclusion criteria: Adult COPD patients; ≥2 exacerbations that required antibiotics for therapy or ≥1 exacerbations requiring hospitalization in last 12 months.</td>
<td>At baseline, four patients were hospitalized, and the average duration of hospitalization was 4.00 ± 2.45 days. After 12 months, there were no episodes of exacerbations, antibiotic prescription, and hospitalization with the use of add-on Pidotimod therapy. Only 3 AEs were reported in the study; one patient reported (0.9%) pain in knee, body pain, and weakness, and 1.8% SAEs were unrelated to the drug.</td>
</tr>
<tr>
<td>Ciaccia et al, 1994&lt;sup&gt;1,3&lt;/sup&gt;</td>
<td>Multicenter, placebo-controlled, double-blind study. Pidotimod group received 800mg BD (N=251) and placebo group received matching placebo dose (N=263). Treatment period was 60 days, with 90 days of follow-up.</td>
<td>Pidotimod group had lesser exacerbations even in winter season as compared to placebo group (p&lt;0.05). Pidotimod group had lesser antibiotic days as compared to placebo group (p&lt;0.05).</td>
</tr>
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</table>

COPD: Chronic obstructive pulmonary disease; BD: Twice a day; OD: Once-daily; CD: Cluster of differentiation; HLA: Human leukocyte antigen. AEs: Adverse events; SAEs: Serious adverse events.

patients on frequent antibiotics due to infection-induced exacerbations; and (iv) frequent smokers.

**Efficacy and safety of Pidotimod in patients with COPD:** Experts opined that Pidotimod is safe, well-tolerated, effective molecule in reducing the number and duration of acute exacerbations in patients with chronic bronchitis (CB) and COPD. Experts suggested recommended dosage of Pidotimod in adult patients with COPD: (i) treatment: 800 mg BD for the first 8 days (loading dose) followed by 800 mg OD for the next 52 days (maintenance dose) on an empty stomach for 2–3 months along with SOC medications; (ii) prophylactic dosage: 800 mg OD on empty stomach (preferably 1–2 hours before breakfast) for two months. Food intake reduces the bioavailability of Pidotimod up to 50%. Experts suggested that Pidotimod should be consumed on an empty stomach two hours before meal or two hours after meal for reaping its full benefits. Experts mentioned that very few patients have experienced nausea and weakness with initial BD dosing of Pidotimod, which was manageable and got relieved with OD evening dosing later.

Pidotimod is a drug used for the prevention of acute exacerbations, and its full clinical benefits can be seen on a long-term basis. However, symptomatic improvement in patients can be observed with a loading dose of 800 mg BD in 15 days. Experts strongly suggested that Pidotimod adjuvant therapy should be taken for two months to realize initial clinical benefits for patients with COPD. Clinical improvement in a patient’s condition (in terms of reduction in exacerbation frequency, reduction in duration, and severity of infectious episodes) with Pidotimod adjuvant therapy can only be assessed in the long run (after 1–2 years). Experts opined that Pidotimod can be administered once a year (in March/April) and influenza vaccination once a year (in October/November). Experts mentioned that the repetition frequency of Pidotimod can be modified depending on the patient’s medical history and frequency of AE attacks/year. For group C and group D COPD patients, experts suggested Pidotimod therapy (as preventive) twice a year (preferably one in winter and another in the rainy season) as COPD exacerbations and hospitalizations are more frequent in these seasons. Experts suggested that for patients with severe symptoms, Pidotimod therapy should be taken twice a year to realize its full clinical benefits.

**Experts’ Opinions:**
- Pidotimod is clinically safe and effective in the treatment of AEs and helps in faster remission of symptoms by repairing and improving immune responses.
- Prophylactic use of Pidotimod can effectively reduce the duration and severity of infectious recurrences in patients with COPD.
- Dose of Pidotimod therapy can be modified depending on patient’s medical history and severity of COPD symptoms.
- Pidotimod adjuvant therapy along with SOC should be taken for two months to realize the initial clinical benefits. The experts suggested the entire two-month therapy is necessary for maintaining the results for a longer period.
- Pidotimod is a drug used for the prevention of acute exacerbations, and clinical improvement in a patient’s condition can only be assessed in the long run.

**Conclusion**

In this article, we have attempted to summarize expert opinions on the burden and unmet needs in the medical management practices of COPD in India. The current treatment options for COPD in India aim for symptomatic relief and not the up regulation of the dysfunctional immune system. Therefore, there is an unmet need for treatment that ameliorates the immune system. Pidotimod is the only potent allopatic immunostimulant available in India till date with proven clinical benefits backed by solid scientific evidence in patients with COPD and recurrent RTIs. Experts opined that Pidotimod adjuvant therapy is safe, cost-effective, and have shown to improve HRQoL in all categories of COPD patients. However, patient subgroups that can realize maximum benefits from Pidotimod adjuvant therapy...
therapy are frequent exacerbator phenotypes who are chronic smokers, severe COPD category, and COPD patients with comorbidities such as diabetes. Experts suggested that the use of Pidotimod is also effective in patients prone to recurrent infectious exacerbations, and it is a suitable treatment approach for prophylaxis in such patients in times like COVID-19.

**Authorship**

This manuscript has been read and approved by all the authors, that the requirements for authorship stated earlier in this document have been met, and that each author believes that the manuscript represents honest work.

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**Conflict of Interest**

AM, AV, PW and AZJM, AV, PW, AZJ are clinical experts in the therapy area and do not have any conflict of interest. AK, SM, RR and VS are from medical affairs team of Dr Reddy’s Laboratories Ltd. and have supported in this scientific data generation have no conflict of interest. AK, SM, RR and VS are paid employees of Dr Reddy’s Laboratories.

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Sentinel Surveillance of Dengue Virus Infection in a Tribal District of Maharashtra, India

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SIR,

Dengue is a systemic vector-borne viral disease of global public health concern and it is transmitted between humans by Aedes mosquitoes. Globally 3.9 billion people are at risk of infection with dengue virus, 1 and 70% of the actual burden is in Asia, of which India alone contributed 34%. 2 As of 30th November 2020, a total of 32,796 cases of dengue fever have been reported in India (National Vector Borne Disease Control Program [NVBDCP]), 3 this number of cases reported are less perhaps due to the ongoing COVID-19 pandemic.

Palghar district is a predominantly tribal district which was separated from Thane district in August 2014. From 2014-2017, all suspected samples were being sent to Civil Hospital Thane for diagnosis. There were no testing facilities for Dengue in government laboratories/centers. Considering the need for availability of such services, diagnostic services were initiated at Model Rural Health Research Unit (MRHRU), Dahanu. It was recognized as 38th Sentinel Surveillance Hospital (SSH) for Dengue and Chikungunya Fever in Maharashtra by NVBDCP in August 2017 in Palghar district and diagnostic services commenced in September 2017.

There was lack of information on seroprevalence and circulating serotypes of dengue virus in Palghar district. Therefore, the present study aimed to understand the seroprevalence and to identify the circulating serotypes using retrospective data analysis of anonymized case records and samples received at SSH from October 2017 to September 2019.

The study was approved by the ICMR-NIRRH Institutional Ethics Committee. Anonymized Dengue case investigation record sheets (both IgM & NS1) from October 2017 to September 2019 were retrieved from the SSH of MRHRU, Dahanu.

Based on the onset of symptoms, samples were tested for the detection of dengue viral non-structural 1 (NS1) antigen (J. Mitra private limited) and dengue specific antibody (IgM) (NIV, Pune) using ELISA. The data was collected for ELISA positive samples, demographic characteristics, clinical, laboratory investigations (if available), mosquito infestation, storage of water, drinking water sources, house surroundings, and travel history. Forty-nine anonymized leftover samples of NS1 positives and/or IgM negatives (based on optical density) were used for the identification of the circulating serotypes. Viral RNA was extracted by using QIAamp Viral RNA Mini Kit (QIAGEN, Hilden, Germany) as per manufacturer protocol followed by a nested RT–PCR using the Lanciotti protocol. 4 The collected data was analyzed using SPSS software version 19.0.

From October 2017 to September 2019, a total of 1,911 samples of suspected dengue cases were screened for detection of dengue NS1 antigen and

Fig. 1: Age-wise (A) and Month-wise (B) distribution of the number of suspected samples & positive cases of dengue virus infection (IgM) from October 2017 to September 2019 in Palghar district.
the IgM antibody by ELISA method. Out of 1911 samples, 562 samples were screened for NS1 ELISA. The overall positivity rate for dengue infection was 22% (419/1911). IgM seropositivity was 28% (390/1349) and NS1 positivity was 51.1% (29/562). These results have shown similarities with previous studies conducted in other areas.\(^7\)\(^8\)

The most common symptoms among dengue positive cases were fever (85.3%), followed by headache (62.3%), body pain (55.6%), joint pain (45.3%), vomiting (34.3%), retro-orbital pain (27.4%). The percentage positivity rate for dengue infection was 40.6% (48/118) in 2017 (October to December), 27.26% (232/851) in 2018, and 27.8% (111/398) in 2019 (until September). Amongst dengue positive cases, 52.5% (205/390) were males and 47.5% (185/390) were females. The mean age group was 28.7 years.

It was observed that about 51.6% (31/60) of dengue positive cases belonged to Wada block (94 PHCs), 49% (46/94) from Vasai (8 PHCs), 35% (7/20) from Talasari, 33% (6/18) from Belapur of Palghar district. Thirty-eight percent (5/13) of NS1 positivity was observed in Wada block (January to September 2019). The seropositivity for dengue infection was observed in all the age groups, with the highest (40.3%) in group of 6-10 years.

Among the 240 case records, 90.8% (218/240) of them had mosquito infestation in their area. Two hundred and twenty case records mentioned that 74% (163/220) people were using plastic drums with a lid for the storage of water which is the most preferred breeding ground.\(^7\) Eight (16.3%) of the 49 samples tested by RT-PCR analysis for dengue virus were positive. DENV-3 (87.5%) (7/8) was the predominant serotype in Palghar followed by DENV-2 (12.5%) (1/8). The majority of the DENV-3 positive cases were less than 25 years of age. Circulation of these serotypes was also identified in the Pune and Nashik regions of Maharashtra.\(^7\)

To the best of our knowledge, this is the first study that has revealed 28% of prevalence and circulation of multiple dengue serotypes (DENV 3 & 2) in Palghar district. Therefore, the existence of multiple serotypes of the virus in the rural area of Palghar district increases the risk of Dengue Haemorrhagic fever/Dengue shock syndrome and future outbreaks could lead to increased morbidity and mortality. The current situation warrants a robust surveillance system and control of *Aedes* spp breeding could prevent outbreak in the future.

**Acknowledgments**

The authors are sincerely thankful to NVBDCP, New Delhi, and the National Institute of Virology, Pune for providing NS1 and IgM Dengue ELISA kits. The authors are thankful to the ICMR - Department of Health Research. Dr. Arun Yadav, Dr. Prabhakar Bhoyle, Dr. Balaji Hengne, Dr. Abhijit Chavan from Sub District Hospital, Dahanu, Public Health Department, Government of Maharashtra are sincerely acknowledged for the help in obtaining samples. We also acknowledge Miss Ruchita Survé, Mrs. Pranali Kadu, and Mrs. Roshni Kadu for their help in data entry and sample collection during the study period. Mrs. Swati is also acknowledged for assistance in statistical analysis.

**Contributions**

IKC, RK NS & SC : Conceptualization, design, planning and implementation of the study and manuscript preparation. IKC, KAN,NNK: Data collection, interpretation of data, data analysis. SP facilitated sample collection from Palghar district. NS: contributed to clinical inputs and review of the manuscript. All authors reviewed the manuscript.

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**References**


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**Spinal Intramedullary Neurocysticercosis—An Unusual Cause of Paraparesis**

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**Sir,**

Spinal cysticercosis is a rare manifestation of neurocysticercosis (NCC) accounting for 0.7 to 5.85% of all cases.\(^1\)\(^2\) Spinal intramedullary cysticercosis (IMC) is infrequent when compared to extra-medullary (intradural or extradural) forms; constituting only 20% of spinal cases.\(^2\)

A 40-year-old male presented with one-month history of low back pain, which was followed by weakness of lower limbs. The weakness was asymmetrical (right > left), associated with reduced sensations in both the lower limbs and urinary retention. Neurological examination revealed power of MRC grade 3/5 (right) and 4/5 (left) in lower limbs (LL) with brisk deep tendon jerks and bilateral extensor plantar response. He had 50% reduced pain sensory loss below L1.

Contrast-enhanced magnetic resonance imaging (CEMRI) of the spine revealed a focal eccentric lesion (8x5mm) with peripheral rim enhancement in conus medullaris at D11 vertebral body level suggestive of NCC in granular nodular stage (Figure 1). CEMRI of brain and cerebrospinal fluid analysis (CSF) were essentially normal.
normal. ELISA for anti–T solium Ig G immunoglobulin was positive in serum.

The patient was started on oral dexamethasone in a dose of 0.1 mg/kg/day followed by a 2-week course of oral albendazole (15 mg/kg/day) 12th hourly. At the time of discharge, he showed significant improvement in power to 4/5 in both lower limbs along with improved sensations. At two months follow up; he had complete resolution of neurological features.

Hematogenous spread and CSF dissemination via ventricular-subarachnoid pathways are the speculated mechanisms of spinal involvement. The common clinical presentations include pain, paraparesis, spasticity, bowel and bladder incontinence and sexual dysfunction.

Contrast enhanced MRI shows a cystic lesion with signal intensities similar to CSF on both T1-weighted and T2-weighted images. The scolex, when present, can be identified on T1-weighted images, as mural nodule isointense to cord parenchyma. A positive serology, preferably antibody by ELISA, either in cerebrospinal fluid or in serum further strengthens the suspicion.

Treatment of spinal NCC includes both medical (Albendazole/Praziquantel) and/or surgical management. Albendazole monotherapy is preferred in selected patients with IMC with stable clinical course. Dexamethasone should be given along with medical therapy as it increases the drug levels in blood and reduces the therapy associated inflammatory reactions. Surgical intervention is required when patients present with severe and progressive neurological deficits regardless of medical therapy.

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References


Upper Gastrointestinal Bleed in Acute Mercury Chloride Poisoning

Pazhanivel Mohan
Department of Gastroenterology, Jawaharlal Institute of Postgraduate Medical Education and Research, Puducherry

Sir,

I read with interest the pictorial CME on Imaging Appearances following Oral and Parenteral Mercury Poisoning by Deepashree T et al. 

I would like to discuss a case of a 27-year old lady with acute mercury chloride poisoning who had an upper gastrointestinal bleed.

A 27-year old woman was admitted following consumption of mercuric chloride swallowed in a capsule. She developed acute kidney injury and

Fig. 1: MRI dorso lumbar spine- Sagittal T1 W (A); Sagittal T2 W (B); STIR (C); Axial T2W (D)- images showing a focal tiny eccentric lesion in conus medullaris at D11 vertebral body level appearing hypointense on T1 and T2 W AND STIR images. On post contrast T1W Image (E) the lesion shows peripheral rim enhancement. No perilesional edema is seen. Findings are suggestive of partly calcified peripherally enhancing lesion in conus medullaris –consistent with NCC in granular nodular stage

Fig. 1: Upper gastrointestinal endoscopy in a woman with acute mercury chloride poisoning showing (A) large areas of necrotic mucosa in the distal body of the stomach; (B) ulceration in the antrum extending to the pylorus and focal areas of hemorrhagic gastric mucosa
was taken up for hemodialysis. She complained of burning sensation and pain in the upper abdomen following intake of food. She had several episodes of hematemesis and melena, 5 days after admission. Upper gastrointestinal endoscopy was done which showed large areas of necrotic mucosa in the distal body of the stomach (Figure 1A) with ulceration and hemorrhagic mucosa in the antrum (Figure 1B) suggestive of hemorrhagic gastritis and corrosive gastric mucosal injury. She was managed conservatively with proton pump inhibitors, sucralfate and blood transfusion.

Mercury chloride is the inorganic form of mercury that exists as white crystals or powder and are frequently used in medicines. Although the poisoning usually follows an occupational exposure, suicidal or accidental ingestion also occur. The gastrointestinal tract and kidneys are most often involved. The direct toxicity of inorganic mercury is due to precipitation of proteins resulting in necrosis of intestinal mucosa and proximal renal tubular cells. The early mortality in severe cases is attributed to the mercury sulphydryl complexes that inhibit enzymes and protein transport mechanisms and result in metabolic acidosis, vasodilation and shock. The gastrointestinal involvement in acute inorganic mercury ingestion include: discoloration of mucous membrane, oropharyngeal pain, metallic taste, excessive salivation, nausea, vomiting, colicky abdominal pain and diarrhoea. Corrosive injury to the mouth and throat, gingivitis, stomatitis, gum bleeding, hematemesis and haematochezia have also been reported. Our patient’s haematemesis can be explained due to corrosive injury preferentially involving the stomach probably because of swallowing mercury chloride in a capsule.

There is no consensus for treatment of inorganic mercury poisoning unlike exposure to elemental mercury. Early recognition and appropriate management are required for better outcome. The treatment is often supportive with chelation and hemodialysis.

References


Ayurveda and Dietary Modification for T2DM Management

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Sir,

Dietary compliance is a challenge in Type II diabetes mellitus (T2DM) management majorly due to leptin resistance. Insulin and leptin act in a dual hormone feedback loop known as the adipoinsular axis. Even after high doses of medicines, glycemic relief is observed in approximately 45% T2DM patients within 1 year. Ayurveda based panchakarma therapy is a traditionally used alternative therapy for T2DM patients and thus can be used as a potential add-on therapy for management of T2DM.

We would like to introduce a study conducted from November 2018 to December 2019 that aimed to record glycemic relief at 1-year post comprehensive diabetic care (CDC) program (a. 12 week intervention consisting of Panchakarma and low carbohydrate prepacked diet of 800 Kcal/day b. Post 12 weeks, 1 sitting of Panchakarma and low carbohydrate, moderate protein diet as per chart upto 1 year).

Panchakarma therapy involved: 1. Snehana (centripetal oleation) that uses of Azadirachta indica (neem) oil (contains bioactive compounds like azadirachtin, meliacin, nimbidin and other glycoside components) used in massage has hypoglycemic effect activating skeletal muscle for better sugar uptake. 2. Svedana (passive heat therapy) induces sweating leading to reduction in sodium thus aiding DM patients in preventing vascular complications. 3. Basti Kadha that has herbs such as Gymnemasilvestre has shown reduction in plasma glucose levels as well as decrease the HbA1c concentration in various clinical trials. Berberisaristate and Glycerhizaglabra have shown anti-hyperglycemic effects in rodent models.

Post the study intervention glycemic control (HbA1c<7) and glucose tolerance test negative status was achieved in 82 (97.6%) patients (mean age of 55.8 years (65 (77.4%) males). The patients showed significant decrease in the weight [t(76)=1.017, p=0.003] post-treatment vs. baseline. At 1-year, 76 (90.5%) patients had maintained glycemic control status while only 8 (9.5%) had glycemic relapse. Out of these 76 patients, 36 (47.4) followed diet chart for a minimum of 6 days/week for 1-year and 70 (92.1) exercised regularly for a minimum of 25 minutes. While 26 (34.2) had their weight decreased or under control. The percentage consumption of concomitant medication had decreased for most of the patients at 1 year follow up.

This study was able to achieve these results due to dedicated compliance to dietary modification. The 12 week of ‘pre-packed’ low carbohydrate diet (800Kcal/day) may have led to appetite regulation due to negative calorie balance that leads to adipolysis, less leptin (satiety hormone) resistance thereby creating satiety signals at limited food in turn causing reduced insulin resistance and controlled glucose levels without the aid of oral hypoglycaemic agents. This reduced insulin resistance further helped to decrease the glycemic relief rate as observed in this study. Thus, in majority of the patients, the leptin levels may have been regulated even at the end of 1 year thereby reducing the insulin resistance.

One may postulate that setting the hunger axis that regularizes leptin function might prevent the risk of glycemic relapse. However, a blinded trial is warranted to re-impose these findings.

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References


Chronic Inflammatory Demyelinating Polyneuropathy with Diabetes, Crohn’s disease and multiple co-infections: A Clinical Quandary

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Sir,

Chronic Inflammatory Demyelinating Polyradiculoneuropathy (CIDP) is an auto-immune inflammatory polyradiculoneuropathy with estimated prevalence of 2.84 per 100,000 adults.¹ Although the exact etiology is unknown, CIDP has been associated with HIV infection, Lyme’s disease, hepatitis B, hepatitis C, multiple myeloma and paraproteinemias.

There are case reports showing co-occurrence of CIDP with established Crohn’s Disease on treatment but from these reports it is difficult to ascertain whether CIDP was a manifestation of the underlying disease or a treatment related complication. The association of CIDP with leptospira has not been reported but scant literature demonstrating its co-occurrence with GBS is known.² We are reporting a rare case of CIDP associated with Diabetes mellitus (DM) and multiple co-infections (hepatitis B, leptospirosis) on a background of possible inflammatory bowel disease (IBD).

A 40 year old male, driver by occupation and a known case of Type 2 Diabetes Mellitus presented with progressive ascending symmetrical weakness of all four limbs since the last six months. There was associated tingling, decreased pin-prick and touch sensation over all four limbs as well. History of intermittent low grade fever was there since six months which had become high grade three days prior to admission. There was history of altered bowel habits (diarrhoea alternating with constipation and diffuse abdominal pain) since the last six months with nocturnal faecal incontinence since last three days.

On examination, he was conscious and oriented to time, place and person. He had pallor, bilateral pitting pedal edema and his temperature was 100.8°F. On neurological examination, the power in upper and lower limbs was MRC grade 4/5 and grade 3/5 respectively. There was diminution of pain, touch, temperature, vibration and joint position sense in all four limbs. Deep tendon reflexes were decreased in the upper limbs and were absent in the lower limbs. Bilateral ulnar and common peroneal nerves were thickened.

His haemoglobin was 7.7 g/dl and total leucocyte count was 13,600/mm³. Blood urea and serum creatinine were 104 mg/dl and 2.6 mg/dl respectively. Chest x-ray, ECG, serum electrolytes, thyroid profile and liver function tests were normal. His fasting blood sugar was 182 mg/dl with HbA1C of 10%. There was hypoalbuminemia (2.0 g/dl), hypolipidemia (HDL-10mg/dl, LDL-15mg/dl, Total cholesterol-23mg/dl & TG-47mg/dl) and INR was 2.2. Autoimmune profile was negative. HIV, Anti-HCV & VDRL were non-reactive. However, HBsAg and IgM-ELISA leptospira antibody were reactive. Ultrasound whole abdomen showed grade 1 fatty liver with and bilateral raised renal cortical echogenicity. Contrast CT abdomen could not be done due to deranged KFT’s. The patient was having altered bowel habits and polyneuropathy, he was investigated for co-existing autoimmune bowel diseases. His serum IgA Anti-Saccharomyces cerevisiae antibodies (ASCA) levels were found to be raised while IgA Anti TTG was normal. Hence, a probable diagnosis of type 2 DM with CIDP and concomitant co-infections (hepatitis B, leptospirosis) was made. Patient received intravenous immunoglobulin 0.4 g/kg per day for 5 days and had slight improvement in power of upper and lower limbs.

Chronic inflammatory demyelinating polyneuropathy (CIDP) is an acquired autoimmune polyradiculoneuropathy in which both cell mediated and humoral immunity act synergistically against an unknown schwann cell antigenic trigger. Our patient was found to have HBsAg without any symptoms of acute hepatitis and may very well be a chronic carrier. Chronic HBV infection has been associated with CIDP and this may be due to deposition of circulating immune complexes in the vasa nervorum leading to a vasculitic polyradiculoneuropathy or via molecular mimicry between host myelin protein and HBV proteins.[³]

This may explain the association of Hepatitis B and CIDP in our case.

Leptospirosis is a zoonotic disease and there is scant literature on its association with GBS.⁴ However, association between leptospirosis and CIDP has not been reported in literature. In our patient, there was high grade fever prior to admission, KFT derangement, ultrasound evidence of acute kidney injury and IgM-ELISA leptospira antibody positivity which signified an acute leptospira infection. Since, his symptoms had progressed over six months, leptospira infection could have been a co-infection in an immunocompromised patient rather than a cause for CIDP. However, leptospirosis may itself trigger an immune mediated reaction leading to myelin damage. Given the incomplete recovery in the patient despite treatment, co-infections might have had a role to play in the overall prognosis in our case.

Recent reports suggest that CIDP like neuropathy can also be an initial presentation of CD.⁴ The link between CIDP and IBD is probably due to autoreactive T cells and B cells which drive the inflammation in both these conditions. Co-existing abdominal symptoms for the same duration as the weakness, a negative evaluation for autoimmune tuberculosis and positive serum IgA ASCA antibodies (having high specificity) was suggestive of CD in our patient.

Thus, we are still evolving our understanding of CIDP and a thorough search for co-existing infections or autoimmune inflammatory conditions should be done in all CIDP cases. Such co-existing conditions with CIDP may lead to sub-optimal response to lIv Ig
alone. To the best of our knowledge, this is the first case of CIDP which is being reported in a diabetic patient with multiple co-existing illnesses along with IBD.

References

Acquisition of Clinical Skills During COVID-19 Pandemic: Medical Interns’ Perspective

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COVID-19 pandemic is having a profound effect on medical education. Medical students in India are required to complete one-year training period known as internship before they are awarded their degree. During this period, interns rotate in various departments for a predetermined period and actively assist in patient management, learn basic medical and surgical procedures and acquire clinical skills of communication. The basic clinical skills interns are expected to learn during this period include sampling (venous and arterial), insertion of nasogastric tube, urinary catheterization, conducting deliveries and patient resuscitation etc.

It was hypothesized that a sense of fear of COVID-19 exposure has led to decreased interest amongst interns in acquiring new skills. An online questionnaire based survey was distributed to 100 “Interns” enrolled in Government Medical College and Hospital, Chandigarh. administered via Google forms. The key findings obtained from this study were as follows:

1. Two-thirds of participants responded that the pandemic has created a sense of fear in their minds with respect to continuing medicine further, considering that they will always be at a higher risk of acquiring and transmitting the disease to their family and friends.
2. 36% respondents felt that once they complete their internship, their understanding of clinical skills and hands-on-training would be inferior to those who graduated during the “pre-COVID era.
3. 73% of the participants felt that internship training during the “COVID era” should be made easier or light because of the risks involved. Also, 34% of the participants considered taking either a leave or postponing their internship and doing it once things normalise.
4. Half of the participants felt that interns are too amateur to work in the hospital during these testing times and careful planning of their work hours along with provision of quarantine leave is needed. The COVID-19 pandemic has affected internship training in various ways. Due to the inherent risk of COVID-19 exposure while working in the hospital during the pandemic, interns have become hesitant to learn new skills and procedures. Interns posted in emergency areas are expected to master skills such as sampling, urethral catheterization, oxygen administration and nasogastric tube insertion among others. However, it was reported that interns were reluctant to learn these skills especially nasogastric tube insertion and oxygen administration via facemask as these procedures involve contact with respiratory secretions of patients. This hesitancy was not limited to rotation in medicine emergency. Interns posted in labor rooms were disclined to assist in vaginal deliveries due to the same apprehension. Similarly, participants posted in surgery were hesitant in performing cardiopulmonary resuscitation and suturing in trauma cases. Those posted in community medicine showed reluctance in organizing public health programs and assisting in contact tracing. Similar results were obtained in studies carried out in western countries. 1, 2

COVID-19 pandemic has not only affected the acquisition of clinical skills but has also left an impact on emotional and mental health of interns. A study by Eltayar et al 3 described similar concerns that final year medical students were coping with stress, anxiety and fear when dealing with this pandemic.

We hope that findings from our study gives further insight into these issues from the standpoint of medical interns.

References

ERRATUM
In the August 2021 issue of JAPI, Review Article entitled “Diabetes in Pre-independence India: Rediscovering a Forgotten Era” the text should read as follows:
1. On page 82 in Figure 2, the legend ‘Fig. 2: Dr. JP Bose (1858 – 1937)’, should be read as ‘Fig. 2: Dr. JP Bose (1894 – 1968)’.
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