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COVID-19 Immunity to Vaccination in India

Shashank R Joshi

Modern Vaccines are one of the great triumphs of medicine, and they are undoubtedly the most cost-effective healthcare interventions. We often fail to realize that rupees spent on a vaccination not only helps to save a life, but also greatly reduces spending on future healthcare. Along with improved sanitation, immunization is humanity’s greatest advance in preventing sickness and death from infectious diseases. Vaccines have helped eliminate or significantly reduce the burden of more than a dozen illnesses. It was not too many years ago when we celebrated the 200th anniversary of Edward Jenner’s first smallpox vaccination in 1796. The development of vaccines continued at a fairly slow rate until the last few decades, when new scientific discoveries and technologies led to rapid advances in Immunology, virology, molecular biology, and vaccinology. Vaccination has prevented several diseases and saved millions of lives—-including the eradication of smallpox and the ongoing fight against Polio, measles, malaria. Prevention is better than cure is an old adage which remains true even today. The success of smallpox eradication and now of the polio eradication programs in the country are testimony to this. Recognizing that childhood is the best time to provide lifelong protection against infections, most countries have put in place universal immunization programs. Specific recommendations are available for adults as well, but have yet not become routine. Various factors may account for these low rates, including the need to create awareness among patients, we need to change behavior of physicians to that they become sensitized to the notion of prevention rather than treating infection after they become apparent. In order to understand the vaccine for a new disease like SARS Cov2 / Covid 19, we need to understand the immunology, molecular biology as well as safety and efficacy protocols which are done in an ethically compliant way across the world.

Medical care is one of the fields where research never ends and the effort to improvise is ongoing with innovation. The micro-organisms which are the etiological factor in most of the sickness are very vicious and at the same time self-preserving, in making sure that their own existence does not end in this planet. It could be developing resistance to our antimicrobial arsenal, change of genetic structure to circumvent existing vaccines changing intermediate hosts to survive or attacking the very innate immunity human beings have against them. This has led to many epidemics/pandemics in the past, resulting in loss of millions of lives. We have been witnessing the same during the current pandemic due to COVID-19. But, humans have always fought back. Research has been the cornerstone of the development of modern medicine and the ultra rapid super pace at which COVID vaccines are being developed is another milestone for us. These vaccines are being researched with extreme care to fight against the viral community acquired pneumonia which has been a scourge since centuries. But, delivering these vaccines and the population making use of this facility is a mammoth task due to various reasons. Virulence, host immune response and COVID-19 risk score and vulnerable groups need to be kept in mind in the global and Indian plan of COVID-19 immunisation which is in its infancy now.

In 2021, we are now past more than a year after discovery of COVID-19 and its microbe the RNA SARS CoV2 virus will Vaccinating Adults Be Enough to Curb Spread of the Virus?. The global spotlight is now how to offer protection and Immunity from COVID-19. Essentially nothing can replace aggressive “masking”, distancing with sanitation apart from avoiding crowded clusters and poorly ventilated spaces. Independent of Covid appropriate behaviour the big question is does exposure to SARS Cov2 confer some degree of protection from COVID-19 reinfection?. It’s still elusive that Anti COVID IgG antibodies don’t mean protection but exposure, we don’t know how long will antibodies stay or decline neither do we know if our human T cells memorise the virus when it was exposed. COVID virus immune equations still are evolving and we only know it’s predictably unpredictable. Herd Immunity is still elusive but still plausible and we are all looking at Vaccines now. Most vaccines use the protein sequences of the SARS Cov2 virus which cover the virus or its crown and generate an immune response. Usually protein based vaccines don’t need very cold storage called “Cold Chain”, while vaccines from platforms like mRNA or DNA may need colder chains right upto-70° which can be a logistic nightmare. These mRNA platform vaccines (Pfizer, Moderna etc) are essentially researched on in USA, UK and Europe and have obtained Emergency Use authorisation (EUA) by the US FDA but are unlikely to be available for India in near future. They offer upto 95 % protection, but side effects are yet not fully known.

In India we have two made in India vaccines in advanced stage and many more in development including a mRNA platform from Pune and Nasal one from Hyderabad. First is the Bharat Biotech ICMR vaccine “Covaxin” which is now in Phase 3 (25,800 subjects planned) after successfully completing Phase 1(375 subjects) and 2 (380 subjects)trials. It is an inactivated whole virus vaccine BBV 152 (virus is killed by a reagent). The virus strain used is from Indian ICMR National Institute of Virology, Pune. The phase
3 trials are being conducted across India including Mumbai, Delhi and if it shows promise in interim data, it may apply for EUA with the Drug controller of India (DCGI) who have allowed it now to proceed with the final phase. The second Indian vaccine is made by Zydus Cadila which is a DNA vaccine “ZyCoV-D”. This DNA based vaccine is delivered via skin by a special mechanism (injection) and may be India’s answer to mRNA vaccine. It’s easy to manufacture and store and can change the genetic mutations like the flu vaccine. It has completed Phase 1 and 2 trials (1048 subjects) and has commenced Phase 3 trials (30,000). It has been safe till date and final data is anticipated. After phase 3, it may get a fast track approval from DCGI if the data is compelling.

The third vaccine in India is being made by Serum Institute with Astra and Oxford university which is leading the race because it’s likely to get EUA in UK and has conducted trials in UK, South Africa, Brazil and USA. In India its undergoing a special phase 2/3 trial under drug controllers supervision. This vaccine uses a “Spike protein “ and the vector is a chimp adenovector. Its does not have the challenges of very low temperature storage and transporation. However it has two issues one is the dose to effect co relation had an issue and second safety. Both will hopefully be dealt with very well by the group. The dose in UK showed better efficacy with lower dose compared to higher dose but this will be sorted out soon by the innovator. The safety pauses of some side effects have now been cleared by the British regulators. Indian regulators will look at both global and India data and may give a fast track emergency approval for the same. The other vaccines in India in trial is Sputnik V with Dr Reddy lab. It contains two vectors adenovirus 5 and 26 and after phase 2 trial got approval in Russia. Many other vaccines will enter trials in India soon like Biological Evans, J&J etc. India has started making syringes, needles, vials, cold chain set up under leadership of Niti Ayog, Government of India in close collaboration of the various state governments. The vaccine will be given in a systematic phased manner to the most deserving covid front line personnel (both health care, police, COVID workers in administration) followed by vulnerable groups above 50 years and comorbidities below 50 years. Overall, prevention through vaccination remains the best strategy to minimize the adverse consequences associated with these infectious diseases in patient.

Recently some mutant novel new strains, have emerged from the genomic surveillance programs from the UK consortium (B.1.1.7; VUI 202012/12), Denmark, Netherlands and South Africa (N501Y). The British new variant, referred to as SARS-CoV-2 VUI 202012/01 (Variant Under Investigation, year 2020, month 12, variant 01), shows an estimated potential to increase the reproductive number (R0) by 20.4, with an estimated increased transmissibility of up to 70%, according to the report. There is no indication, as of now, of increased infection severity associated with the new variant. SARS-CoV-2 VUI 202012/01 is defined by multiple spike protein mutations (deletion 69-70, deletion 144, N501Y, A570D, D614G, P681H, T716I, S982A, D1118H), as well as mutations in other genomic regions. These may lead to higher binding affinity to human ACE 2, evasion of the immune system but the clinical significance of this mathematically modelled genome sequences are unknown. A rapid increase in COVID-19 cases in the United Kingdom prompted an epidemiological and virological investigation. The most affected region was in Kent/South East England, which saw an increase in the 14-day case notification rate from 100 cases per 100,000 population in week 41 of 2020 to over 400 per 100,000 in week 50 of 2020. Analysis using viral genome sequence data identified a large proportion (>60%) of cases belonging to novel variant. As of December 13, 2020, a total of 1,108 individuals had been identified with the novel variant in England, with the earliest case identified on September 20, 2020.

Usually when a new virus strain or mutation arises transmissibility, pathogenicity/virulence and immunogenicity may be impacted in a pandemic as seen with earlier flu pandemics. Viruses often have small changes in their genome (mutations) which lead to modifications in the surface proteins which is often termed as “Antigenic Drift”. The surface proteins are “antigens,” which means they are recognized by the immune system and are capable of triggering an immune response, including production of antibodies that can block infection. The small changes that occur from antigenic drift usually produce viruses that are closely related to one another, which can be illustrated by their location close together on a phylogenetic tree. Antigenic shift is an abrupt, major change in a virus, resulting in new proteins in viruses that infect humans. One way viruses change is called “antigenic drift.” These are small changes (or mutations) in the genes of the viruses that can lead to changes in the surface proteins of the virus. The changes associated with antigenic drift happen continually over time as the virus replicates. Most vaccines are designed to target the spike proteins. Currently three major antigenic drifts in COVID-19 have been identified namely the D 614 G amino acid 614 on spike protein RBD part now contains G (Glycine) in place of aspartic acid (D).The second one is the UK Strain which have multiple gene mutations also called VUI 2020-12/01:N501Y highlighted earlier. Finally the South Africa drift: also 3 gene mutationN501Y: amino acid N (asparagine) replaced with Y tyrosine in this amino acid in spike RBD location and two other gene mutations. Currently, the clinical significance of these antigenic drifts is unknown. Other than potential higher transmissibility, early indicators don’t allow us to predict if it will be more virulent or will lead to a severe outcome. Also currently it appears to be unlikely to impact the ongoing vaccine programs, though it may get incorporated in the future.

References
Post COVID-19 Mucormycosis - from the Frying Pan into the Fire

Rajeev Soman¹, Ayesha Sunavala²

While our country battles with COVID-19, the issue of post COVID-19 sepsis has emerged as a significant problem. India bears the dubious distinction of being both the diabetes, as well as the mucormycosis, ‘capital’ of the world. COVID-19 and its treatment, against this backdrop, amounts to a recipe for disaster.

With an estimated 77 million cases in the adult population, diabetes is India’s fastest growing epidemic. A recent cross-sectional study from all states of India, revealed that 47% of Indians are unaware of their diabetic status and only a quarter of all patients achieved adequate glycemic control on treatment.¹ The unholy association between diabetes and the severity of SARS-CoV-2 infection has been repeatedly established in various studies from across the world.²

Mucormycosis sometimes appears as the diabetes-defining illness, and remains one of the most devastating complications in uncontrolled diabetics with mortality rates ranging between 40-80%. India contributes to 40% of the global burden of this “rare mould” infection as it is called in western literature, with an estimated prevalence of 140 cases per million population.³

Post COVID-19 sepsis is what occurs after SARS-CoV-2 has had a rampage in the human body and we are literally left picking up the pieces. It leads to a dysregulated innate immune response, ciliary dysfunction, cytokine storm, thrombo-inflammation, microvascular coagulation and eventual immune exhaustion. This cascade of events facilitates secondary bacterial and fungal infections especially in critically ill patients subjected to emergency invasive procedures, mechanical ventilation, CRRT, ECMO, poor nursing ratios, prolonged hospital stays and breaches in asepsis. Further, the use of corticosteroid treatment and anti-IL-6-directed strategies in these highly susceptible hosts along with high fungal spore counts in the environment creates the perfect setting for mould infections.

While COVID-19-associated pulmonary aspergillosis (CAPA) has received much international attention, the Indian epidemiology of invasive mould infections in the ICU reveals a significant burden of invasive mucormycosis.⁴ This has recently emerged as a life threatening complication of COVID-19 in our country. Although the predisposing factors and pathogenesis are somewhat similar to that of other mould infections, certain unique characteristics and key distinguishing factors must be kept in mind in order to promptly suspect the infection, confirm the diagnosis and offer timely therapeutic intervention.

Mucorales are ubiquitous moulds, abundantly found in the environment on decaying organic matter. Various studies from hospitals across the country have revealed heavy mould spore counts even in hospital air due to predominantly hot, humid conditions in our tropical climate.⁵

Unlike CAPA, invasive mucormycosis has been observed even in patients with mild to moderate SARS-CoV-2 infections. The strongest predisposing factor appears to be hyperglycemia in undiagnosed or uncontrolled diabetics. Hyperglycemia leads to increased expression of the endothelial receptor GRP78, resulting in polymorphonuclear dysfunction, impaired chemotaxis and defective intracellular killing. An important virulence trait of Mucorales is the ability to acquire iron from the host which is an essential element for its growth. In conditions of ketoacidosis, free iron becomes readily available in the serum. This excess endogenous iron is efficiently taken up by the Mucorales through siderophores or iron permeases, further enhancing their virulence. These effects are greatly amplified by the use of corticosteroids and immunosuppressants in susceptible hosts. Corticosteroids themselves cause impairment in the neutrophil migration, ingestion, and phagolysosome fusion. Coupled with the potential implications of steroid-induced hyperglycemia, the diabetic COVID 19 patient receiving corticosteroids or other immunosuppressants is exceptionally vulnerable to the development of mucormycosis.⁶ ⁷

The landmark RECOVERY trial published in June 2020 has served as a ‘licence’ to use steroids in patients with COVID-19. However, the fine print clearly revealed some important messages that we seem to have overlooked. Benefit was specifically shown with low dose, short duration dexamethasone in moderate to severe illness. Although, higher doses and longer durations may be used in exceptional cases due to compelling reasons, such patients should be evaluated for undiagnosed diabetes, checked for strict glycemic control and closely monitored for secondary infections. A cavalier attitude to the use of steroids should be discouraged at all costs.

The two most important manifestations of Mucormycosis in this setting are rhino-orbital-cerebral and pulmonary. Suspicion is based on subtle clinical and imaging clues, risk factors and disease development or progression while on any antibacterial or antifungal therapy that does not cover Mucor. Physicians need to have seen a ‘critical’ number of cases to recognize the signature of Mucor.

The clinical hallmark is tissue necrosis manifested as a necrotic lesion, eschar or black discharge in the nasal or oral cavity. Orbital, ocular and cranial nerve involvement are ominous
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signs that must be taken seriously. Alternative erroneous diagnoses lead to antibacterial and further steroid use which add fuel to the fire. Pulmonary Mucormycosis has certain radiologic findings which help to distinguish it from Aspergillosis. There is no biomarker for mucormycosis and hence a negative galactomannan and beta-d-glucan are useful pointers to rule out other mould infections. A false positive galactomannan due to generic piperacillin tazobactam use etc. can lead to the erroneous diagnosis of invasive aspergillosis. Although challenging, the need to distinguish Mucor from bacterial infections and from aspergillosis in a timely fashion is of essence. Treatment with voriconazole for suspected invasive aspergillosis increases the pathogenicity of Mucor with obvious dire consequences.

Rapid diagnostic methods include biopsy, KOH mount and Calcofluor stain. Mucor is difficult to routinely culture. Biopsy remains the mainstay of diagnosis and the benefits of the procedure outweigh the risk, even in a ‘difficult to access’ location or in the presence of coagulopathy.

Treatment principles include antifungal agents, surgical debridement, reversal of underlying predisposing factors and adjuvant therapy. Amphotericin B has been the standard of treatment for invasive mucormycosis. COVID-19 patients may have developed acute on chronic renal failure which may be mitigated by switching to a less- or non-nephrotoxic alternative. Therefore Posaconazole or Isavuconazole may have to be used. The latter has the added advantage of shortening the QT interval which may have been affected by HCQ, Azithromycin which many patients still continue to receive. Surgical debridement, the earlier the better, is pivotal in the management of mucormycosis. The optimal time of surgery to reduce the operative risk to the patient with COVID-19 and the risk of transmission to the operating team is a contentious issue. Replication competent virus has not been recovered from patients with mild to moderate illness after ten days, from patients with severe illness after fifteen days or from any critically ill patient after twenty days.

Adjuvant therapy with caspofungin, deferasirox, statins, aspirin, and hyperbaric oxygen may have to be considered. Mucormycosis needs to be actively managed by a team which includes members from almost all departments in the hospital. Therapy is toxic and very resource intensive. In a recent Indian study, 24.3% patients left the hospital against medical advice due to the anticipated cost, morbidity of surgery and prognosis.

Mucormycosis developing in the post COVID-19 setting ‘breaks the back’ of a patient’s family that is barely recovering from a treacherous viral infection. This scenario is nothing short of ‘RECOVERY from the frying pan and into the fire.’

References


(Advertorial) Repurposing Veteran Antibiotic in COVID-19 Nationally & Internationally

Introducing Respilax Capsules
Doxycline Hyclate 100mg + Lactic acid bacillus 5 Billion spores
Antibiotic with Pleiotropic Potential

Zinconia 30table Syrup
The Health Catalyst

Scavista-12 Ivermectin Tablet 12mg
A Vista to Scavenge Effectively

ZU-Ç 500 Ascorbic Acid 500mg + Scavite Ascorbate 50mg supplement to Ascorbic Acid 500mg + Ascorbic Acid 500mg + L-Carnitine Hydrochloride 3 mg Natural Vitamin

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- Dr. Pradip K. Bhattacharya, Medical Superintendent, Chirayu Medical College & Hospital, Bhopal.
Clinical Presentation of Cases with SARS-CoV-2 Reinfection/Reactivation

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Abstract

Background: Reinfection/reactivation of SARS-CoV-2 has been a matter of great interest from the immunological and vaccine perspective. However, little is known about the clinical presentation of such reinfection/reactivation. We report a case series of 9 COVID-19 patients having experienced two clinically- and/or virologically-confirmed episodes of COVID-19.

Methods: Epidemiological and clinical characteristics of 9 healthcare workers (HCWs) with two episodes of SARS-CoV-2 are described.

Results: The incidence of reinfection/reactivation amongst the HCWs was 2% (9 out of 491) with an average remission period of 66 days (range 43-78 days). Amongst the cases of reinfection 4/9 were asymptomatic in first episode were symptomatic in second episode. There is negative correlation between numbers of days the patients took to become SARS-CoV-2 negative by RT-CPR and/or clinically recover in the first episode and the second episode irrespective for the time spent in remission.

Conclusion: Shorter durations of SARS-CoV-2 infection in the first episode are associated with longer time to recovery in the second episode in patients with re-infection/reactivation.

Introduction

The current COVID-19 pandemic is growing rapidly and healthcare workers (HCWs) are at a high risk of contagious SARS-CoV-2 infection.1 Front-line HCWs are at increased risk of COVID-19 as compared to the general population. With the passing time in the COVID-19 pandemic, the possibility of reinfection is an emerging threat. Although it is generally assumed that an episode of infection with SARS-CoV-2 would generate enough immune response providing protection for future infections. Notwithstanding this, there are a few case reports demonstrating the possibility of re-infection.2-4

Like other coronaviruses, SARS-CoV-2 was expected to induce a monophasic disease with at least transient immunity. Nevertheless, rare cases of suspected COVID-19 “recurrence” or “reactivation” have been reported (REFS). Reinfection/reactivation of SARS-CoV-2 has been a matter of great interest from the immunological and vaccine perspective. However, little is known about the clinical presentation of such reinfection/reactivation. We report a case series of 9 COVID-19 patients having experienced two clinically- and/or virologically-confirmed episodes of COVID-19 among healthcare workers at a dedicated COVID-19 hospital in Mumbai, India.5

Methods

The study was approved by the Institutional Ethics Committee of Topiwala National Medical College and BYL Nair Charitable Hospital (NH), Mumbai (ECARP/2020/78). NH was converted into a dedicated COVID-19 facility with since 18th April with 1043 beds and treated more than 7000 patients till 31st October. The data was collected from medical case records and interviews of HCWs as described elsewhere.6 All patients gave informed consent and agreed with the use of their anonymous medical data. The study is registered with clinical trial registry of India (CTRI/2020/09/027516). During the course of this study, 491 HCWs observed infected with SARS-CoV-2 (unpublished data). Epidemiological and clinical characteristics of 9 HCWs with two episodes of SARS-CoV-2 are described. The calculations were done using the online version of social science statistics software (https://www.soscistatistics.com/)

Results

In all, 491 HCWs had RT-PCR confirmed SARS-CoV-2 infection (April 2020 - Oct 2020). Amongst these, 9 HCWs were readmitted for a second episode of SARS-CoV-2 infection 16-154 days of the first episode. The clinical course of these 9 HCWs is presented in Table 1. All the 9 cases were positive by RT-PCR in the first episode, 5/9 had mild symptoms while four were asymptomatic. All the 9 cases were confirmed negative by RT-PCR testing twice 48-72 hrs apart. In the second episode 8/9 cases, were subjected to retesting, due to symptomatic presentation, one asymptomatic individual was detected positive in as he underwent testing during the course of contact tracing in the family. The median duration of remission...
### Table 1: Epidemiological, clinical, investigations and treatment characteristics of healthcare workers with SARS-CoV-2 reinfection in India

<table>
<thead>
<tr>
<th>Patient #</th>
<th>Age (years)</th>
<th>Gender</th>
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<th>Days to recover</th>
<th>Symptomatic</th>
<th>Symptoms</th>
<th>HCQ prophylaxis</th>
<th>Treatment</th>
<th>RT-PCR and/or Clinical recovery</th>
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<td>38</td>
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<td>AB and supportive</td>
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<td>43</td>
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<td>AB and Supportive Treatment</td>
<td>Positive</td>
</tr>
</tbody>
</table>

* Suspected of COVID-19 on HRCT thorax which was suggestive of moderate right sided pleural effusion with passive sub-segmental collapse of right lower lobe, fibrocalcific nodular changes in apical segment of right upper lobe and fibro-atelectasis changes in superior segment of right lower lobe. Pleural fluid studies were negative for Acid Fast Bacillus on smear, negative for gram positive cocci and Mycobacterium tuberculosis was not detected on (GeneXpert) NAAT. SARS-CoV-2, Severe Acute Respiratory Syndrome Coronavirus 2; RT-PCR, Reverse Transcriptase Polymerase Chain Reaction; COVID-19, coronavirus disease 2019; ILI, Influenza Like Illness; AB, Antibiotic; HCQ, Hydroxychloroquine; HRCT, High Resolution Computed Tomography.

### Discussion

Previous studies have reported SARS-CoV-2 reinfection of asymptomatic individuals which were serendipitously diagnosed during screening programmes in high-risk settings. In this study, all HCW who were assumed to have been infected were screened on a daily basis, and the cases of reinfection/reactivation were diagnosed based on new onset of symptomatic presentation days after resolution of the primary infection. In a controlled high-risk hospital setting, we found the incidence of reinfection/reactivation was 2% in HCW who were serendipitously diagnosed during screening programmes.

In nine health care workers the numbers of days that patients took to revert to RT-PCR negative and/or recover from clinical symptoms were noted in two episodes of SARS-CoV-2 infection. Each dot represents one patient and the regression line is shown. The R value is -0.7562 and P-value is 0.018434.

In time health care workers the number of days that patients took to revert to PCR negative was 66 days (range 42-78 days) between the two episodes. In first episode 6/9 cases were positive for SARS-CoV-2 by RT-PCR, one patient was persistently negative but had HRCT changes resembling COVID-19. Amongst the patients who were asymptomatic in the first episode, 4/5 were also symptomatic in the second episode; all had mild to moderate symptoms. We found a negative correlation between time spent in remission and duration of SARS-CoV-2 positivity in the second episode (Figure 1). The patients who recovered quickly in the first episode (2-6 days from PCR and symptom positive to PCR negative and clinical recovery) took longer to clear the virus and clinical recovery in the second episode (5-18 days) and vice versa (Figure 1). The value of R is -0.7562 (P-value is 0.018434) indicating a strong negative correlation between numbers of days in first and second episode. There was no association between time spent in remission and duration of SARS-CoV-2 positivity in the second episode. Overall, HCW who took longer to revert to RT-PCR negative and/or recover from clinical symptoms were also symptomatic in the second episode.

In conclusion, the incidence of reinfection/reactivation was 2%. This reaffirms the notion that chance of reinfection/reactivation for SARS-CoV-2 in general population can be very low.
Exposure to the infectious agent is a primary determinant of re-infection/reactivation as all the cases were persistently exposed to COVID-19 environment and prophylactic HCQ or previous treatments did not seem to have any protective effects. A surprising but not unexpected observation made herein was the patients who had shorter duration of SARS-CoV-2 positivity in the first episode, typically had a longer duration in second episode. These observations imply that either the duration of exposure in the first episode was not sufficient to generate enough immune-response to be protective resulting in a second episode. Four cases who had a viremia of 4 days or more in the first episode recovered quickly in the second episode and had milder symptoms. In contrast, the patients who had a short duration of viremia in the first episode not only had longer duration of viremia in the second episode but so had more numbers of symptoms, one even progressed to ARDS. Intriguingly the duration of remission had no influence on clinical presentation or duration of viremia in the second episode.

The present study is limited by the fact that the antibody titers could not be investigated in the first episode. Also in absence of molecular evidence we cannot conclusively indicate if these were cases of reactivation or reinfection. Nevertheless, our data has highlights some crucial aspect on the determinants of relapse of SARS-CoV-2 infection. Large cohort studies will be essential to have greater insights on the emerging problem of re-infection/reactivation.

Acknowledgements
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Trial Registration
Study is registered with Clinical Trial Registry of India (Registration no: CTRI/2020/09/027516).

Ethical Approval
The study was approved by the Ethics Committees of TNMC (No. ECARP/2020/78 dated 13.08.2020).

Consent to Participate
All patients gave informed consent to participate.

Consent to Publish
Written informed consent was obtained from patients for publication of their Cases with the use of their anonymous medical data.. A copy of the written consent is available for review by the Editor of this journal.

Authors Contributions
NM had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Concept and design: NM, RG. Acquisition of data: PL, SB, AM. Analysis, or interpretation of data: All authors. Drafting of the manuscript: RG, NM, DM. Critical revision of the manuscript for important intellectual content: NM, RG, DM. Statistical analysis: NM, RG, DM. Administrative and technical or material support: NM, RB, SR, SM.

Availability of data and materials
All the data reported in the manuscript is presented in the table and manuscript. The additional data if needed is available with corresponding authors and can be shared if requested.

References
Role of Mycobacterium w for the Treatment of COVID-19: An Observational Study

Atul Ingale1, Farah Ingale2, Brajesh Kunwar3, Shakeel Ahmed4, Kumar Salvi5, Vishwas Chavan5, Manish Sontakke6, Chandrashekhar T7

Abstract

Background: COVID-19 has taken a big toll on the world in terms of morbidity and mortality. The disease may progress in some of the patients leading to trigger of “cytokine storm” which is shown to be associated with adverse outcomes. Heat killed Mycobacterium w (Mw) is a known immunomodulator which is approved for the treatment of gram negative sepsis. This study was carried out to evaluate the role of Mw in the treatment of COVID-19 early in the course of the disease.

Method: In this retrospective observational study, 117 (84 males, 33 females) COVID-19 patients admitted between July 3, 2020 and Aug 26, 2020 in the covid ward of Fortis Hiranandani hospital, Mumbai, were enrolled. Patients were tested COVID-19 positive on RTPCR and were treated with standard of care treatment along with Mw 0.3 ml intradermal injection per day for 3 consecutive days. Patients were evaluated for live discharge as well as changes in the levels of inflammatory markers.

Results: Use of Mw was seen to be associated with rapid recovery in 116/117 patients from COVID-19 who were discharged from the hospital within 10 days. A decrease in the levels of CRP and IL6 was observed after the administration of Mw. This decrease was associated with improvement in the patients’ condition. The use of Mw was seen to be associated with no systemic side effects.

Conclusion: The patients of COVID-19 may deteriorate due to exaggerated production of cytokines which may result in adverse outcomes. Mw used earlier in the disease not only effectively prevents excessive cytokine production but also contribute to rapid recovery. Mw was also found to be safe in use. Larger randomized controlled trials are recommended to assess the role of Mw in COVID-19.

Introduction

The corona virus cases were initially reported as viral pneumonia of unknown origin from Wuhan, China at the end of 2019. The causative agent was identified to be coronavirus species and the condition was named as Severe Acute Respiratory Syndrome Corona Virus 2.1 COVID-19 may progress from mild disease to viral pneumonia leading to Acute Respiratory Distress Syndrome (ARDS).2 Recent evidences suggest that severe COVID-19 is a state of dysregulated immunity, which is one of the major cause of mortality and morbidity.3

The term “Cytokine Storm” is being widely used by researchers in multiple articles, which is characterized by pronounced activation of the immune system and production of various inflammatory markers.4 It was reported that patients infected with SARS-CoV-2 show increased production of large amount of various cytokines (IFNα, IFNγ, IL-1β, IL-2, IL-6, IL-10, IL-12, IL-18, IL-33, TNFα, TGFβ) and chemokines (CXCL10, CXCL8, CXCL9, CCL2, CCL3, CCL5) which results in setting-in of the cytokine storm.5 In a transcriptome sequencing analysis of the pro inflammatory genes performed on the polymorphonuclear cells and bronchoalveolar lavage fluid of the COVID-19 patients, it was shown that there was upregulation of the genes encoding for some immune regulatory molecules.6

The immunological response seen in the patients of COVID-19 infection is observed to be sharing many features with the patients of bacterial sepsis. This led to the conceptualization of immunomodulation as an essential therapeutic approach for the treatment of COVID-19.7

The heat killed Mycobacterium w (Mw) (Inj Sepsivac®, Cadila Pharmaceuticals Limited, Ahmedabad, Gujarat) was originally developed for the treatment of leprosy and non-small cell lung carcinoma along with chemotherapy. It is a known immunomodulator which acts through the toll like receptors (TLRs) pathway and modulates the T cell responses of the host cells.8

Method

Study design

This retrospective observational cohort study was carried out in the patients diagnosed with COVID-19 by reverse-transcriptase polymerase-chain-reaction assay (RT-PCR) and consecutively admitted to Fortis Hiranandani hospital, Mumbai between July 3, 2020 and Aug 26, 2020. Being this a retrospective study, timeframe and sample size were not predetermined. All the patients admitted in the hospital with COVID-19 positive status, not in need of oxygen supplementation and received Mw along with standard of care treatment.
care treatment were included in the study.

Treatment for COVID-19

On admission, all the patients received standard pharmacological treatment as per institutional protocol, including antiviral drugs (lopinavir 400 mg + ritonavir 100 mg twice daily), antibiotic prophylaxis (azithromycin or ceftriaxone), antipyretic medication (paracetamol 1500 mg/day), zinc and vitamin C supplementation. Majority of the patients were given corticosteroid (dexamethasone), as there was no standard protocol in place for use of steroids in patients with COVID-19 at hospital. Mw was administered on a compassionate basis at the dose of 0.3 ml (0.1 ml X 3 injections at three different sites) per day for three consecutive day by intradermal route as per the approved dosage in gram negative sepsis.

Study variables and assessments

Clinical and laboratory data of all patients were available at various time points. Values at admission, before and after completion of Mw therapy were retrieved for these patients along with data on symptoms, demographics characteristics, diagnostic workup, laboratory values and concomitant medications.

Results

Baseline characteristics

A total of 117 COVID-19 patients who were treated with at least one Mw injection were included in the present study. Of these, 84 were males and 33 were females. Demographic parameter age, sex, weight etc. were noted for each of the patients. Majority of them were evaluated for biochemical parameters like IL6, CRP, neutrophils, lymphocytes and neutrophil to lymphocyte ratio. (Table 1). In all patients, SARS-CoV-2 infection was confirmed by real-time-PCR on nasopharyngeal swab.

At 10th day after the first dose of Mw, 116 patients were observed to improve and were successfully discharged from the hospital. There was only one patient who succumbed to the disease. (Table 2). There was no deterioration in patients’ condition observed in terms of oxygen requirement. This improvement was reflected by reduction in the important laboratory parameters.

Table 3 shows values of CRP and IL6 after single dose, two doses and complete therapy of Mw. The post Mw values of CRP and IL6 after single dose administration were available for 24 and 25 patients respectively. A decreasing trend in both the parameters were observed however the change in median was non-significant for CRP (8.335 to 4.67 mg/dl; p = 0.086). However, levels of IL6 was seen to be reducing immediately after the single dose of Mw. This reduction was statistically significant. (9.31 to 3.9 pg/dl; p = 0.001).

The post Mw median values for CRP and IL6 after two doses of Mw

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<th>SD</th>
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<td>Age (yrs)</td>
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<td>IL-6</td>
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<tr>
<td>CRP</td>
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<td>Ferritin</td>
<td>535.37</td>
<td>426.74</td>
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Table 2: Status post 10 days of hospitalization

| Death        | 1      |
| Discharged   | 116    |
| Total        | 117    |

Fig. 1: Change in mean CRP values after single dose, two doses and complete therapy of Mw

Fig. 2: Change in mean IL6 values after single dose, two doses and complete therapy of Mw
were available for 29 and 28 patients respectively. Values of both the parameters were observed to reduce significantly after two doses. (CRP: 23.44 to 6.33 mg/dl; p < 0.001, IL6: 17.7 to 4.4 pg/dl; p < 0.001).

Those patients whose CRP (n=64) and IL6 (n=64) were available after the completion of Mw therapy (3 doses) decreasing trend was observed for the values of both the parameters. However, the change for IL6 was statistically non-significant. (CRP: 24.335 to 7.88 mg/dl; p < 0.001, IL6: 16.85 to 8.56 pg/dl; p = 0.125) (Figures 1 and 2).

Safety

Use of Mw in COVID-19 patients was observed to be safe and well tolerated, without any major safety concerns in patients with COVID-19. Local site reactions were observed at the site of injection of Mw in 85.47% of the patients. Out of which majority of the patients had mild reaction (54%). Patients developed erythema at the site of injection which was followed by development of induration and pustule formation. This was converted in to a small punched out ulceration which healed by a formation of healthy scar without the need of any specific treatment. Rest of the patients who had moderate (31%) or severe reaction (14%) were given nonsteroidal anti-inflammatory (NSAID) drugs, local steroid cream and dry dressing as required.

Discussion

This is the largest study of the compassionate use of Mw for the treatment of COVID-19 till date. The role of such dysregulated immune response or so called "cytokine storm" is well established in the pathogenesis of bacterial sepsis also. The excessive production of various cytokines ultimately leads to pathological inflammation and its sequels like capillary leakage, multiple organ dysfunction syndrome and coagulation pathway activation. The cytokine profile of COVID-19 infection shares many similarities with the same of bacterial sepsis.

Mw is approved in India for the treatment of gram negative sepsis. It is a potent TLR2 agonist and a poly TLR antagonist (4, 5, 7, 9). Mw is a potent inducer of Th1 response. Intradermal injection of Mw results in increased number of stimulated macrophages. These activated macrophages are responsible for the viral load clearance. It was also observed with SARS CoV infection that the function of dendritic cells were impaired. Mw is known to induce potent activation of the dendritic cells by its TLR2 agonistic property, which further helps in curbing the viral infection.

Induction of Th1 response results in the production of INF-γ. INF-γ is known to reduce the expression of Angiotensin Converting Enzyme 2 which is essential for the entry of corona virus in to the cell. Mw being an antagonist of TLR 4 receptor inhibits the downstream cytosolic inflammatory pathway activation and reduces the production of various cytokines.

Based on the published case series on the usage of Mw in COVID-19 patients as well as its applicability for the treatment of gram negative sepsis patients, the compassionate use of Mw was planned in these patients to stop progression of the disease and faster recovery. We observed mortality of COVID-19 in the patient cohort of the present study to be less than 1%. As all the patients received standard of care recommended, the lower mortality observed in our study could be attributed to Mw. It was also observed in the present study that inflammatory markers start decreasing soon after the single dose of Mw showing faster onset of action. However, clinically recognizable response to the treatment was observed second day onwards. We could successfully prevent the progression of patient to the stage of the disease requiring oxygen supplementation or mechanical ventilation.

IL-1β and TNFa are two of the major activators of the expression of IL-6 along with TLRs and other cytokine which ultimately promote the synthesis of IL-6. We observed that Mw given to the patients of COVID-19 was able to contain the worsening of the disease further and could successfully bring down the elevated IL6 levels which resulted in successful discharge of the patients. We believe that owing to the unique mechanism of action of Mw, levels of multiple cytokines including IL-1β, IL-6 and TNFa were decreased reflected by faster recovery. Administration of Mw earlier in the course of COVID-19 could successfully avoid the trigger of cytokine storm.

Injections site immunological reaction to Mw is a known phenomenon. Sharma SK et al reported injection site reaction in 82.4% of the patients. 68% of the patients experienced mild intensity of the reaction whereas 12.91% had moderate to severe reaction at local site. We also observed similar response in the present study. d’Aleo F reported exaggerated response at the injection when BCG was administered in to the subcutaneous space instead of intradermal inoculation which resulted in development of local abscesses.

Looking in to the skills required for the intradermal injection and paramedical staff working with PPE kits on, we believe there are chances of erroneous injection of Mw in to the subcutaneous space, instead of intraderal space, in some of the patients. This could be the reason for the moderate to severe local reactions registered in the present study.

Conclusion

Majority of the patients of COVID-19 patients improve with in some days being it a self-limiting disease. However it becomes of paramount importance to stop the progression of the disease in patients who are not getting recovered and deteriorate. Control of the exaggerated cytokine production is seemingly an effective modality for such patients. Mw was found to be rapidly effective in the COVID-19 resulting in faster discharge within 10 days. The use of Mw in these patients was found to be extremely safe. The larger randomized controlled trials are recommended to generate data on larger population.

References


pneumothorax, pneumomediastinum, and pneumopericardium, even in absence of mechanical ventilation.

Alveolar Air leak comprising Pneumothorax, pneumomediastinum and subcutaneous emphysema have been known complications of organizing pneumonias\(^2\). These complications have been observed in the context of COVID-19 pandemic also. The exact mechanism and management guideline has not been established yet. We aim to demonstrate few cases of “Alveolar Air leak Syndrome” which could enable researchers new insight of this complication and possible preventive or management strategy.

Here we review the incidence and outcomes of 10 cases with alveolar air leaks either pneumothorax / Pneumomediastinum / Pneumopericardium or Subcutaneous Emphysema in moderate to severe COVID-19 patients admitted to our institution.

### Methods

We conducted a retrospective review of patients admitted with moderate to severe COVID-19 disease at our tertiary hospital between June 1 and 25th September 2020. During this period we managed 670 patients with COVID-19. There were 419 cases with moderate to severe disease as per the Indian Council of medical research guidelines. Their diagnosis was based on rapid antigen testing (RAT) or polymerase chain reaction (PCR) testing of nasopharyngeal swab sampling. All patients had a routine chest x-ray on admission. The presence of alveolar air leak – Pneumothorax/pneumomediastinum/pneumopericardium/subcutaneous emphysema was based on an audit of clinical documentation and chest radiographic imaging. Patients who had an air leak at any time during their management course were thoroughly reviewed. Baseline laboratory parameters including inflammatory markers C-reactive protein (CRP), lactate dehydrogenase (LDH), Ferritin, D-dimer, Interlukin-6 were documented for each patient. The incidence of pulmonary leaks in COVID-19 patients was then calculated.

### Results

During the audit period, we reviewed over 670 patients, admitted with confirmed COVID-19 pneumonia. Out of these 419 patients required intensive care for moderate to severe disease. Ten patients developed Pneumothorax / pneumomediastinum / pneumopericardium or subcutaneous emphysema - referred as Air leak syndrome; the incidence of alveolar air leak was found to be 2.39%. The characteristics of these patients are summarized in Tables 1 and 2.

### Case 1

A 46-year-old male with a background of Diabetes presented...
with a week’s history of fever followed by breathlessness. He required oxygen supplementation with nasal cannula eventually needing noninvasive ventilation.

He received broad spectrum antibiotics, corticosteroids, low molecular weight heparin, Remdesivir, convalescent plasma and off label Tocilizumab. A week later, the patient developed worsening hypoxia, A CT Pulmonary angiogram was done to rule out possible Pulmonary Embolism but demonstrated a large Pneumomediastinum (Figure 1). Patient developed intractable respiratory failure and died despite providing resuscitative measures.

Case 2

A 62-year-old hypertensive female presented with 5 days history of fever followed by breathlessness. She required oxygen supplementation with high concentration mask.

She received broad spectrum antibiotics, corticosteroids, Remdesivir, convalescent plasma and low molecular weight heparin. Patient was being weaned off oxygen when she developed acute chest pain and breathlessness. A CT scan of thorax was done along with cardiac investigation. The CT Thorax showed Pneumomediastinum (Figure 2). Positive pressure ventilation was avoided, and patient was managed conservatively. She was discharged after a week with complete resolution.

Case 3

A 60-year-old male was referred to our Hospital as difficult to wean off oxygen, after being managed with broad spectrum antibiotics, corticosteroids, anticoagulants, Remdesivir. A CT scan of thorax was done which showed a small Pneumomediastinum (Figure 3). Patient was managed conservatively on high flow nasal cannula and recovered after a long course of Hospitalization.

Case 4

A 61-year-old Diabetic male presented with a history of fever followed by breathlessness. He required oxygen supplementation with non invasive ventilation. He received broad spectrum antibiotics, corticosteroids, Remdesivir, DVT prophylaxis and convalescent plasma.

Patient had a stormy stay in the hospital eventually needing mechanical ventilation. An HRCT Thorax was done which showed an extensive Pneumomediastinum and subcutaneous emphysema (Figure 4). Patient developed multiorgan failure and died despite providing resuscitative measures.

Case 5

A 64-year-old male with a background of Chronic Obstructive Pulmonary Disease and Diabetes presented typical symptoms. He developed type II respiratory failure requiring Bilevel Positive Pressure support with an IPAP of 16 and EPAP of 6 cm of water.

Two days later he developed acute hypoxia, a chest X-ray was done which showed a right sided Pneumothorax (Figure 5). An intercostal chest drain had to be inserted. He had to be intubated and put into mechanical ventilation. Patient developed multiorgan respiratory failure and died despite providing resuscitative measures.

Case 6

A 63-year-old female with a background of Diabetes was referred to our center as a case of severe hypoxia, a chest X-ray was done which showed a right sided Pneumothorax (Figure 5). An intercostal chest drain had to be inserted. He had to be intubated and put into mechanical ventilation. Patient developed multiorgan respiratory failure and died despite providing resuscitative measures.
Case 7

A young 37-year-old male with a severe COVID-19 pneumonia was referred to our center with difficulty to wean oxygen. He required Noninvasive ventilation with 12/8cm support for a long period of time. He then developed acute decompensation; a chest X-ray was done which showed a left tension pneumothorax. An intercostal chest drain (ICD) had to be inserted. The collapsed lung took a long time to re-expand and he had to be discharged with ICD in situ.

Case 8

A 70-year-old Diabetic male presented with fever, cough, and breathlessness. He required oxygen supplementation with high concentration mask. He received broad spectrum antibiotics, corticosteroids, Remdesivir, convalescent plasma and LMWH. Patient was being weaned off oxygenation when he developed acute onset chest pain and breathlessness. She developed rapid subcutaneous emphysema extending up to the neck area. Her Chest X-ray revealed extensive subcutaneous emphysema with pneumomediastinum (Figure 6). Patient developed intractable respiratory failure and died despite providing resuscitative measures.

Case 9

An 81-year-old retired Physician male presented with a history of acute decompensation following fever. He required oxygen supplementation with non invasive ventilation. He received broad spectrum antibiotics, corticosteroids, Remdesivir and convalescent plasma.

Patient had a stormy stay in the hospital eventually needing mechanical ventilation for refractory respiratory failure. He was ventilated as per ARDS-Net protocol and needed PEEP below 10 cm of water. Just a day after intubation, he developed massive subcutaneous emphysema (Figure 9). An HRCT Thorax was done which showed an extensive Pneumomediastinum with small pneumothorax and subcutaneous emphysema. Patient developed multigorgan failure and died despite providing resuscitative measures.

Case 10

A 54-year-old male admitted as case of severe COVID Pneumonia and ARDS. He had a long course. In the ICU and was discharged after 3 weeks with significant recovery. He returned within few hours to the emergency with acute left sided chest pain. A CT Thorax done, showed left sided pneumothorax (Figure 10). An emergent Chest drain was done and patient was managed for a week more in the ICU. He was discharged in stable condition after a good recovery.

Discussion

Patients with COVID-19 disease can progress to severe Pneumonia and acute respiratory distress syndrome (ARDS). Their infection is characterized radiologically by ground glass opacities mostly peripherally placed progressing into consolidations and then in later stages to Organizing pneumonia/fibrosis. Organizing pneumonia (OP) first described by Davison and Epler et al. in the 1980s is a clinicopathologic pattern of lung injury characterized by the filling of alveoli and alveolar ducts with spindle-shaped fibroblasts and myofibroblasts that later form granulation tissue.3

Organizing pneumonias and its histological variant, acute fibrinous organizing pneumonia (AFOP) were commonly recognized during the severe acute respiratory syndrome (SARS), Middle East respiratory syndrome (MERS) and H1N1 viral pandemics.4

Alveolar air leak comprising of pneumothorax, pneumomediastinum, and subcutaneous emphysema have been presenting feature of Organizing pneumonia.5 A similar spectrum of complications is being observed in patients with COVID 19 infections as per many reports published world over.6 Aiodfi et al reported a couple of persistent pneumothorax in COVID-19 pneumonia patients while on mechanical ventilation.7 There are also case reports wherein patients have developed Pneumothorax/Pneumomediastinum/subcutaneous emphysema when spontaneously breathing or not on mechanical ventilation.8 9

In this case series we observed that Ten patients with COVID-19 pneumonia developed air leaks out of four hundred odd cases with moderate and severe disease; the incidence of 2.39% is much higher than what has been recently reported in the literature.10

Although over 30 million confirmed cases of COVID-19 worldwide, patient management recommendations are not very clear. It was widely known that respiratory failure in patients with COVID-19 infection was due to pneumonia progressing to ARDS; hence many moderate to severely ill patients receive noninvasive and invasive ventilation with high positive end-expiratory pressure (PEEP). High-flow oxygen therapy may be a safer alternative to avoid the potential complications of positive pressure ventilation in these types of patients.

In several COVID-19-ARDS cases, severe hypoxemia along with preserved lung compliance was observed, prompting to Atypical ARDS Syndrome and micro-vascular obstructive thrombo-inflammatory syndrome hypothesis.10 Our observations of air leaks without an obvious barotrauma supports emerging theories of lung damage in SARS Co-V2 infection.

In infections like COVID-19, the virus can infect both type I and II pneumocytes which results in the breakdown of alveolar membrane integrity.11 Viral infections can cause an increase of alveolar pressure due to violent coughing and eventually causing alveolar damage. Selective overdistention of the alveoli owing to mucus impaction, inflammation...
and consolidative phase of COVID-19 pneumonia can lead to alveolar rupture.

The mechanism of alveolar leak in organizing pneumonia is a ball valve effect by localized plugs of fibrous tissue in bronchiolar lumen causing alveolar hyperinflation and resultant rupture. Another possible triggering mechanism is severe coughing seen commonly in patients with COVID-19 disease. Coughing may increase the leakage of air out of the alveoli by leading to sudden lengthening followed by shortening of the pulmonic vessels, associated bronchus during respiration, further moving the “train of bubbles” into the vascular sheaths.  

COVID-ARDS healing with organizing pneumonia might be a possible pathological condition underlying alveolar leak and we suspect this mechanism to be playing the key role in alveolar air leaks. There is need for more research to determine the pathological mechanism of hypoxemia in COVID-19 patient to enable better ventilation strategies.  

After the RECOVERY trial role of steroids in management of COVID-ARDS has been established with mortality benefits. This finding would tilt the mechanism of the disease in the favour of organizing pneumonia, which responds well to steroid treatment.

We also observed rise in inflammatory markers like CRP, LDH, Ferritin, D-dimer, and IL-6 levels in almost all patients in our study. However, there was no correlation with mortality or alveolar leak syndrome to the level of inflammatory markers. Patients in our study did not have a consistent trend of high inflammatory parameters unlike those seen in recently published works. In conclusion, pneumonia and pneumomediastinum, Pneumopericardium or subcutaneous emphysema are possible complications of COVID-19 pneumonia, causing acute decompensation that can worsen the prognosis of patients. 

Learning Points
1. Pneumomediastinum, pneumopericardium, pneumothorax or subcutaneous emphysema may be a possible cause of sudden deterioration in COVID patients.
2. COVID-pneumonia—ARDS—Acute fibrinous Organizing pneumonia might be a most likely course of disease, although it needs further biopsy/autopsy studies and research.
3. Avoiding any kind of high PEEP and use of HFNO or other high-low oxygen devices might prevent alveolar-air-leaks and may improve the outcome in COVID-ARDS.

References
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Demographic Characteristics, Outcome and Complications of Renal Transplantations at a Tertiary Care Center in South India

Vijoy Kumar Jha1*, Debasish Mahapatra1, Anantharam Jairam2, Vishal Singh1

Abstract

Background: Renal transplantation is the treatment of choice for selected patients with end-stage renal disease. In this study, we present our experience and follow up data of renal transplantations done at this center with special emphasis on demographic characteristics, outcome and its complications.

Materials and Methods: All those patients who underwent renal transplantations and had been followed up at this center were studied and their details were recorded. For living donor transplantation, donor and recipient were evaluated in detail. Graft loss was defined as the patient became dialysis-dependent or underwent second renal transplantation.

Results: A total of 250 renal transplantations were done during the study period. 16.4% of total transplantations were cadaveric transplants. Recipients mean age was 38.5±11.64 yrs and donor mean age was 42.25 ±10.79 yrs. The majority of the recipients were male (72.4%) while female donors were predominant among living donors (59.3%). Mean graft survival time was 98.2 months (95% confidence interval [CI]:72.2-114.4). Mean patient survival time was 104.5 months (95% confidence interval [CI]:82.4-126.2).

Conclusion: There is increasing no. of cadaveric renal transplants due to well established deceased donation programs in the state. Our patient and graft survival are comparable. Most of the immediate graft loss was due to acute rejection and late graft loss was due to chronic antibody-mediated rejection.

Introduction

Renal transplantation is the treatment of choice for many people with end-stage renal disease (ESRD).1-4 The living renal transplantation program in India has evolved in the past 45 years and is the second-largest program in numbers after the USA at present.5 The first successful live donor renal transplant in India was done at CMC Hospital, Vellore in January 1971.6 The first renal transplantation in an Armed Forces Hospital was done on 11 Feb 1991 at INHS Asvini, Mumbai.7 Subsequently, the renal transplantation program started in Army Hospital Rand R New Delhi in May 1991.8 In our center, the first live related renal transplantation was done on 01 Jun 1998. Though renal transplantation in this center started late, the hospital completed 250 renal transplantations in Oct 2019 and is the third leading renal transplantation center among armed forces hospitals.

In this study, we present our experience and follow up data including patient and graft survival of renal transplantations done at our center and also the evolving evaluation protocol and immunosuppression regimen over the years.

Materials and Methods

All the renal transplantations from June 1998- Oct 2019 done at this hospital were included in the study and their follow up details were recorded.

This center performs both cadaveric or living-related/unrelated donor transplantation. All the live donations were emotionally related and altruistic and were as per the Human Organ Transplantation Act 1991 and Transplantation of Human Organs and Tissue Rules, 2014. For living donor transplantation, donor and recipient were evaluated in detail as for their cardiac status, lung condition, psychiatric conditions, occult dental infections/diseases, gynecological conditions, premalignant conditions, tuberculosis, and other organ involvement. The urological evaluation was done before transplantation. The cutoff DTPA GFR taken for a renal donor was 80 ml/min. HLA typing and CDC cross-match of both donor and recipient were being done. In high-risk patients, a single antigen bead- donor-specific antibody was being done. Viral screening for HIV, Hepatitis B and Hepatitis C was being done.

As per our center protocol immunosuppression protocol was started two days before renal transplantation. Induction was by Simulect (Basiliximab)-20 mg on Day 0 and Day 4 in case of living donor transplantation except in high-risk cases in which injection rabbit Anti thymocyte globulin (Thymoglobulin) was used. In the initial few transplantations, no induction agents were used. In cadaveric transplantation injection rabbit anti-thymocyte globulin was used in 3mg/kg total doses over 3 days. Mycophenolate mofetil was used in the dose of 2 gm/day if weight >50 kg and 1500mg /day if weight remained <50 kg. Those patients who were intolerant of mycophenolate mofetil or having severe gastrointestinal complaints were switched to azathioprine. All the patients received cytomegalovirus prophylaxis for an initial 3 months and pneumocystis jiroveci prophylaxis for 1 year. Patients were being followed up twice a week for the initial three months

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Table 1: Early (< 1 month) fatal complications and graft loss

<table>
<thead>
<tr>
<th>Early fatal complications – No.(percentage)</th>
<th>No of recipients (percentage)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Acute coronary syndrome</td>
<td>2/0.8</td>
</tr>
<tr>
<td>2. Septicemia /Pneumonia</td>
<td>3/1.2</td>
</tr>
<tr>
<td>3. Disseminated mucormycosis</td>
<td>1/0.4</td>
</tr>
<tr>
<td>4. Unknown</td>
<td>2/0.8</td>
</tr>
<tr>
<td>Total</td>
<td>8/3.2</td>
</tr>
</tbody>
</table>

Early graft loss (Patient remained/became dialysis dependent within 1 month)

| 1. Acute antibody-mediated rejection          | 5/2.0                        |
| 2. Acute antibody-mediated rejection +vascular rejection | 10/0.4                    |
| 3. Nonfunctioning of cadaver graft           | 2/0.8                        |
| 4. Graft artery thrombosis                   | 2/0.8                        |
| 5. Graft mucormycosis leading to graft nephrectomy | 1/0.4                     |
| Total                                       | 11/4.4                       |

Table 2: Nonfatal complications without graft loss up to 1 yr post-renal transplant

<table>
<thead>
<tr>
<th>Non-fatal complications up to 1 yr post-renal transplant</th>
<th>No of recipients (percentage)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Acute cellular rejection</td>
<td>28 (11.2)</td>
</tr>
<tr>
<td>2. Acute antibody-mediated rejection</td>
<td>6 (2.4)</td>
</tr>
<tr>
<td>3. Urinary tract infections</td>
<td>46 (18.4)</td>
</tr>
<tr>
<td>4. Acute tubular necrosis</td>
<td>32 (12.8)</td>
</tr>
<tr>
<td>5. Bacterial pneumonia</td>
<td>12 (4.8)</td>
</tr>
<tr>
<td>6. Pneumocystis jiroveci pneumonia</td>
<td>2 (0.8)</td>
</tr>
<tr>
<td>7. Cytomegalovirus infection</td>
<td>8 (3.2)</td>
</tr>
<tr>
<td>8. BK Virus nephropathy</td>
<td>2 (0.8)</td>
</tr>
<tr>
<td>9. Fungal Infections</td>
<td>2 (0.8)</td>
</tr>
<tr>
<td>10. Varicella-zoster infection</td>
<td>2 (0.8)</td>
</tr>
<tr>
<td>11. Post-transplant diabetes mellitus</td>
<td>31 (12.4)</td>
</tr>
<tr>
<td>12. Wound infections/dehiscence</td>
<td>18 (7.2)</td>
</tr>
<tr>
<td>13. Post-transplant erythrocytosis</td>
<td>21 (8.4)</td>
</tr>
<tr>
<td>14. Pulmonary tuberculosis</td>
<td>5 (2.0)</td>
</tr>
<tr>
<td>15. Disseminated tuberculosis</td>
<td>3 (1.2)</td>
</tr>
</tbody>
</table>

Table 3: Long term complications

<table>
<thead>
<tr>
<th>Long term complications (Complications persisting more than 1 year or occurring after 1-year post-renal transplant)</th>
<th>No of recipients (percentage)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Acute rejection</td>
<td>18 (7.2)</td>
</tr>
<tr>
<td>2. Urinary tract infections</td>
<td>12 (4.8)</td>
</tr>
<tr>
<td>3. Recurrence of glomerular disease</td>
<td>19 (7.6)</td>
</tr>
<tr>
<td>4. Bacterial pneumonia</td>
<td>4 (1.6)</td>
</tr>
<tr>
<td>5. Pneumocystis jiroveci pneumonia</td>
<td>1 (0.4)</td>
</tr>
<tr>
<td>6. Cytomegalovirus infection</td>
<td>2 (0.8)</td>
</tr>
<tr>
<td>7. Varicella-zoster infection</td>
<td>3 (1.2)</td>
</tr>
<tr>
<td>8. Post-transplant diabetes mellitus</td>
<td>12 (4.8)</td>
</tr>
<tr>
<td>9. Chronic active antibody-mediated rejection (CABMR)</td>
<td>4 (1.4)</td>
</tr>
<tr>
<td>10. Post-transplant erythrocytosis</td>
<td>11 (4.4)</td>
</tr>
<tr>
<td>11. Pulmonary tuberculosis</td>
<td>3 (1.2)</td>
</tr>
<tr>
<td>12. Disseminated tuberculosis</td>
<td>2 (0.8)</td>
</tr>
<tr>
<td>13. Malignancy – Breast carcinoma-1 Disseminated Carcinoma prostate-1</td>
<td>2 (0.8)</td>
</tr>
</tbody>
</table>

and this was mandatory for all patients.

Graft dysfunction was defined as a rise in serum creatinine by 25% above the baseline. After ruling out the obvious causes in the form of infections, calcineurin inhibitor toxicity, all patients with an acute rise in serum creatinine were subjected to graft biopsy. Patients with slowly rising serum creatinine were also screened for Cytomegalovirus infection, BK virus infection, tuberculosis, and other occult infections. Graft loss was defined as the patient became dialysis-dependent or underwent second renal transplantation.

Statistical Analysis

Patient data were first entered on Microsoft Excel 2013 spreadsheet. The descriptive analysis was first done. The data were imported to the MedCalc statistical program for analysis (Medcalc software byba version 16.1USA). Data are presented as mean ± standard deviation unless otherwise specified. The confidence interval was 95%. Details of patients remaining at various time intervals have been provided along with survival graphs.
Renal transplantation in developing countries like India depends largely on living donor transplantation. Cadaveric renal transplantation is still infrequent in India, constituting 2-5% of the total renal transplants. This center has done 41 cadaveric renal transplants which constitute 16.4% of total renal transplantations. Men are more likely than women to receive a kidney transplant (72.4% vs 27.6%) and are less likely to donate (40.6% vs 59.4%). In one Indian study in living donor renal transplantation, out of 682 recipients, 606 (88.9%) were males and 76 (11.1%) were females (P<0.0001) and among the donors, there were 451 (66.1%) females and 231 (33.9%) males (P<0.001). In the spousal group (26.71%), the greatest gender disparity was observed with predominantly wives donating for their husbands (73.21% vs 26.71%). This trend was evident in data from other centers in India where wives constitute about 90% of all spousal donors. The majority of the living donors were genetically related constituting 67.4% of the study population. 32.53% of all living donors were genetically unrelated, predominantly the spouse (82.35%) and wife donating 60.29% of all unrelated renal transplants. The long term survival rates for both spouse and living unrelated transplants are essentially the same and similar to that of parent donor grafts in a study of 2500 living unrelated donor transplants performed in the United States.

Till 2009-2010, all our patients received steroids, cyclosporine, and azathioprine. From 2010, the immunosuppressive regimen consisted of steroid, tacrolimus and mycophenolate mofetil. Among kidney transplant recipients, tacrolimus is more effective than cyclosporine at lowering the rate of acute rejection. Overall, allograft and patient survival rates are similar with two agents. Mycophenolate mofetil as an antimetabolic agent has substituted azathioprine, based upon multiple large trials and meta-analysis showing lower acute rejection rates, and possibly improved graft survival with mycophenolate mofetil. Our acute graft rejection rate of 2.4% within 1 month and 13.6% within 1 yr post-renal transplantation is similar to the rate of other centers using tacrolimus based immunosuppression. 78.2% of our patients were on tacrolimus while 28.6% of our patients were on cyclosporine as maintenance immunosuppression in our study.

Fig. 2: Graft Survival and patient survival probability

Discussion

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Chronic allograft nephropathy is the second most common cause of allograft failure after the most common cause, death with a functioning graft. In our study also, chronic rejection is the most common cause of graft loss followed by the recurrence of glomerular disease. The cumulative proportion of graft survival and patient survival were comparable to other studies from India. Mean graft survival time was 98.2 months (95% confidence interval [CI]:72.2-114.4) and mean patient survival time was 104.5 months (95% confidence interval [CI]:82.4-126.2) in present study. The induction/maintenance immunosuppression, acute rejection and graft/patient survival in different studies including the present study are as in Table 5.

Infections are an important complication leading to death/graft loss in post-transplant patients. Urinary tract infection was the most common infection in 18.4%, followed by bacterial pneumonia in 4.8%. In one Indian study, the most common infections were those of urinary tract (34.5%) followed by viral (31.2%),...
sepsis (15.2%), mycobacterial (9.7%) and fungal (6.2%).27 From April 2017 a total of six ABO-incompatible renal transplantation has been done till now. All the patients underwent antibody depletion with Adsopack immunoadsorption column. There were two episodes of acute rejection that responded to methylprednisolone therapy. There was no patient and graft loss in the ABO-incompatible transplant subgroup. The mean serum creatinine in this subgroup, at the last follow up was 1.4±0.3 mg/dl.

Limitation of the study: This is a retrospective study with a large no of patients who lost to follow up at this center. Patient survival and graft survival were measured from the present period of study.

Conclusion
Renal transplantation in this center has evolved over the last two decades and is currently the third-largest transplantation program among armed forces hospitals. There is increasing no. of cadaveric renal transplants due to well established deceased donation programs in the state. Though the sample size is small, the patient and graft survival is comparable to other studies. Immediate fatal complications were due to cardiovascular diseases and infections. Most of the immediate graft loss was due to acute rejection and late graft loss was due to chronic antibody-mediated rejection.

References
Study of Association of Metabolic Syndrome and Risk Factors of Nephrolithiasis

Ritu Karoli, Jalees Fatima, Yogesh Karoli, Prem Shanker Singh, Zeba Siddiqi, Vaibhav Shukla, Faraz Ahmad Khan

Abstract

Background and Aim: The increasing incidence of nephrolithiasis in recent decades is coinciding with rising epidemic of obesity, metabolic syndrome, and type 2 diabetes. This temporal concordance suggests that a link might exist between these metabolic abnormalities and urinary stone disease. Therefore, the present study was aimed to investigate the association between presence of risk factors of nephrolithiasis and metabolic syndrome.

Methods: In a hospital-based, case control study, hundred patients of metabolic syndrome diagnosed according to IDF criteria and hundred age and matched controls were studied for presence of risk factors of nephrolithiasis.

Results: Patients with metabolic syndrome had significantly higher uricosuria, hypercalciuria, oxaluria and hypocitraturia. The prevalence of risk factors of nephrolithiasis was also higher in patients with metabolic syndrome. The most prevalent was low urinary pH in 40% patients with mean pH of 5.8±1.6. Amongst other factors, 33% had hyperuricemia, 29% had hypercalciuria, 15% had oxaluria, 13% had hypocitraturia and 10% had hyperuricosuria. Significant correlation was observed between risk factors of nephrolithiasis and components of metabolic syndrome.

Conclusion: The present study provides an evidence of association between risk factors of nephrolithiasis and metabolic syndrome and suggests that nephrolithiasis may be a systemic disorder representing the interaction of multiple metabolic derangements. Determining common modifiable risk factors for the development of kidney stones might uncover new preventive strategies.

Introduction

The metabolic syndrome is a compilation of metabolic disarray namely insulin resistance, glucose intolerance, hypertension and dyslipidemia that predispose individuals to the development of type 2 diabetes and cardiovascular disease. It has clinched heightened attention in view of growing incidence. Nephrolithiasis is a common entity and has become a pandemic. The prevalence of nephrolithiasis in the United States is 8.8%, and carries high risk of recurrence after the initial episode, with lifetime recurrence of around 50% and risk of end stage renal disease in around 0.6 - 3.2%. Nephrolithiasis has shown significantly growing incidence in recent times in concordance with increased incidence of systemic disorders such as obesity, metabolic syndrome, coronary artery disease and type 2 diabetes. A higher prevalence of uric acid stones has been described among obese stone formers and in patients with type 2 diabetes mellitus. Idiopathic uric acid nephrolithiasis has been regarded as a renal manifestation of the metabolic syndrome.

There appears some bidirectional relationship between nephrolithiasis and metabolic syndrome as epidemiologic evidence suggest renal stone formation is more common in patients with metabolic syndrome and stone formers have increased prevalence of components of metabolic syndrome. Metabolic syndrome, a cluster of cardio metabolic alterations, causes an increase of urinary acid secretion, thereby lowering the urine pH leading to crystal deposition and stones. In patients with metabolic syndrome, not only the prevalence of uric acid calculi is increased but risk of calcium stone formation also increases with the number of features of the metabolic syndrome, although further studies are needed to disclose the potential mechanisms.

Till date, not much data is available to support a relationship between metabolic syndrome and nephrolithiasis in our populations. Nephrolithiasis is associated with a significant social and financial burden, so appropriate metabolic evaluation of stone formers is warranted in certain situations. We therefore investigated the association of metabolic syndrome with risk factors of nephrolithiasis in North Indian population.

Material and Methods

The present study was carried out in a medical college hospital situated in North India as a case control study, which was conducted between January 2014 to December 2015. In this study, hundred patients of metabolic syndrome as defined by International Diabetes Federation (IDF), aged greater than 18 years were enrolled from medical/endocrine outpatient departments.

The metabolic syndrome was defined according to International...
Diabetes Federation (IDF) criteria, which has been defined as Central obesity (defined as WC ≥94 cm [male], ≥80 cm [female]) and any two of the following:

1. Triglycerides >150 mg/dl (1.7 mmol/L)

2. High-density lipoprotein-cholesterol <40 mg/dl (1.7 mmol/L)

3. Blood pressure ≥130/85 mmHg

4. Fasting plasma glucose >100 mg/dL (5.6 mmol/L).

At enrolment demographic details of the patients were obtained, presence of co-morbidities, all medical, family and personal history was noted. The patients who had history of significant hepatic/renal disease, pregnancy and chronic diarrhea, subjects taking any medications that influence uric acid excretion or those who were taking drugs that could affect mineral metabolism (corticosteroids, diuretics, anticonvulsants, potassium citrate, sodium bicarbonate, allopurinol or febuxostat, alkaliphilic treatment for osteoporosis and/or other metabolic bone disorders) hyperthyroidism, primary or secondary hyperparathyroidism, congenital abnormalities and dysgenesis of the kidneys and of the renal pelvis, major debilitating physical illnesses, including neoplastic disease were excluded from the study. Patients with creatinine clearance < 60 ml/min, prolonged immobilization, were not included.

The study was approved by Institutional Ethics Committee and written informed consent was obtained from all the study participants.

Table 1: Clinical and Anthropometric data of study Participants

<table>
<thead>
<tr>
<th>Variable</th>
<th>Patients with Metabolic syndrome (n=100)</th>
<th>Controls (n=100)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age(years)</td>
<td>47±12.6</td>
<td>44±14.0</td>
<td>0.08</td>
</tr>
<tr>
<td>Male gender</td>
<td>64(64%)</td>
<td>60(60%)</td>
<td>0.6</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>26.1±3.56</td>
<td>25.7±3.33</td>
<td>0.23</td>
</tr>
<tr>
<td>WC(cm)</td>
<td>99.62±8.73</td>
<td>87.8±6.84</td>
<td>0.001*</td>
</tr>
<tr>
<td>Waist/hip ratio</td>
<td>1.2±0.45</td>
<td>0.7±0.45</td>
<td>0.001*</td>
</tr>
<tr>
<td>Systolic BP (mm Hg)</td>
<td>152.6±7.49</td>
<td>148.25±7.56</td>
<td>0.02*</td>
</tr>
<tr>
<td>Diastolic BP (mm Hg)</td>
<td>96±6.4</td>
<td>82±4.3</td>
<td>0.003*</td>
</tr>
</tbody>
</table>

Data is shown as Mean ± SD (Standard deviation); *statistically significant

Table 2: Biochemical parameters of study participants

<table>
<thead>
<tr>
<th>Variable</th>
<th>Patients with Metabolic syndrome (n=100)</th>
<th>Controls (n=100)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>HbA1C (%)</td>
<td>6.9±2.6</td>
<td>5.2±0.85</td>
<td>0.02*</td>
</tr>
<tr>
<td>Total cholesterol (mg/dL)</td>
<td>192±24</td>
<td>178.98±18</td>
<td>0.04*</td>
</tr>
<tr>
<td>HDL-cholesterol (mg/dL)</td>
<td>36.8±8.16</td>
<td>44.85±6.0</td>
<td>0.01*</td>
</tr>
<tr>
<td>Triglycerides (mg/dL)</td>
<td>178.4±34</td>
<td>148.6±30</td>
<td>0.03*</td>
</tr>
<tr>
<td>LDL-cholesterol (mg/dL)</td>
<td>112.8±16</td>
<td>104±12.2</td>
<td>0.2</td>
</tr>
<tr>
<td>Uric acid (mg/dl)</td>
<td>5.8±1.6</td>
<td>3.2±1.56</td>
<td>0.01*</td>
</tr>
<tr>
<td>Creatinine (mg/dl)</td>
<td>1.1±0.4</td>
<td>0.8±0.3</td>
<td>0.5</td>
</tr>
<tr>
<td>Fasting glucose (mg/dl)</td>
<td>119.23±13.09</td>
<td>96.4±12.0</td>
<td>0.02*</td>
</tr>
<tr>
<td>Insulin (µU/mL)</td>
<td>9.28±2.62</td>
<td>6.28±2.12</td>
<td>0.01*</td>
</tr>
</tbody>
</table>

Data is shown as Mean ± SD (Standard deviation); *statistically significant

In all study participants, anthropometric measurements were recorded. Weight was measured in light clothing to the nearest 0.1 kg (using an electronic scale), and height was measured without footwear to the nearest 1 cm on a standardized, wall mounted height board.

Waist circumference (WC) and hip circumference were measured to the nearest 0.1 cm using measuring tape while the subjects were standing. Waist-hip ratio was calculated and WC was measured laterally on the midway between the lowest portion of the rib cage and iliac crest, and anteriorly midway between the xiphoid process of the sternum and the umbilicus at the end of normal expiration. Hip circumference was measured at the maximum circumference of the buttocks. Body mass index (BMI) was calculated as the ratio of the weight (kg) to the square of height (m²). Systolic and diastolic blood pressures were measured 2 times by a physician with the mercury sphygmomanometer and mean was calculated.

Fasting venous blood specimens were taken for glucose, uric acid, insulin, calcium, phosphorus, creatinine, renal, liver and lipid profile.

Urine volume was measured in the 24-hour urine collections, and urinary pH was determined immediately post voiding urine sample with a pH electrode. If pH was less than 5.5 another sample was taken. Urine was kept between 8-12 centigrade degrees after collection avoiding extreme heat or cold, and analyzed for calcium, sodium, potassium, creatinine, uric acid, citrate and oxalate. Analyses in serum and urine were measured using J&J, Ortho-Clinical Diagnostics, VITROS 5600 Integrated System, NJ, USA.

Hypercalciuria was defined as 24 hours of urinary calcium more than 4mg/kg, hyperuricosuria as uric acid excretion > 750 mg/24 h for women, and > 800 mg/24 h for men; hypocitraturia (CIT) as urinary citrate excretion (< 450 mg in men, < 550 mg in women per day and hyperoxaluria (urinary oxalate excretion > 45 mg / d).

Statistical Analysis

All analyses were performed using SPSS version 10.0 for windows. Descriptive statistics were computed for all biochemical variables for each of the diagnostic categories. Categorical variables are reported as number (percentage) and continuous variables as mean ± standard deviation. Between-group differences were compared using chi-square tests for categorical variables and Student’s t-tests, Mann–Whitney U test, or analysis of variance for continuous variables. Relationships between continuous variables were assessed by Pearson’s correlation test. P values were reported for all statistical tests and a value <0.05 was considered significant.

Results

We studied hundred patients of metabolic syndrome, out of which 54% were males and 46% were females. Table 1 summarizes demographic and clinical characteristics of the study participants. Our study also included 100 controls that were matched for age, gender and BMI. The mean age of participants was 47 ± 12.6 years in study group and 44±14.5 years in control group. The biochemical parameters of patients with metabolic syndrome and controls have been shown in Table 2.

Patients with metabolic syndrome had high prevalence of multiple co-morbidities. Hypertension was present in 61%, hypertriglyceridemia in 59%, type 2 diabetes in 48% and participants had low HDL cholesterol in 42 % patients as shown in Table 3.

24 Hour urinalysis which is showing urinary parameters of study participants (Table 4). It demonstrates...
Table 3: Prevalence of Co-morbidities among patients with metabolic syndrome

<table>
<thead>
<tr>
<th>Co-morbidities</th>
<th>Prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetes</td>
<td>48(48%)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>61(61%)</td>
</tr>
<tr>
<td>Hypertriglyceridemia</td>
<td>59(59%)</td>
</tr>
<tr>
<td>Low HDL</td>
<td>42(42%)</td>
</tr>
<tr>
<td>Hyperuricemia</td>
<td>43(43%)</td>
</tr>
</tbody>
</table>

Data is shown as n(%); Hypertriglyceridemia was defined as triglyceride level>150/mg/dl; Low HDL was defined as HDL level<45mg/dl in males and<45 mg/dl in females.

Table 4: 24 hour Urinalysis of study participants

<table>
<thead>
<tr>
<th>Variable</th>
<th>Patients with Metabolic syndrome (n=100)</th>
<th>Controls (n=100)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urine volume</td>
<td>2320±730</td>
<td>2450±940</td>
<td>0.7</td>
</tr>
<tr>
<td>Fasting urine pH</td>
<td>4.5±0.35</td>
<td>6.6±0.45</td>
<td>0.02*</td>
</tr>
<tr>
<td>Uric acid (mg/day)</td>
<td>915.12±58.10</td>
<td>800±46.8</td>
<td>0.01*</td>
</tr>
<tr>
<td>Creatinine (mg/day)</td>
<td>1350±65</td>
<td>1456±42</td>
<td>0.43</td>
</tr>
<tr>
<td>Calcium (mg/day)</td>
<td>410±30</td>
<td>287±24</td>
<td>0.04*</td>
</tr>
<tr>
<td>Sodium (mmol/day)</td>
<td>200.65±12</td>
<td>210.8±18</td>
<td>0.12</td>
</tr>
<tr>
<td>Oxalate (mg/day)</td>
<td>70±5.74</td>
<td>56±5.74</td>
<td>0.01*</td>
</tr>
<tr>
<td>Citrate (mg/day)</td>
<td>550±78.6</td>
<td>658±54.2</td>
<td>0.04*</td>
</tr>
</tbody>
</table>

Data is shown as Mean±SD (Standard deviation); *statistically significant.

Table 5: Prevalence of various risk factors of Nephrolithiasis in study participants

<table>
<thead>
<tr>
<th>Variable</th>
<th>Patients with Metabolic syndrome (n=100)</th>
<th>Controls (n=100)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low Urine pH</td>
<td>40(40%)</td>
<td>23(13%)</td>
<td>0.001*</td>
</tr>
<tr>
<td>Hyperuricemia</td>
<td>33(33%)</td>
<td>10(10%)</td>
<td>0.001*</td>
</tr>
<tr>
<td>Hypercalciuria</td>
<td>29(29%)</td>
<td>12(12%)</td>
<td>0.01*</td>
</tr>
<tr>
<td>Hypercitratia</td>
<td>13(13%)</td>
<td>6(6%)</td>
<td>0.03*</td>
</tr>
<tr>
<td>Hyperoxaluria</td>
<td>15(15%)</td>
<td>7(7%)</td>
<td>0.04*</td>
</tr>
<tr>
<td>Hyperuricosuria</td>
<td>10(10%)</td>
<td>4(4%)</td>
<td>0.08</td>
</tr>
</tbody>
</table>

Data is shown as n(%); *statistically significant.

Table 6: Correlation of components of metabolic syndrome with risk factors of nephrolithiasis

<table>
<thead>
<tr>
<th>Metabolic parameter</th>
<th>Fasting urine pH</th>
<th>Hyperuricemia</th>
<th>Hypercalciuria</th>
<th>Hyperuricosuria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Waist circumference</td>
<td>r= -0.324</td>
<td>r= 0.46</td>
<td>r= 0.544</td>
<td>r= 0.374</td>
</tr>
<tr>
<td>p= 0.01*</td>
<td>p= 0.001*</td>
<td>p= 0.002*</td>
<td>p= 0.01*</td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>r= -0.489</td>
<td>r= 0.38</td>
<td>r= 0.468</td>
<td>r= 0.285</td>
</tr>
<tr>
<td>p= 0.001*</td>
<td>p= 0.02*</td>
<td>p= 0.03*</td>
<td>p= 0.01*</td>
<td></td>
</tr>
<tr>
<td>Impaired fasting glucose</td>
<td>r= -0.424</td>
<td>r= 0.44</td>
<td>r= 0.42</td>
<td>r= 0.36</td>
</tr>
<tr>
<td>p= 0.01*</td>
<td>p= 0.03*</td>
<td>p= 0.01*</td>
<td>p= 0.03*</td>
<td></td>
</tr>
<tr>
<td>Low HDL</td>
<td>r= -0.524</td>
<td>r= -0.174</td>
<td>r= 0.03</td>
<td>r= 0.047</td>
</tr>
<tr>
<td>p= 0.001*</td>
<td>p= 0.097</td>
<td>p= 0.40</td>
<td>p= 0.66</td>
<td></td>
</tr>
<tr>
<td>Hypertriglyceridemia</td>
<td>r= -0.414</td>
<td>r= 0.32</td>
<td>r= 0.198</td>
<td>r= 0.062</td>
</tr>
<tr>
<td>p= 0.001*</td>
<td>p= 0.01*</td>
<td>p= 0.116</td>
<td>p= 0.126</td>
<td></td>
</tr>
</tbody>
</table>

Table 7: Association of risk factors of nephrolithiasis with number of components of metabolic syndrome

<table>
<thead>
<tr>
<th>Variables</th>
<th>Three Components (n=45)</th>
<th>Four Components (n=34)</th>
<th>Five Components (n=21)</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urine pH</td>
<td>5.59±0.5</td>
<td>5.36±0.45</td>
<td>5.12±0.32</td>
<td>0.001*</td>
</tr>
<tr>
<td>Hyperuricemia</td>
<td>5.66±0.52</td>
<td>5.88±0.51</td>
<td>6.24±0.54</td>
<td>0.03*</td>
</tr>
<tr>
<td>Hypercalciuria</td>
<td>319.29±37.86</td>
<td>303.71±37.48</td>
<td>315.03±38.01</td>
<td>0.174</td>
</tr>
<tr>
<td>Hyperuricosuria</td>
<td>878.55±96.29</td>
<td>912.25±103.22</td>
<td>948.2±102.20</td>
<td>0.06</td>
</tr>
</tbody>
</table>

Data is shown as Mean±SD (Standard deviation); *statistically significant.

Discussion

Traditional risk factors for nephrolithiasis include age, gender, ethnicity, nutritional factors and genetic properties.16 The profound escalation in prevalence of obesity, hypertension, diabetes, and metabolic syndrome, appears to be associated with increase in the incidence of nephrolithiasis.17,18 An independent association of nephrolithiasis with all traits of metabolic syndrome has been noted including diabetes, cardiovascular disease, hypertension, and dyslipidemia but no similar study has been done in our patient population as yet. We, therefore investigated the association of metabolic syndrome with risk factors of nephrolithiasis in the present study.

We conducted this study including patients with metabolic syndrome and age-gender matched controls. Important risk factors of nephrolithiasis observed in patients with metabolic syndrome were low urine pH (48%), hyperuricemia (43%), hyperuricosuria (10%) hypocitraturia (13%) and hypercalciuria (29%).

A nationwide study of 30,448 Japanese patients with urolithiasis, confirmed that metabolic syndrome was associated with a significantly increased risk of hypercalciuria, hyperuricosuria, hyperoxaluria, and hypocitraturia, independent of age and sex.19 Higher excretion of calcium, uric acid and oxalate and lower urine pH and citrate excretion have been described in patients with metabolic syndrome by other studies as well.20-21 We observed that fasting urine pH exhibited significant negative correlation with waist circumference, hypertension, fasting glucose, and impaired lipid parameters. Hyperuricemia had shown significant positive correlation with waist circumference, hypertension, impaired fasting glucose and hypertriglyceridemia while hypercalciuria and uricosuria exhibited a positive correlation with waist circumference, hypertension and impaired fasting glucose.

A progressive significant decline in urine pH was observed with increasing number of components in the patients with metabolic syndrome (Table 7). A significant increase in serum uric acid was noted with increasing features of metabolic syndrome. Hypercalciuria and hyperuricosuria also showed an increasing trend with increasing features of metabolic syndrome but had no statistically significant correlation.
and impaired fasting glucose.

The number of metabolic syndrome components seems to be a useful predictor for the risk of kidney stones. The increasing trend in level of each risk factor with increase in the components of metabolic syndrome in the present study could further confirm the association. A population-based cross-sectional study by West et al. including 15,000 participants reported that the presence of 4 or more traits of metabolic syndrome doubled the risk of kidney stones in relation to the absence of the traits.22 The study by Kabeya et al. found that the presence of all 5 traits was associated with a 2.7-fold increase in the risk of kidney stones compared with the presence of 2 or less traits.23 In another study by Liu et al. showed a correlation between nephrolithiasis and metabolic syndrome and its components. The multivariate-adjusted odds ratio (OR) (95% confidence interval [CI]) of metabolic syndrome for nephrolithiasis was 1.318 (1.083-1.604).24

Rendina et al. in a systematic review and meta-analysis concluded that metabolic syndrome-related nephrolithiasis shows peculiar clinical and biochemical characteristics and should be considered a multifactorial systemic disorder needing a multidisciplinary approach for adequate prevention and management.25

Metabolic syndrome has been characterized as the most prevalent cause of uric acid nephrolithiasis. The underlying pathophysiological mechanisms responsible for it are unduly acidic urine and hyperuricosuria. The two principal causes for acidic urine are impaired ammonia NH₃+ excretion and increased endogenous acid production. Renal ammonium production and excretion are regulated by the ambient acid-base environment. Insulin influences these two processes and mechanisms of acid-base homeostasis may be altered in a state of insulin resistance.

The pathophysiologic mechanism of calcium stones is more complex than that of uric acid stones; the mechanism includes low urine volume, hypercalciciuria, hyperuricosuria, hypocitraturia, hyperoxaluria, and the abnormalities in urine pH.27

It is reported that the compensatory hyperinsulinemia as a result of insulin resistance leads to an increase in urinary calcium excretion.29 The studies have showed an association of obesity and insulin resistance and calcium stone disease.30

Considering the above observations and growing incidence of obesity and metabolic syndrome worldwide, our study provides evidence that metabolic syndrome patients are prone for risk factors of nephrolithiasis which can lead to occurrence of nephrolithiasis.

Nephrolithiasis presents as an important and challenging problem and a systemic disorder. Not much data has been available to support a relationship between metabolic syndrome and nephrolithiasis in our population so the present study provides an evidence of association between the two common clinical entities. Limitations of this study are many. Our study has small sample size. We did not study the prevalence of nephrolithiasis in patients with metabolic syndrome. In addition, our study is being a cross-sectional one, could not provide any conclusive causal inference from its findings between risk factors and formation of renal stones. Other limitations of our study are not measuring the ammonium ions and net acid excretion in the urinalysis. Also, we did not control the dietary intake to minimize its effect on hyperuricosuria in the study participants. The recurrence of this disease is quite high, so appropriate metabolic evaluation of stone formers might be needed. Determining common modifiable risk factors for the development of kidney stones might uncover new strategies for treatment and prevention.

Conclusion

Our study shows higher prevalence of risk factors of nephrolithiasis in patients with metabolic syndrome than the controls. A significant correlation was also observed between risk factors of nephrolithiasis and various components of metabolic syndrome.

References


Prevalence and Clinical Correlates of Myositis Specific Autoantibodies in Idiopathic Immune-Mediated Inflammatory Myositis - Results from a Multicentric Cohort (MyoIN) from India

Liza Rajasekhar1*, Vineeta Shobha2, Anitha Narasimhan3, Vasudha Bhat4, SN Amin5, Ramnath Misra6

Abstract
There is a need to understand the clinical and antibody associations in patients with IIM in various ethnicities and geographical areas. Patients who fulfilled Bohan’s and Peter criteria of IIM and seen between October 2017 through Jan 2020 were enrolled in this study at 3 centres. Clinical and relevant laboratory parameters were recorded in a pre designed case record form. MSA and MAA to 16 antigens were performed by line blot assay using Euroimmun (Luebec, Germany) as per manufacturer’s instruction. Of the 150 patients, 13 were juvenile onset. Ninety sera had either one MSA or MAA. Sixty sera had neither MSA/MAA. anti-Ro 52 were the commonest antibody and anti-Mi-2a and b the commonest MSA. Novel associations identified were severe myositis with anti-Ro 52, cutaneous ulcerations with anti-MDA5 and anti-PM-Scl and calcinosis with anti-PM-Scl. One-third sera had no MSA or MAA. Larger sample size and use of antibody assays together with muscle biopsy will improve subtyping and phenotype associations in IIM.

Introduction
Immune-mediated inflammatory myositis (IIM) is a heterogenous group of rare multisystem disorder predominantly affecting skeletal muscles and often affecting the skin, joints, and lungs. Their sera often have antibodies designated muscle-associated autoantibody (MAA) or muscle-specific autoantibody (MSA). Over the last three decades, these autoantibodies are being increasingly used to classify IIM into phenotypic and prognostic subgroups and to predict outcome or therapeutic response. Substantial overlap exists between various clinical phenotypes and autoantibody presence. Earlier, their detection methods were complex and were time and labour consuming such as immunoprecipitation and immunodiffusion. With the availability of ELISA and line immunoblot assays, MAA/MSA are being increasingly used in day-to-day clinical practice. Yet, the recent EULAR/ACR classification for criteria for adult and juvenile IIM1, could use only anti Jo-1 as a criteria since not enough data was available for other autoantibodies. There is uncertainty whether MSA/MAA assays would truly prove to be useful as diagnostic or prognostic tools in the long term. Presence of these autoantibodies in the normal and the non-IIM population and determination of appropriate cut-offs to balance sensitivity and specificity also needs attention.

Genetic and or environmental factors impact the clinical phenotype and the autoantibody distribution of IIM2. There is a difference of opinion if these MSA/MAAs are truly mutually exclusive, and that the distinct or unique clinical features are probably not sacrosanct. There is only one published report from North India of MSA and MAA occurrence in patients with India which studied earlier targets (Jo-1, PL-7, PL-12, Mi-2, SRP) with increased prevalence of antibodies to Mi-2 as DM was the predominant subtype. There is an urgent need to clarify the extent and scope of clinico-serologic association in IIM and to establish its prevalence and consistency in various ethnicities and geographic regions across the world. Current study was undertaken to describe the prevalence of extended profile MSA and MAAs in IIM cohorts collected from across India and to study their clinical associations.

Patients and Methods
Patients who fulfilled Bohan’s and Peter criteria of IIM and seen between October 2017 through Jan 2020 were enrolled in this study at 3 centres, two of them tertiary teaching referral centres and one specialist clinic. Consecutive patients were enrolled into MyoIN cohort3 as inception cohort (newly diagnosed) or prevalent cohort. Overlap with connective tissue disease and cancer associated myositis were considered if they met their respective clinical criteria. Those with muscular dystrophy, metabolic myopathy or neurogenic myopathy were excluded. Clinical and relevant laboratory parameters were recorded in a pre-designed case record form and data was entered into the Microsoft

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Received: 06.10.2020; Accepted: 20.11.2020
Access database developed for this purpose. Electromyography (EMG) was performed in all cases but muscle biopsy was undertaken as per physician’s investigator discretion. Interstitial lung disease (ILD) was diagnosed based on HRCT and or restrictive physiology in presence of dry cough or dyspnoea. Antinuclear antibody assay was performed by IIF on the Hep-2 cell line in 1:100 dilutions. MSA and MAA to 16 antigens were performed by line blot assay using Euroimmun (Luebec, Germany) as per manufacturer’s instruction. These antigens were Mi-2α, Mi-2β, TIF-1γ, MDA5, NXP-2, SAE1, Ku, PM-Scl100, PM-Scl75, Jo-1, SRP, PL-7, PL-12, EJ, OJ, Ro-52. Results were categorised as 0–5 (neg), 6-10 (borderline), 11–25 (+) and 26-50(++), strong positive (+++) respectively. In this study antibody positivity was defined by a blot intensity of 25 or more. Correlations between phenotypic features and antibodies and between various antibodies was performed using Pearson’s correlation coefficient, in the SPSS version 20. Correlation of multiple antibodies with clinical features were done using the Kruskal Wallis test. Comparison of multiple group means with ANOVA.

Results

Of the 150 patients, 63 were newly diagnosed (inception cohort) and 87 belonged to the prevalent cohort. These included 13 juvenile onset myositis. The ACR/EULAR score for classification as IIM was applied to 137 adult participants. Sixteen of 137 (11%) adult patients could not meet the ACR/EULAR IIM score criteria for definite or probable myositis.

The demographics, clinical phenotype and MSA/MAA details of the 150 patients are provided in Table 1.

Patients diagnosed with polymyositis were older with a longer duration of follow-up. The Venn diagram (Figure 1) shows the spread and overlap of the MSA/MAAs. Ninety sera had either one MSA or MAA. Sixty sera had neither MSA/MAA. Dual antibodies were identified in 30 patients and 4 had ≥3 autoantibodies.

There was a strong association between anti- Mi-2α, Mi-2β antibodies (p=0.002) and between anti-PM-Scl75 and 100 (p=0.00). antiMi-2α, Mi-2β, MDA5, NXP-2, Ku, PM-Scl100, PM-Scl75, Jo-1, SRP, PL-7, PL-12, Ro-52 all were significantly associated with more than one antibody in 2+ titres. Only anti-TIF-1γ, SAE1, EJ had no association with another antibody. Figure 2 shows the distribution of the intensities of each MSA/MAA.

Table 2 summarises the significant associations between a phenotype and antibodies.

As is evident from Table 2 associations of ILD with ARS, cutaneous ulcerations with anti-MDA5 and DM with anti-Mi-2α and anti-NXP-2 antibodies...
were confirmed. Dermatomyositis was associated with anti-Mi-2α, Mi-2β and NXP-2. Additionally, we discovered an association between dysphagia and anti-Mi-2β anti-TIF-1γ, anti-Jo-1. anti-Ro52 antibodies were associated with worse functional outcome. No association was found between ILD and MDA5. There were too few malignancies and anti-TIF-1γ to derive an association.

Correlation of ANA with MSA/MAA

ANA by IIF at a dilution of 1:100 with an intensity of 2+ and above was positive in 105 of 136 (77.2%). Only anti-Mi-2β correlated with ANA positivity (p=0.00). Cytoplasmic staining was noted in 20/105. In 55 sera with no MSA/MAA, 21 were negative for ANA as well. In the 34 with a positive ANA, the most frequent pattern was nuclear speckled (11/34). Cytoplasmic staining pattern was noted in almost a quarter (8/34).

MSA/MAA negative patients

In 60 patients with no antibodies 27 had DM with 20 having a DM specific rash. In 34 patients ANA were detected. Twenty five of these 60 subjects had undergone a muscle biopsy, 23 had unequivocal evidence of IIM on biopsy in this subset. In two, biopsy was not consistent with myositis. One of them had anti-Jo-1 positive done by ELISA elsewhere and the second patient had elevated CPK and a cytoplasmic speckled ANA with anti-Ro52 positive by ELISA and the rest.

Histopathology

Muscle biopsies were done in 62 patients. Table 3 lists the major findings in the various subtypes of IIM.

Discussion

There is increasing consensus among experts that MSA/MAA define relatively homogenous subsets of IIM4. We present cross-sectional multicentre data of MSA and MAA in 150 patients of IIM from India, using the 16Ag EUROIMMUN line-blot assay which includes the first reports of anti-TIF-1γ, MDA5, NXP-2, SAE1 antibodies. While giving an overview of distribution of MSA/MAA in IIM populations spread across the country, we also report a large subset of MSA/MAA negative myositis patients, a strong association...
reported Indian cohort (23.4%), the Euromyositis cohort (22.2%), Chinese (26.4%) and Japanese (40%) cohorts. It is pertinent to note that all three cohorts used immunoprecipitation, the Euromyositis cohort used [35S]-methionine labelled K562 cell extract, while the Chinese and Japanese cohorts used HELA cell lines. As is now well established, even in our cohort ILD was strongly associated with anti-Jo-1 and anti-PL-7 antibodies.

Polymyositis proportion was higher in the previous cohorts, probably attributable to prevalent understanding of IIM at that time. As we have learnt since the discovery of MSA and recognition of MAA and with the use of muscle biopsy findings of perimysial inflammation and perifascicular atrophy more and more PM can be classified either as DM, OM, IMNM or IBM.

The concept of overlap myositis is evolving from a myositis associated with an established disease like scleroderma or lupus to one where the myositis is accompanied by either a complete disease or an association with one of many clinical feature like Raynaud’s phenomenon or an antibody which can be ANA or a myositis associated antibody like anti-Ro-52 or anti-PM-Scl etc. Two third of our overlap myositis cohort consisted of scleromyositis. Six OM patients (2 SSc, 3 SLE and 1 is Sjogren’s) had one or more MSAs (Mi-2 β, MDA5, SRP, NXP-2, TIF-1γ, PL-7 one each) suggesting that MSA can add value to clinical features to accurately categorise subsets.

In the MSA/MAA negative subset 11 of 25 who had a muscle biopsy had PFA, considered the hallmark of DM. This gives value to muscle biopsy as a tool in subclassification in autoantibody negative patients, at least till the time more antisyntetase or other novel antibodies are discovered or incorporated into assays.

There have been increasing concerns regarding ideal cut-offs and sensitivity for various autoantibodies in the 16Ag EUROIMMUN line-blot assay. Our data (Figure 2) reveals many antibodies (anti-Mi-2α and β, PM-Scl100, anti SRP and anti-Ku were frequently (in more than 10 patients each) positive at lesser titres. In our cohort, 3 patients negative for MSA/MAA had ELISA positive for anti-Jo-1, anti Mi-2α and anti-Ro52.

### Table 4: Comparison of autoantibody prevalence in various IIM cohorts

<table>
<thead>
<tr>
<th></th>
<th>Myosin cohort</th>
<th>Pan Indian</th>
<th>Srivastava</th>
<th>North Indian</th>
<th>Platteel Dutch</th>
<th>Chen, Chinese cohort</th>
<th>Chen, Japanese cohort</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Type of IIM subsets included</strong></td>
<td>DM, OM, PM, ASS, CAM INNM, IBM</td>
<td>150</td>
<td>124</td>
<td>187</td>
<td>145</td>
<td>165</td>
<td></td>
</tr>
<tr>
<td><strong>Age mean (yrs)</strong></td>
<td>40</td>
<td>30.4</td>
<td>62</td>
<td>49.3</td>
<td>51.2</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>ANA pos (%)</strong></td>
<td>77</td>
<td>68.9</td>
<td>ND</td>
<td>NA</td>
<td>NA</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>MSA/MAA (%)</strong></td>
<td>60</td>
<td>73.4</td>
<td>47.1%</td>
<td>16.6%</td>
<td>cannot be compared</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Cut-off intensity levels &gt;25</strong></td>
<td>moderate reactivity</td>
<td>intensity levels &gt;25</td>
<td>IP ELISA (MDA5) Immunoblot</td>
<td>IP ELISA (MDA5) Immunoblot</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>ARS (Jo-1 and Non Jo-1 (%))</strong></td>
<td>14 (10&amp;4)</td>
<td>23(11&amp;12)</td>
<td>18.2(10&amp;8)</td>
<td>27.6</td>
<td>40</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Mi-2 (%)</strong></td>
<td>11</td>
<td>21</td>
<td>7.5</td>
<td>4.1</td>
<td>2.4</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>PM-Scl75/100 (%)</strong></td>
<td>5.3</td>
<td>14.5</td>
<td>12.4</td>
<td>ND</td>
<td>ND</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Ro-52 (%)</strong></td>
<td>30</td>
<td>36.3</td>
<td>NA (excluded)</td>
<td>ND</td>
<td>ND</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>TIF-1γ (%)</strong></td>
<td>4.6</td>
<td>not reported</td>
<td>7.0</td>
<td>5.5</td>
<td>8.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>NXP-2 (%)</strong></td>
<td>4</td>
<td>Not reported</td>
<td>2.1</td>
<td>4.8</td>
<td>3.6</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>MDA5 (%)</strong></td>
<td>4.6</td>
<td>not reported</td>
<td>5.4</td>
<td>36.6</td>
<td>15.8</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>SRP (%)</strong></td>
<td>2.6</td>
<td>not reported</td>
<td>5.9</td>
<td>1.4</td>
<td>7.9</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Ku (%)</strong></td>
<td>5.3</td>
<td>10.5</td>
<td>4.3</td>
<td>0.7</td>
<td>0.6</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>2 antibody pos (%)</strong></td>
<td>20</td>
<td>30</td>
<td>23/119</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Ro Jo correlation</strong></td>
<td>r=0.41</td>
<td>r=0.31</td>
<td>Ro excluded</td>
<td>ND</td>
<td>ND</td>
<td></td>
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</tbody>
</table>

between anti-Ro 52 and anti-Jo-1, and demonstrate that apart from known association of ILD was associated with the anti-synthetase antibodies, anti-Ro-52 was also associated with ILD and severe myositis. Patients with anti MDA5 antibodies had cutaneous ulcerations as did those with anti-PM-Scl, the latter also associated with calcinosis. Of the 90 patients with at least one antibody, in 38% we report the presence of more than antibodies in significant titres.

While Heliotrope rash was associated with anti-TIF-1γ antibodies, Gottron’s papules and sign were associated with anti-MDA5 antibodies. Mechanic’s hands were seen in patients with OM also and ARS antibodies were not more frequent than other antibodies in these patients. Cutaneous ulcerations were almost always associated with the presence of either MSA/MAA, and correlated with presence of anti-MDA5 and PM-Scl75. Of 75 DM patients 65% were MSA negative. We had very few patients with malignancy in our cohort to comment on the association of anti-TIF-1γ with malignancy.

Comparative data of MSA/MAA prevalence from various cohorts is presented in Table 4. The Indian and Dutch studies used the Euroimmun platform however the study comparing the Chinese and Japanese population used IP, IB and ELISA. Anti Ro-52 was the most prevalent antibody in our cohort either alone or in combination with anti Jo-1, which is similar to previous reports.

We report a low prevalence of anti-MDA5 positivity in our cohort. A much higher frequency of 36.6% has been mentioned in recent reports of DM from China, Japan and Mediterranean population of DM (12%). Prior reports from Japan, China, and Korea have demonstrated high mortality and poor prognosis in these cohorts. Despite CPK being only half the patients had a DM specific clinical diagnosis of DM. anti-Mi-2α antibodies were tightly correlated. Of DM than anti-Mi-2β, however both antibodies were associated with a high mortality rate of 28.7%. As expected, cutaneous ulceration correlated with anti MDA5.

As in other cohorts, anti-Mi-2 antibodies were associated with a clinical diagnosis of DM. anti-Mi-2α had stronger correlation with diagnosis of DM than anti-Mi-2β, however both antibodies were highly correlated. Clinical phenotype of anti-Mi-2 is described as classic DM skin rash, good response to steroid resulting in good prognosis. However, in our cohort, only half the patients had a DM specific rash, the majority had poor functional status and very high CPK levels. No association was found with ILD.

The prevalence of anti-aminooacyl t-RNA synthetase antibodies (ARS) of 14% is far lesser than the previously reported Indian cohort (23.4%).
It has been reported and analysed by others\(^8,9\) that we may need different cut-offs for the different antigens present in the line immunoblot.\(^8\) As and when more information is available in this field the antibody-phenotype associations may change. While immunoprecipitation is more specific and sensitive it is not available for routine use. Therefore, understanding the results of line immunoblot in different populations and identifying appropriate titre cut-offs becomes important. A Dutch study,\(^4\) analysed sera of IIM and non-IIM patients using cut-offs identical to our cut-off of ≥25 to define positivity for all autoantibodies. In this study, 18% of even non-IIM sera were MSA positive while 19% of IIM and 12.5% of non-IIM sera had multiple antibody positivity. suggests the need for critical awareness of the sensitivity of the line immunoblot assay.\(^8\)

The EuroMyositis registry reported radiolabelled-immunoprecipitation for 23 antibodies in 1673 sera.\(^7\) In this report, of the 62% sera in which MSAs/MAAs were detected, 85% had a single MSA while MAA was detected in 11%. The only previous report from India is a single centre cohort which evaluated SRP, Mi-2, Jo-1, PL-7, PL-12, EJ, OJ, Ro-52, Ku, PM-Scl70 and PM-Scl100 using similar immunoblot platform with results being reported semi-quantitatively and a ++ intensity being considered positive. From the Indian subcontinent, through our study and the previous Indian study also we report a prevalence of multiple antibodies in almost 30% of patients. In our cohort the antibodies present in isolation were anti-TIF-1γ, SAE1 and EJ.

The 2017 ACR/EULAR criteria has been reported to be less sensitive than the Bohan-Peter criteria.\(^11,12\) In our cohort of 16 patients who did not meet the score for classifying as IIM, 8 had antibodies present in sera, suggesting that adding more antibodies to the laboratory criteria of the ACR/EULAR score will improve the sensitivity of the criteria. Additionally, in the one third of patients, in whom the muscle biopsy variables listed in ACR/EULAR IIM classification criteria were available, it is clear that perifascicular atrophy is often found in patients with clinical features and autoantibody profiles consistent with OM or PM and not restricted to DM.

In our cohort while ANA was positive in 77.2% which is higher than all cohorts in which it is reported, there was no specific correlation between the presence of an MSA/MAA antibody with either presence or pattern of ANA, though a speckled pattern was the commonest pattern though this as has been suggested previously.\(^13\) ANA was positive in half of those who are MSA/MAA negative suggesting the possibility of discovering more antibodies/those not covered by the 16 Ag myositis profile.

**Strengths**

This study derives from a multicentric cohort thus deriving from a population which is not restricted to one geographical area of the country.

**Limitation**

Since this report includes both prevalent and incident patients ongoing immunosuppressive therapy may have modified the titre of antibodies. The need to capture perspectives of experienced physicians in categorising subsets clinically and then looking at whether the antibodies added value resulted in a decision not to validate the clinician diagnosis by an independent observer. Evaluation for ILD/cardiac disease was need based rather than uniform assessment methods across the entire cohort. A comparator non-IIM cohort or normal population was not included.

**Conclusions**

Almost one third of our entire cohort is autoantibody negative thereby suggesting yet unidentified antibodies involved in IIM initiation and perpetuation. MSA are often present in association with MAA. In Indian patients with IIM, ILD is associated with anti-synthetase and anti-Ro-52 antibodies. Cutaneous ulcerations are almost always associated with the presence of MSA/MAA in serum and specifically with anti-MDA5 and anti-PM-Scl antibodies. Dysphagia is associated with anti-Mi-2a, anti-Jo-1 and anti-TIF-1γ antibodies. Calcinosis was associated with anti-PM-Scl antibodies.

The best way forward to truly understand the relative importance of clinical features, autoantibodies and biopsy in clustering subsets of IIM to define treatment and prognosis is to have a cohort with all three accurately recorded and patient followed up longitudinally.

**Acknowledgements**

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**References**

Psychosocial Effects of Isolation on Nipah Virus Infection Suspects during an Outbreak

Shyam Mohan Kannampulakkal¹, Swathy Sheela Sudevan², Harish M Tharayil³, Chandni Radhakrishnan⁴

Abstract

Background and Methodology: Nipah Virus (NiV) belonging to the genus Henipavirus is a biosafety level 4 pathogen with high human to human transmission. Nipah Virus outbreak of 2018 in Kozhikode, Kerala has evoked immense panic and fear in the system. Other viral infections with similar transmission pattern (Ebola, SARS, MERS or COVID 19) also identified with the negative impacts of isolation. This retrospective observational study was planned during November –December 2018 to understand the psychosocial effects among the subjects in Nipah isolation facility. The symptoms of Post-traumatic stress disorder (PTSD) were assessed using the Impact of Events Scale-Revised version (IES-R).

Results and Conclusions: Of the 81 subjects, 73 could be contacted with a response rate of 90.12%. The mean age was 38 years (SD = 15.43) and 13.7% were health care workers. 63% of the subjects experienced fear of death during isolation stay and 12.3% of the subjects had lost their relatives or friends to Nipah infection. The mean IES score obtained was 10.78 (SD: 9.679, range 0-49) and 5 subjects had above the cut off 22. Nipah outbreak had evoked significant psychological disturbances in subjects who remained in isolation with its negative impacts.

Introduction

Nipah Viral infection is included in the WHO published list of top emerging diseases likely to cause major epidemics. Using the prioritization elements as a guide, 7 diseases were identified for urgent action: (1) Crimean Congo haemorrhagic fever; (2) filovirus diseases (i.e. EVD & Marburg); (3) Highly pathogenic emerging coronaviruses relevant to humans (MERS Co-V & SARS); (4) Lassa Fever; (5) Nipah; (6) Rift Valley Fever, and (7) a new disease.¹ Nipah is one among them and this list also includes no 7 as “a new disease” that might emerge at any time. In the current global health scenario, on January 30, 2020, The World Health Organization (WHO) Director-General has also declared another public health emergency of international concern over the global outbreak of novel coronavirus (COVID-19).²

Nipah viral (NiV) infection is a zoonotic disease caused by Nipah virus, an RNA virus belonging to the Henipa virus genus of the paramyxoviridae family. There are two strains of the virus: The Malaysian strain and the Bangladesh strain which differ in their infectivity, clinical profile, and genetic makeup. Studies showed that Nipah virus strain responsible for Kozhikode, Kerala outbreak is close to Bangladesh strain with 96.15% homology.³ Fruit bats of Pteropus genus are the reservoirs of this virus. Humans get the infection directly from bats (as in Bangladesh) or through other infected animals like pigs (as in Malaysia). Human-to-human spread of the infection, through contact with an infected person’s body fluid, was noted in the disease outbreaks in Bangladesh and Siliguri, West Bengal.⁴ Because of this risk of human to human transmission and a very high mortality, NiV infection was associated with lot of fear and stigmatization during and after the outbreak among the affected groups.

There has been three outbreaks in India: A major one occurred in 2001 in Siliguri (case fatality rate; CFR 68%) and an isolated incident happened in Nadia, also in West Bengal, in 2007 (CFR 100%). The average CFR was around 40% in the Malaysian outbreaks and nearly 75% in Bangladesh and India. The incubation period of the illness varies from 4 to 18 days.⁵ The third outbreak in India happened in Kozhikode and Malappuram districts of Kerala state, India during May–June 2018. The CFR of the illness has come to be 91 %.⁶ The outbreak of NiV disease in Kozhikode in May 2018 presented as encephalitis, acute respiratory distress and myocarditis or combinations of these.⁷ The high case fatality rate and risk of human to human transmission raised a panic in the health care system as well as in the natives. Nipah suspects were kept in isolation wards in Government Medical College Kozhikode [GMCK] till confirmed negative by tests for NiV infection or for care in those diagnosed with NiV infection.

Similar isolation techniques had been adopted during the Ebola outbreak in Nigeria in 2014 and the influenza outbreaks in South East Asia. Studies have shown that there had been significant psychological distress in the subjects who were kept in isolation resulting in a negative impact in their quality of life.⁸⁹ With the present study, we aimed to understand the psychosocial impact of the recent Nipah...
outbreak in the subjects who were kept in isolation in GMCK during May –June 2018.

Quarantine is known to bring unpleasant experience in people during COVID 19. A recent review article listed the following stressors during quarantine - longer quarantine duration, infection fears, frustration, boredom, inadequate supplies, inadequate information, financial loss, and stigma. It also highlighted the long lasting effects like post traumatic stress disorder (PTSD) using the Impact of Events Scale-Revised version (IES-R). The IES-R is a self-report measure designed to assess current subjective distress for a specific traumatic life event. Items are rated on a 5-point scale ranging from 0 (“not at all”) to 4 (“extremely”). Responses to 22 items are scored and summed to a maximum score of 88. The IES-R is not meant to be diagnostic. While there is no specific cut-off score, scores higher than 22 are of concern; the higher the score the greater the concern for PTSD with associated health and well-being consequences. The mean score provides an indication of the level of distress related to the stressor. This was found to have a sensitivity of 0.89–1.00 and a specificity of 0.78–0.94 for PTSD symptoms.

Statistical analyses were performed using the statistical software package SPSS V.18.0 for Windows. Continuous data were described as the mean and standard deviation (SD). Categorical variables were displayed as numbers (percentages).

**Results**

The total number of persons isolated was 81 of which 73 could be contacted over the phone and agreed to participate in the study. Eight of the 81 could not be contacted for the following reasons. One expired in that hospitalization due to NiV infection, one was disoriented during the period of quarantine, and the rest six could not be traced from the telephone numbers given in the isolation register. Hence the response rate for this study is 90.12%. All those who could be contacted, were agreed to participate in the study and included.

The mean age was 38 years (SD = 15.43) and 45.2 % were males. Majority of the study participants were having secondary school level education (49.3%), 34.2 % were graduates and 13.7 % had primary schooling. The proportion of post graduates was 2.7%. Of the total sample, 13.7 % were health care workers (HCWs) which included 3 doctors, 3 staff nurses and the rest were paramedical staff. Two subjects had past history of psychiatric illness and 9 had family history of psychiatric illness.

The study subjects had different levels of understanding about the need for isolation. 41.1% opined that isolation was for the protection of the community, 17.8% were of the view that isolation was for the safety of their family members and 8.7% pointed out self-protection as the reason for isolation. The remaining 32.9% attributed to all the three as reason for isolation. 46.6% of the subjects got referred to GMCK from peripheral hospitals via health care workers whereas 53.4% reported by themselves. 12.3% of the subjects in the study group had lost their relatives or friends to NiV infection.

Among the total contacted, 93.2% were having symptoms when reported to the hospital. 16.4% had reported that they faced a delay in transportation to GMCK. 12.3% reported delay in getting tested for NiV infection, whereas 27.4% reported that they encountered a delay in receiving the results. 82.2% of subjects reported that they were not given proper instructions to be followed during isolation. 63% of the subjects experienced fear of death during stay in isolation and firmly believed that “they have contracted Nipah for sure”. 50.7% were worried that they would infect others.

During the stay in isolation ward, the subjects had to address various types of difficulties like difficulty in wearing the mask, non availability of amenities (Table 1).

The most reported emotions during isolation were loneliness (87.3%) and fear (86.3%). After getting discharged and going back to the community, 95% of the subjects reported they were reluctant in revealing that they were Nipah suspects fearing discrimination. 97.3% reported that they were facing some sort of discrimination from the public. 84.9% avoided going to public places for at least 2 weeks. 53% of the study subjects avoided further contact with people having fever. 27.4% were having fear of bats, 68.5% had fear to buy fruits. A significant proportion constituting 95% of the subjects were of the strong opinion that if they had

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**Table 1: Difficulties faced by respondents in isolation ward - N (%)**

<table>
<thead>
<tr>
<th>Difficulty</th>
<th>N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stay alone</td>
<td>35(47.9)</td>
</tr>
<tr>
<td>Wearing mask</td>
<td>46(63)</td>
</tr>
<tr>
<td>Obtaining amenities</td>
<td>36(49.3)</td>
</tr>
<tr>
<td>Communication with relatives</td>
<td>41(56.2)</td>
</tr>
<tr>
<td>Getting updated about NiV</td>
<td>36(49.3)</td>
</tr>
<tr>
<td>Job related</td>
<td>18(24.7)</td>
</tr>
<tr>
<td>Financial problems</td>
<td>23(31.5)</td>
</tr>
</tbody>
</table>
received timely counselling, it would have been a great mental relief.

The mean IES score obtained was 10.78 (SD: 9.679, range 0-49). Five subjects had scored above the cut off 22. There was no statistically significant difference in mean IES scores among HCWs and non-HCWs or among symptomatic and asymptomatic individuals. But the mean IES score was significantly higher in respondents with a history of NiV related death in their dear or near ones (mean=26.22, SD =17.26, p=0.02) when compared with those who did not had that history.

Among the study participants kept in isolation as NiV suspects, only one subject was tested positive and later he had a full recovery. He was one among the two survivors of this outbreak.

**Discussion**

Kerala witnessed an outbreak of NiV infection in 2018 May-June which demanded rapid and effective outbreak response to tackle the situation. The crisis was handled well though the state had no previous experience of a similar situation, promptly curtailing further spread in the community.

Strategies were specifically designed for the purpose of effective contact tracing and preventing further human to human transmission. People who had history of high risk contact with symptoms were kept in isolation, but a few asymptomatic cases were also came in the isolation because of their very close proximity to positive cases or having felt subjective symptoms like feverishness. The high mortality of the outbreak resulted in considerable psychosocial trauma among those kept in isolation as well as in their relatives and friends. The isolation was continued till they were clinically free of symptoms and tested negative.

Two patients were tested positive from the isolation ward, one of them succumbed to the illness and the other was included in this study. The study was aimed at understanding in detail the mental perceptions of the individuals isolated. The conclusions thus gained via this study could be of value in managing infections of similar types having epidemiological link with risk of human to human transmission and high mortality in the future.

The results of present study emphasize the need for addressing the psychological issues during and after isolation, this is as important as screening for the illness among the isolated individuals. This should, ideally be incorporated to the care at the outset itself when an isolation is planned. The primary purpose of quarantine is to prevent transmission of an infectious agent from those who are potentially incubating the disease. The isolation procedures adopted during the Nipah outbreak aimed at reducing the risk of transmission via body fluids or droplets from symptomatic to the healthy individuals as well as the daily monitoring of all the individuals in the isolation facility for symptoms. This could be helpful in rapid and safe medical assessment and timely initiation of treatment if indicated. In our study though the study subjects had different levels of understanding about the need for isolation, majority were of the view that the isolation is for the benefit of the community and almost a similar percentage opined that it is for community as well as for individual benefits. But a small proportion of the study subjects opined that isolation is only for individual benefits. Such people lacking the proper knowledge about the exact indication of quarantine or isolation may continue with their routine social interactions, increasing the chances of transmission. Hence health education and awareness in the right direction is essential.

16.4% of the study subjects had reported a delay in transportation facility to the GMCK. The reasons attributed for this include the lack of proper awareness among the ambulance drivers regarding NiV infection, its mode of spread and the necessary safety precautions to prevent its spread among the general public. During the initial period of the outbreak, more people with the history of contact reported themselves but as the effective infective control measures are implemented and effective communicational messages were provided, the patients coming under the case definition and having symptoms were transferred to the isolation facility in designated ambulances with ensured safety precautions. Initially, most of the ambulance drivers had expressed fear and refusal in accompanying the Nipah suspects and patients to health care facility. Hoax informations about NiV infection circulated in social media platforms added to their insecurities and refusal to work. The hospital had deficiency of enough number of dedicated ambulance vehicles to deal with the unexpected peaking of cases. But the Government authorities identified this challenge and soon a dedicated team of ambulance drivers identified and trained for the purpose within a week and this aborted the crisis towards the later periods of the outbreak. It was suggested that the existing system of ambulance services of the system should be reinforced and backed up effectively by introducing adequate number of vehicles, ensuring that the ambulance staff trained in infection prevention and control to tide over these sorts of situations in future. It is also imperative that the drivers getting trained via awareness classes on the common medical emergencies and basic life support training should have adequate knowledge about infection control and prevention so that such challenges as delay in getting vehicles for proper transfer to hospitals in future similar outbreaks can be avoided.

In the present study, 12.3% of the subjects had reported a delay in getting tested and 27.4% had confronted with delay in getting the results. The NiV infection, being an outbreak with no previous experience for the state and with known risk of human to human transmission having high mortality had raised unprecedented concerns among the healthcare providers too. The health care system was not fully equipped during the maiden phase of the outbreak as it needed definite infection control practices (ICPs) and system change.

This emphasises the need for proper training in an effective manner in handling and processing with proper ICPs and good laboratory practice, for sample collection and testing. In the subsequent days following the presentation of the primary case at GMCK emergency department and declaration of the outbreak, the steps were taken to ensure timely sample collection, testing and providing the results, thus rectifying the initial hurdles and lag period of achieving the skills and implementing the strategies.

82.2% of the subjects were of the opinion that they were not provided the proper instructions to be followed after reaching the hospital. During the period of outbreak, the basic necessary healthcare instructions for the general public were provided by
counselling as a continued service under close follow up. The outbreak 2018 was of an unprecedented scale as it was least expected and system not prepared. At community level, a multipronged approach was instituted for public awareness, social support and breaking the chain of transmission. We recommend such preventive and managerial measures should be instituted for epidemics of similar type with human to human transmission and high mortality. The IES-R score of 22 and above was seen in 5 subjects. Though not diagnostic of PTSD this data states that there were a proportion of people who had prominent psychological distress in the form of symptoms of PTSD. A study by Hawryluck L et al on psychological effects of quarantine of persons in Toronto, Canada reported high prevalence of psychological distress. Symptoms of posttraumatic stress disorder (PTSD) and depression were observed in 28.9% and 31.2% of respondents, respectively. In our study higher IES-R scores were observed in non-health care workers, those who had symptoms at admission and those with death in dear and near ones. This group with death in near ones should receive proactive interventions considering them as a high risk group. The lack of proper awareness about this new disease and misinformation spread in social media could have increased the stress level among the quarantined individuals. The respondents who reported significant distress were advised to attend Psychiatry OPD at GMCK for further assessment and management.

Conclusions

The zoonotic diseases like NIV infection, requires a “one health approach” and the surveillance and outbreak management involves a collective response from a collective animal and human health management approach. This needs successful incorporation of the timely public health response and team work. The results of this study suggest that being in isolation during Nipah outbreak had resulted in significant psychological disturbances in those subjects who remained in isolation. There are several concerns which should be assessed and addressed in individuals who are kept under isolation. These include providing a focussed education of the need for being in isolation, continued psychological and social support and continued community-based psychosocial care. Improved preparation for being in isolation may better or limit the psychological impact of their experience. We also recommend the follow up of all contacts with increased risk of developing psychological distress or disorders for a minimum period of 6 months by mental health professionals, thus speeding up their social rehabilitation. One of the major limitations for the study includes difficulty in contacting all the study subjects over telephone but the response rate was good.

Footnotes

Authors state that they do not have any commercial or other association that might pose a conflict of interest. No financial support received for this study. This paper is not presented in any meetings or conferences. Approved by the Institutional Ethics Committee

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10. Brooks SK, Webster RK, Smith LE, Woodward L, Wessely S, Greenberg N, Rubin GJ. The psychological impact of quarantine and how to reduce it: rapid review of the
Isolated Acute Cerebrovascular Involvement in COVID-19 without Fever and Respiratory Symptoms: An Indian Perspective

Sripadma PV1*, Rajendra Singh Jain2, Arvind Vyas3, Bhawna Sharma2, Trilochna Srivastava2, Sourabh Murarka1, Piyush Saavaliya1, Jitesh Agrawal1, Kaavya Rao1

Abstract

Background: Stroke in COVID-19 has been reported in critically ill patients globally. Stroke as a singular manifestation of COVID-19 in absence of typical symptoms (fever, cough and dyspnea) is under-recognized.

Objective: Comparative study of clinical and laboratory parameters of COVID-19 stroke patients without typical symptoms at onset with stroke cases without COVID-19 infection.

Methods: 28 consecutive stroke patients, eight with coronavirus infection and twenty without COVID-19 admitted to neurology department of a tertiary care centre of North West India between 20 June, 2020 and 19 July, 2020, were enrolled in this retrospective study.

Results: COVID-19 patients had higher frequency of seizures (4 [50%]) vs 2 [10%]; p = 0.03) and altered mental status (6 [75%] vs 6 [30%]; p = 0.04). Severity of ischemic stroke (NIHSS >20, 3 [75%] vs 2 [18%]) and mortality (p = 0.04) despite comparable vascular risk factors for stroke between the two groups was higher in COVID-19 patients. Three out of four COVID-19 young strokes died. Two females with COVID-19 and two females with non-COVID-19 developed fever with dyspnea after a mean delay of 2.7 days (Standard deviation 1.7) from stroke onset. All six patients who developed fever subsequently expired. Inflammatory markers (neutrophil to lymphocyte ratio; p < 0.001 and ESR; p < 0.001), transaminases (p = 0.038) and creatinine (p = 0.009) were significantly elevated in COVID-19 patients.

Conclusion: Isolated cerebrovascular involvement can be a presentation of COVID-19. Stroke severity and mortality is higher in COVID-19 with young strokes being no exemption. Development of fever was associated with clinical worsening. COVID-19 pandemic is far from over in India, such atypical presentations need to be recognized early and warrant stringent diagnostic protocols.

Introduction

COVID-19 pandemic emerged as an outbreak of atypical cases of pneumonia in Wuhan, China in December 2019 and rapidly spread globally affecting more than 10 million people worldwide.1 Swift enforcement of stringent lockdown from March 25, 2020-May 31, 2020 temporarily curtailed the spread of COVID-19 in India.2,3 However, we are now witnessing an exponential surge in COVID-19 cases with gradual easing of lockdown measures. India alone added 26.2% of cases to the global COVID-19 burden last week and currently is the second most affected country in the world.4

The World Health Organization case definition of a suspected COVID-19 patient describes presence of fever, cough and shortness of breath as typical clinical symptoms.5 Neurological manifestations like headache, dizziness, anosmia, taste impairment, cerebrovascular disease, encephalopathy, myositis have been previously reported in COVID-19 patients displaying the classic symptoms of fever and respiratory involvement.6

A recent review from the Global COVID-19 ischemic stroke registry mentions median delay from onset of typical symptoms to stroke as seven days with inter-quartile range of 2-15 days.7 In line with the global literature we had patients at our infectious disease centre with fever, cough who tested positive for COVID-19 and subsequently developed stroke.

Stroke as a singular manifestation of COVID-19 in absence of typical
symptoms is however an uncommon presentation. Herein, we report the clinical characteristics of COVID-19 patients presenting with isolated acute cerebrovascular involvement. Further, we also clinically compared our COVID-19 cases presenting as stroke with COVID-19 negative stroke patients admitted during the same time period. The neurological spectrum of COVID-19 appears to be more diverse in India and merits a closer look.

**Methods**

Sawai Man Singh Medical College and Hospital (SMSMCH) is the largest tertiary care centre of North West India in the state of Rajasthan. This retrospective study was done from 20 June, 2020 to 19 July, 2020 on patients presenting with acute cerebrovascular involvement without any history of fever, cough or dyspnea admitted in the department of neurology at SMSMCH, Jaipur. Acute cerebrovascular involvement included intracranial hemorrhage, and ischemic cerebrovascular disease, diagnosed by clinical history and appropriate neuroimaging.

As per the department protocol all inpatients were subjected to COVID-19 nasopharyngeal swab based reverse transcriptase polymerase chain reaction (RT-PCR) testing within 4 hours of admission. A patient was deemed COVID-19 positive on basis of a positive result in the RT-PCR based assay. Laboratory testing and radiologic assessment (magnetic resonance imaging of brain, computed tomography of head, computed tomography or magnetic resonance angiography and high resolution computed tomography of thorax) were performed for all patients as per their clinical care requirements. All confirmed COVID-19 positive patients were immediately transferred to isolation ward or ICU in infectious disease center of SMSMCH. Written informed consent was obtained from patients or a relative. The study was performed in accordance with the principles of the Declaration of Helsinki.

**Data Collection**

28 consecutive stroke patients, 8 with COVID-19 infection and 20 without the infection were included. Medical, radiologic records and laboratory findings for all patients were systematically reviewed and data collected on age, sex and comorbidities (old stroke, diabetes, hypertension, cardiovascular or chronic kidney disease). Special emphasis was laid on presence of typical symptoms of COVID-19 infection (fever, shortness of breath and cough) at stroke onset. Two certified and experienced neurologists confirmed the neurologic symptoms and a third senior neurologist resolved any disagreement between the earlier reviewers. Ischemic stroke severity was graded using the National Institute of Health Stroke Scale (NIHSS) and intracerebral hemorrhage severity using the ICH score.

<table>
<thead>
<tr>
<th>Table 1: Comparison of clinical characteristics of stroke patients with and without COVID-19</th>
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<tbody>
<tr>
<td></td>
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<tr>
<td>Age (years)</td>
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<tr>
<td>&lt;60</td>
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<td>&gt;60</td>
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<tr>
<td>Sex</td>
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<tr>
<td>Female</td>
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<tr>
<td>Hypertension</td>
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<td>Diabetes</td>
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<td>No</td>
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<tr>
<td>Old Stroke</td>
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<td>Myalgia</td>
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<td>No</td>
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<td>Headache</td>
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<td>Seizures</td>
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<tr>
<td>Altered Sensorium</td>
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<td>No</td>
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<tr>
<td>NIHSS (&gt;20)</td>
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<td>Yes</td>
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<tr>
<td>No</td>
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<tr>
<td>Stroke Type</td>
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<tr>
<td>Ischemic</td>
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<tr>
<td>Hemorrhagic</td>
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<tr>
<td>ICH Score (&gt;3)</td>
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<tr>
<td>Yes</td>
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<tr>
<td>No</td>
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<tr>
<td>Mortality</td>
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<td>Yes</td>
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</tbody>
</table>
Fig. 1: MR DWI (A) Right frontal, left corona radiata and left MCA-PCA watershed acute infarct (B) Left MCA-PCA watershed and internal borderzone acute infarct, infarcts in 1(A) and 1(B) appear athero or cardioembolic, CT Head (C) Right MCA infarct, MR DWI (D) Bilateral cerebellar infarct, CT head and angiography (E & F) Left sylvian fissure SAH with intraventricular extension, left MCA aneurysm, CT head (G) Acute left fronto-parietal-temporal SDH, CT head and MR angiography (H & I) Left capsuloganglionic hemorrhage with normal intracranial angiography, MR DWI (J) Right capsuloganglionic hemorrhage, CT head (K) Left thalamoganglionic hemorrhage, (L) Left capsuloganglionic hemorrhage
Results

COVID-19 pandemic and lockdown plummeted admission rates in our department by more than 50%. During the study period 31 consecutive patients with acute cerebrovascular involvement were admitted, of these 11 patients were diagnosed with COVID-19. Of the 11 patients, 8 were diagnosed tested positive for COVID-19. Of the 11 patients admitted, of these 11 patients were COVID-19 stroke patients (75%) with critical morbidity and mortality was higher in them compared to non-COVID-19 ischemic strokes (50%) (Figure 1 A,B,C & D). Although COVID-19 patients had ICH score < 3 (75% vs 44.5 %) the morbidity and mortality was higher in them compared to non- COVID-19 hemorrhagic stroke patients. Mortality in COVID-19 patients was significantly higher (6[75%] vs 6[30%]; p= 0.04). They also had more severe ischemic strokes with NIHSS > 20 (3[75%] vs 2[18%]) with a p value tending towards significance (p= 0.07).COVID-19 ischemic strokes included large vessel (50 %) and watershed strokes (50%) (Figure 1 A,B,C & D). 

Table 2: Comparison of salient laboratory parameters of stroke patients with and without COVID-19

<table>
<thead>
<tr>
<th>Laboratory parameter at admission</th>
<th>COVID 19 stroke (N= 8) Median (IQR)</th>
<th>COVID 19 negative stroke (N=20) Median (IQR)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutrophil to Lymphocyte ratio</td>
<td>6.5 (2.2)</td>
<td>3.3 (0.9)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Erythrocyte sedimentation rate (mm/hour)</td>
<td>58 (8.5)</td>
<td>35.5 (13.5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Creatin Phosphokinase (U/L)</td>
<td>624.5 (352)</td>
<td>165(40)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Lactate Dehydrogenase(U/L)</td>
<td>592 (432)</td>
<td>181.5 (44)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Aspartate Aminotranferase (U/L)</td>
<td>68.5 (45)</td>
<td>35 (8.5)</td>
<td>0.038</td>
</tr>
<tr>
<td>Alanine Aminotranferase (U/L)</td>
<td>45(18.7)</td>
<td>40(12)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Urea (mg/dL)</td>
<td>59.5 (27.7)</td>
<td>35.8(7.8)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Creatinine (mg/dL)</td>
<td>1.2(0.8)</td>
<td>0.9(0.3)</td>
<td>0.009</td>
</tr>
</tbody>
</table>

Discussion

With its low case fatality rate (1.8 % versus global average of 3.4%) and high asymptomatic cases India seems to be having a different clinical presentation of COVID-19.14 Distinct viral clades of SARS CoV-2, cross-reactivity with de-novo humoral immunity, vegetarianism, continuance of BCG vaccination are some of the plausible explanations being offered for the low fatality rate with high recoveries in India.15,16 Existing literature is succinct on stroke presenting in patients with severe COVID-19 infection (Table 3). However, there is scant literature on stroke in patients with COVID-19 lacking the typical symptoms. We observed isolated presentation of stroke in COVID-19 at our centre in11 patients over a brief span of 4weeks. All COVID-19 patients presented within 24 hours of onset of neurological ...
symptoms and underwent RT-PCR testing within the first 4 hours of admission. This essentially means that all these patients were infected with COVID-19 at time of stroke.

Further, ischemic stroke severity was higher in patients with COVID-19 (NIHSS > 20, 3(75%) vs 2(18%)) with a poor outcome. Of the four ischemic COVID-19 strokes, two were older than 60 years, 3 patients including one older than 60 years expired. Death of both young ischemic stroke patients despite comparable vascular risk factors and NIHSS with young patients without COVID-19 could be attributable to increased stroke severity and multiorgan dysfunction syndrome associated with COVID-19. Ischemic cortical strokes in COVID-19 patients predisposed to seizures (4 [50%]) vs 2 [10%]; p = 0.03) and contributed to morbidity. In comparison COVID-19 negative stroke patients had both subcortical and cortical strokes with fewer seizures. Altered mental status at admission attributable to predominant cortical involvement was significantly more in COVID-19 cases and associated with increased mortality (8 [66.6%] vs 4 [25%]; p =0.05).

SARS CoV1 &2 viruses use spike proteins on their surface to bind to angiotensin- converting enzyme 2 (ACE2) receptor on mammalian host cells. Reports are now emerging of widespread expression of ACE2 receptors on neurons, astrocytes and oligodendrocytes besides respiratory epithelium, gut, renal and vascular endothelia (17). We speculate that acute cerebrovascular involvement in COVID-19 patients could be mediated via trans-synaptic retrograde neuroinvasion of the virus from peripheral nerve terminals and spread via transcribrial route along the olfactory nerve to the olfactory bulb which has been demonstrated earlier for several coronaviridae. Alternatively, the virus could also gain access across blood brain barrier by direct invasion of vascular endothelial cells which express ACE2 or via the Trojan horse mechanism. Four COVID-19 patients with hypertension (50%) had intracerebral hemorrhage at hypertensive site (Figure 1H, 1J,1K,1L). All except one of them was previously well controlled on single antihypertensive. With hypertension being well controlled, the sudden rise in blood pressure precipitated by cerebral autoregulatory dysfunction could have been triggered by COVID-19 leading to arterial rupture at vulnerable sites affected by chronic hypertensive small vessel vasculopathy. A similar mechanism could have caused aneurysmal subarachnoid hemorrhage in two of our COVID-19 patients (Fig. 1E,1F). Patients with COVID-19 despite lower ICH score had high mortality, likely due to critical illness requiring prolonged ventilator support and an increased risk of other infections (Table 1).

In a retrospective study by Mao et al on 214 COVID-19 patients from Wuhan, China 2.8% had acute stroke. These patients were older with cardiovascular risk factors unlike our patients who were younger but had vascular risk factors. Additionally, smoking from an early age contributes to accelerated atherosclerosis and young ischemic strokes in our population. A study from New York reported ischemic large vessel strokes in young COVID-19 patients similar to this study. Males were more affected with COVID-19 strokes than women (75% vs 25%) with 100% fatality in men. Higher mortality has been observed in men presumably due to different coagulation patterns, smoking, drinking habits and effects of sex hormones on immune regulation. All males (75%) with COVID-19 developed high grade fever after a mean delay of 2.7 days (Standard deviation 1.7) from stroke onset, following onset of fever their clinical course rapidly deteriorated. Onset of fever in these patients could be indicative of ‘cytokine storm’ which inexcorably is associated with high mortality. One COVID-19 patient with acute subdural hematoma and mild thrombocytopenia at admission was treated with cerebral decongestants. On follow up there was no drop in Glasgow Coma Scale or hematoma expansion on computed tomography of head and only masterly inactivity was needed (Figure 1G). Marked thrombocytopenia has been noticed in COVID-19 with severe pulmonary infection. However, our COVID-19 patient had transient mild thrombocytopenia with quick recovery to normal counts over five days. Ultrasound abdomen was suggestive of early chronic liver disease. It is likely that this patient had baseline low platelet counts which worsened with coronavirus infection and recovered as infection subsided. All our COVID-19 stroke patients had lymphopenia with significantly raised neutrophil to lymphocyte ratio, elevated erythrocyte sedimentation rate, transaminases and creatinine consistent with a proinflammatory state in COVID-19. Elkind et al have linked stroke with infection previously, suggesting the possibility that systemic inflammatory response in COVID-19 patients rather than viral invasion predisposed the hosts to stroke. Immunosuppression with heightened inflammatory markers can result in erosion of atherosclerotic plaques predisposing to atheroembolic stroke. COVID-19 patients with myalgia also had elevated creatine phosphokinase and lactate dehydrogenase indicating significant muscle injury. To our knowledge, this is the first report on clinical characteristics of ischemic and hemorrhagic stroke in COVID-19 from India.
Limitations
Firstly, a relatively small sample size in our study may not be a true representation of the pandemic in the general population of India. Second, cerebral angiography was not done for all patients to avoid cross-infection. Third, inflammatory cytokine profile and COVID-19 associated coagulopathy markers were also not studied in detail. Fourth, multivariate logistic regression analysis for predictors of mortality was not done due to small sample size.

Conclusion and clinical implications
Acute cerebrovascular involvement in COVID-19 can occur in absence of typical symptoms. Seizures, altered mental status, more severe ischemic strokes, high neutrophil to lymphocyte ratio and high mortality were noted in COVID-19 strokes. Young with COVID-19 were no exemption to stroke. Development of fever was associated with clinical worsening and mortality. Early recognition of this atypical isolated cerebrovascular involvement in COVID-19 is essential to avoid delays in diagnosis and spread of infection as this pandemic evolves and a vaccine seems to be the only hope in near future.

References
Abridged Prescribing Information: COMPOSITION:
Glycomet GP 0.5: Each uncoated tablet contains metformin hydrochloride BP (as sustained release) 500 mg and glimepiride USP 1 mg.
Glycomet GP 1: 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 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: Each uncoated tablet contains metformin hydrochloride BP (as sustained release) 500 mg and glimepiride USP 2 mg.
Glycomet GP 2/850: 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) 1000 mg and glimepiride USP 2 mg.
Glycomet GP 4 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.

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.

ADMINISTRATION: Dosage of Glycomet GP should be individualized on the basis of effectiveness and tolerability while not exceeding the maximum recommended daily dose of metformin hydrochloride 2550 mg and glimepiride 20 mg. Initially 1 tablet of Glycomet GP should be administered once daily during breakfast or the first main meal. Do not crush or chew the tablet. In severe cases the tablet may remain intact during transit through the gastrointestinal (GI) tract and will be eliminated in faeces as such. Patients should be advised that in some cases the tablet may not break down completely and may be eliminated unchanged in the faeces. Patients should be advised that this is normal as all drug components have already been released during GI transit.

CONTRAINDICATIONS: In patients hypersensitive to glimepiride, other sulfonylureas, other sulfonamides, metformin or any of the excipients of Glycomet GP; pregnancy and lactation; conditions with the potential to alter renal function (dehydration, severe infection, shock, intravascular administration of iodinated contrast agents), acute or chronic disease which may cause tissue hypoxia (myocardial infarction, shock, cardiac/respiratory failure, hepatic insufficiency, acute alcohol intoxication, alcoholism).

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 every 6 months. At the time of or prior to the procedure and 48 hours thereafter, serum creatinine should be evaluated. Use of Glycomet GP should be discontinued 48 hours before any surgical procedure. Use of Glycomet GP should be discontinued 48 hours before any surgical procedure.

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For glimepiride - Hypoglycemia
For metformin – Gastrointestinal symptoms like nausea, vomiting, abdominal pain or discomfort may occur.
Rise above, Vitamin-D Deficiency in Winter & COVID-19 Era

**D-Rise**

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Endocrine Society Clinical Guidelines

In Winter maintain Vitamin-D levels in normal range

Start with 60,000 IU / 8 weeks & Additional 2,000 IU alternate day

Available in WIDE RANGE

60,000 IU Capsules & Sachets

2,000 IU Capsules

IT TAKES A *rose-vala statin*
TO SHOW ONE TRULY CARES

Roseday®-10
Rosuvastatin 10 mg

Rapid & Robust Plaque Stabilization
Rosuvastatin 10mg > Atorvastatin 20mg

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In hypertensive patients with CV risk, Tazloc-CT Telmisartan 40/80 mg + Chlorthalidone 12.5 mg

START EARLY FOR EXTENSION IN LIFE EXPECTANCY

CV RISK
Consideration for better hypertension control

START EARLY
For extension in life expectancy

ALSO AVAILABLE
Tazloc-CT 6.25
Telmisartan 40 mg + Chlorthalidone 6.25 mg

Role of Platelet to Lymphocyte Ratio (PLR) and its Correlation with NIHSS (National Institute of Health Stroke Scale) for Prediction of Severity in Patients of Acute Ischemic Stroke

Deepti Sharma¹, Nikhil Gandhi²*

Abstract

Background and Objectives: Stroke is the second leading cause of death and third most common cause of disability-adjusted life years in the world. Atherosclerosis plays a key role in the pathogenesis of stroke and inflammation is central in the initiation, progression and complications of atherosclerosis by mediating every stage of atheroma development. High platelet counts may increase thrombocyte activation and aggravate the release of inflammatory mediators. In contrast, lymphocytes exert anti-inflammatory response in atherosclerosis development. The advantage of platelet to lymphocyte ratio (PLR) is that it reflects the condition of both inflammation and thrombosis pathways and is more valuable than either platelet or lymphocyte counts alone. This emerging marker has not been frequently studied with acute ischemic stroke; hence aim of the present study was to find out the role of PLR (Platelet to lymphocyte ratio) in patients of acute ischemic stroke and correlating with NIHSS for predicting the prognosis.

Material and Methods: 100 cases of AIS and equal number of age and gender matched control were enrolled in the study. NIHSS score and PLR (from the CBC test) was calculated both at admission and on day 7 or discharge.

Results: Maximum subjects in our study were in the age range of 61-70 years with males (69%) outnumbering females (31%). Incidence of hypertension, diabetes mellitus, hyperlipidemia, smoking and alcoholism was more in the cases than controls. Mean PLR was higher in the patients of AIS (235.98±93.92) as compared to control group (115.60±27.87) (p=0.0001). Moreover, there was statistically significant, positive correlation between PLR and NIHSS score both at admission and discharge. PLR value increased significantly from the baseline in patients who deteriorated (263.42±108.98 to 346.28±125.35; p=0.016), decreased drastically in patients who improved (242.27±75.14 to 167.19±57.91; p=0.0001) and did not change much in patients who tend to remain static (181.35±105.40 to 183.36±111.61; p=0.955).

Conclusion: Platelet to lymphocyte ratio (PLR) is a simple, cost effective and easily obtainable novel inflammatory marker that may help in predicting the severity of disease and prognosis in terms of functional outcome as evidenced by its increased value in patients of acute ischemic stroke as well as its linear positive correlation with NIHSS score.

Introduction

Stroke or cerebrovascular accident is defined as an abrupt onset of focal neurological deficit that is attributable to vascular cause. It accounts for 80% to 85% of all cerebrovascular disease. Stroke is the second leading cause of death worldwide causing 6.2 million deaths in 2011, and third most common cause of disability-adjusted life years in the world. Atherosclerosis is central in the pathogenesis of stroke. Inflammation plays a key role in the initiation, progression and complications of atherosclerosis by mediating every stage of atheroma development. Thrombosis, platelet activation and inflammation are essential in the pathophysiology of acute ischemic stroke. Platelets represent an important linkage between inflammation, thrombosis, and atherogenesis in acute ischemic stroke.¹ Higher platelet counts may increase thrombocyte activation and aggravate the release of inflammatory mediators, prompting a harmful inflammatory process (2). Studies have demonstrated relationship between mortality and high platelet in patients with acute coronary syndrome. In contrast, lymphocytes are blood cells responsible for cellular and humoral immunity in the body that have shown to modulate the immunologic response in our body. Lymphocytes modulate the mononuclear cell phenotype and induce tissue inhibitor of metalloproteinase-1 expression that have key role in tissue healing. Experimental models have also revealed that lymphocytes exert anti-inflammatory response in atherosclerosis development. Recently, lymphopenia was associated with the increased risk for developing adverse outcome in terms of morbidity and mortality in cardiovascular diseases particularly MI.³ Studies have clearly demonstrated a negative correlation between lymphocyte counts and severity of coronary atherosclerosis.¹ Physiologic stress during acute ischemic stroke leads to high level of cortisol which leads to lower lymphocyte counts.³ Moreover, acute stressful conditions cause activation of sympathetic nervous system which causes redistribution of lymphocytes.
to lymphatic organs and also promotes apoptosis of lymphocytes leading to lymphopenia. Recently, interest in the study of PLR has grown because this ratio has been found to be predictor of prognosis in patients with diverse inflammatory and ischemic conditions. High PLR as an inflammatory marker has been correlated with the poor prognosis in various diseases like Myocardial infarction, critical limb ischemia, end-stage renal failure, pulmonary embolism and various malignancies including breast, ovarian, pancreatic, hepatobiliary carcinoma and other solid tumors. The advantage of PLR is that it reflects the condition of both inflammation and thrombosis pathways and is more valuable than either platelet or lymphocyte counts alone. This emerging marker has not been frequently studied with acute ischemic stroke; hence present study was done to find out the role of PLR (Platelet to lymphocyte ratio) in patients of acute ischemic stroke and correlating with NIHSS for predicting the prognosis

### Objectives

The main objective of our study was to determine the value of Platelet to lymphocyte ratio (PLR) in patients of acute ischemic stroke and correlate it with NIHSS score to predict the severity of stroke.

### Materials and Methods

After obtaining approval from institutional ethical committee, a hospital based prospective and observational study was conducted on 100 patients of acute ischemic stroke admitted in Department of Medicine, Govt. Medical College and Associated M.B.S. Hospital, Kota from 2018 to 2020 and compared with 100 equal number of age and gender matched controls. All acute ischemic stroke patients who had symptom onset within 7 days and had given written informed consent to participate were included in our study whereas patients with hemorrhagic Stroke, venous sinus thrombosis, hepatic or renal disease, connective tissue disorders, autoimmune disease, sepsis, malignancy, psychiatric illness, moribund condition and unwillingness to participate in the study were excluded. The diagnosis of acute stroke was made on the basis of temporal profile of clinical syndrome, clinical examination and CT scan / MRI of brain. A detailed history taking, clinical examination, and routine lab investigations were done to identify ischemic stroke risk factors (non modifiable and modifiable). Severity of stroke was determined with the National Institute of Health Stroke Scale (NIHSS) in all patients at initial presentation and at discharge. Stroke severity was grouped in minor stroke (1-4), moderate stroke (5-15), moderate to severe stroke (16-20) and severe stroke (21-42). For calculating PLR (Platelet to lymphocyte ratio), CBC (Complete Blood Count) test was performed by fully automated five part hematology analyzer (SYSMES) available at our central laboratory. 2 ml of peripheral venous sample with all aseptic precaution was taken just after admission before starting any treatment and another sample just before discharge. The samples were processed immediately. Thus, two CBC test were performed from which Platelet to lymphocyte ratio was obtained by dividing total platelet count by total lymphocyte count. This platelet to lymphocyte ratio was then compared with the reference value calculated from control group of same age and gender and with NIHSS severity score (calculated at the time of admission and discharge).

### Statistical Analysis

Continuous variables were presented as mean±sd, categorical variables were expressed in frequency and percentages. Demographic, haematological (PLR) and clinical parameters were compared between cases and controls by performing independent t- test. Categorical variables were compared by performing chi-square test. Statistical method used was unpaired Student's t-test and chi-square test between Platelet to Lymphocyte ratio and severity of ischemic stroke including other variables using Graph pad In Stat Version 3.10. A value of p<0.05 was considered as not significant and p<0.05 as statistically significant. Pearson correlation coefficient was also assessed to study nature and magnitude of correlation between PLR and NIHSS both at admission and discharge.

### Observation and Results

In our study, cases had mean age of 60.79±13.86 years which was comparable with the mean age of control group i.e. 61.33±10.96 years and both groups had maximum subjects in the range of 61-70 years i.e. 36 and 34 respectively. Males (69%) outnumbered females (31%) with a ratio of 2.2:1. Table 1 depicts the age and gender distribution of subjects in case and control group.

Left hemiparesis was the most common focal neurological deficit observed in 48% of the patients as compared to right hemiparesis (29%). Features of posterior circulatory stroke like vertigo, blurring of vision, incoordination etc. without weakness was present in only 13% of the patients. MCA territory infarction was the dominant CT/MRI finding (65%) followed by PCA (19%) and ACA (16%) territory stroke. Distribution of acute ischemic stroke patients in different NIHSS score shows that maximum cases were present in NIHSS score group 5-15 (moderate stroke) both at the time of admission and discharge i.e. 47 and 41 respectively (Table 2). Mean NIHSS score in AIS patients at admission was 10.80±6.33 as compared to 10.01±7.54 at discharge.

In our study, hypertension was the most common risk factor (64%) followed by smoking (59%), hyperlipidemia (48%), diabetes mellitus (31%) and alcoholism (27%) as shown in (Table 3). Biochemical and hematological profile of both case and control groups shows that the value of random blood

### Table 1: Age and gender distribution of subjects in case and control group

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Cases (n=100)</th>
<th>Control (n=100)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yrs)</td>
<td>60.79±13.86</td>
<td>61.33±10.96</td>
<td></td>
</tr>
<tr>
<td>Male (%)</td>
<td>69</td>
<td>63</td>
<td></td>
</tr>
<tr>
<td>Female (%)</td>
<td>31</td>
<td>37</td>
<td></td>
</tr>
</tbody>
</table>

### Table 2: Distribution of AIS patients in different NIHSS score group

<table>
<thead>
<tr>
<th>NIHSS Score</th>
<th>At the time of admission</th>
<th>At the time of discharge</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-4</td>
<td>28</td>
<td>34</td>
</tr>
<tr>
<td>5-15</td>
<td>47</td>
<td>41</td>
</tr>
<tr>
<td>16-20</td>
<td>15</td>
<td>12</td>
</tr>
<tr>
<td>21-42</td>
<td>10</td>
<td>13</td>
</tr>
<tr>
<td>Total</td>
<td>100</td>
<td>100</td>
</tr>
</tbody>
</table>

### Table 3: Comparison between case and control group on the basis of risk factors

<table>
<thead>
<tr>
<th>Risk factors</th>
<th>Cases (%)</th>
<th>Controls (%)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension</td>
<td>64%</td>
<td>30%</td>
<td>0.005</td>
</tr>
<tr>
<td>Smoking</td>
<td>59%</td>
<td>31%</td>
<td>0.020</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>48%</td>
<td>24%</td>
<td>0.022</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>31%</td>
<td>30%</td>
<td>0.973</td>
</tr>
<tr>
<td>Alcoholism</td>
<td>27%</td>
<td>21%</td>
<td>0.537</td>
</tr>
</tbody>
</table>
sugar, urea, creatinine, total cholesterol, triglyceride, hemoglobin, platelet count was significantly higher (p<0.05) in the study group as compared to control group whereas the value of total lymphocyte count was significantly lower in AIS patients than control subjects (Table 4).

When PLR was calculated by dividing absolute platelet count with absolute lymphocyte count, it was observed that PLR was significantly higher in patients with acute ischemic stroke (235.98±72.29) as compared to control group (115.60±27.87) with p-value of 0.0001. Moreover, this ratio did not change significantly with gender of the patients followed by smoking, diabetes and hyperlipidemia (p>0.05).

The value of PLR was higher in patients with MCA infarct (245.34±100.60) followed by ACA (219.91±73.37) and PCA infarct (216.16±82.68). On comparing PLR with patients of different NIHSS score, it was found to be lowest in NIHSS score group 1-4 i.e.171.23±48.14 which increased to 229.66±98.57 in NIHSS score group 5-15, 296.23±44.09 in NIHSS score group 16-20 and was highest in NIHSS score group of 21-42 amounting to 356.63±43.90 such that a positive, moderately strong and statistically significant correlation was found between PLR and NIHSS score at the time of admission (Figures 1 to 4).

Table 5 shows the distribution of AIS patients according to clinical status in different NIHSS score group assessed on day 7 or at discharge. From this table, we found that out of 100 patients, 56 got improved, 25 got deteriorated and 19 remained static.

Comparison of PLR value according to clinical status in acute ischemic stroke patients showed that PLR value increased drastically in deteriorated patients from 263.42±108.98 at admission to 346.28±125.35 at discharge. On the other hand, PLR value decreased significantly in improved patients from 242.27±75.14 at admission to 167.19±57.91 at discharge whereas value of PLR did not change much in patients who remained static (Table 6).

Discussion

Our study included 100 patients of acute ischemic stroke and 100 age and sex matched control subjects. Although the control subjects were free from acute ischemic stroke, some of them had risk factors for ischemic stroke. Our study had male preponderance with male to female ratio of 2.2:1 which was similar to all other studies done by Aiyar et al, Kay Sin Tan et al and R P Eappen et al etc. The mean age of our study group was 60.79±13.86 years with the maximum cases in the age range of 61 to 70 years. This is in accordance with various other studies done by Grau et al, Aiyar et al and Naik M, Rauniyar, Sharma U.K et al. In our study hypertension was the most common risk factor detected in 64% of the patients followed by smoking (59%), hyperlipidemia (48%), diabetes mellitus (31%) and alcoholism (27%). This is similar to the recent studies by Grau et al, Tallawy et al, Essa et al, El Sayed et al and Benerjee TK et al. Random blood sugar level was higher in the study group (196.33 ± 92.26 mg/dL) as compared to control group (148.97 ± 87.75 mg/dL) with a statistically significant p-value of 0.0001 and was similar to other studies done by Gauri et al, Dalal et al, Nagraja et al, Grindal et al, Bogousslavsky et al, Zunni et al and Alverez et al. Mean total cholesterol and triglyceride level was also higher in patients of AIS than control and this correlate with the findings of Togha et al and Aabadzhieva et al.
In present study we tried to evaluate the value of PLR in patients of AIS and observed that the mean PLR value in AIS patients was 235.98±93.92 which was significantly higher than the control group (115.60±27.87) with a p value of 0.0001. To the best of our knowledge, this is the first study which has tried to correlate the value of PLR with NIHSS score both at the time of admission as well as discharge. In our study positive, moderately strong and statistically significant correlation was found between PLR and NIHSS score at the time of admission such that the value of PLR increased proportionately with the increasing NIHSS score. (p=0.0001) and (r=0.753). Our study is similar to the studies done by Andres Perez et al.,
Pei-Hsun Sung et al. and Xu J-H et al. in which there was a positive correlation between PLR and NIHSS score at the time of admission. In our study, a statistically significant positive correlation between PLR and NIHSS was also observed during the discharge (p=0.0001) and (r=0.8564). In our study out of 100 patients 56 got improved, 25 deteriorated and 19 remained static. It was observed that mean PLR in 56 patients who improved was 242.27±75.14 at admission which decreased to 167.19±57.91 at discharge and this was found to be statistically significant (p= 0.0001). Thus, as the patients in our study improved the value of this ratio also improved (decreased). On the other hand, 25 patients who got deteriorated, their PLR value increased significantly from 263.42±108.98 at admission to 346.28±125.35 at discharge (p=0.016). This highlighted that as the patient got deteriorated the value of PLR also deteriorated i.e. increased. In 19 patients who remained static, their PLR value was nearly similar both at the time of admission and discharge being 181.35±105.40 and 183.36±111.61 respectively and the difference was also not statistically significant (p=0.955). This shows that the patient who neither gets improved nor gets deteriorated, the value of their PLR also doesn’t change significantly.
Our study supports the finding of Ozge Altintas et al.,
Andres Perez et al.,
Stella Bouziana et al.
and Xu J-H et al WHICH demonstrated that patients of acute ischemic stroke with higher PLR had poor outcome as compared to patients with lower PLR values.

Conclusion
Platelet to lymphocyte ratio (PLR) is a simple, cost effective and easily obtainable novel inflammatory marker that may help in predicting the severity of disease and prognosis in terms of functional outcome as evidenced by its increased value in patients of acute ischemic stroke as well as its linear positive correlation with NIHSS score. This ratio can be obtained even at primary health set ups and may be used for decision making in urgent referral of the patient for better outcome. Though, more studies are needed to validate our results, our study completely support the routine calculation of this ratio that may add to risk stratification of patients with acute ischemic stroke.

Limitation of Study
Despite our best efforts our studies had few limitations
1. The sample size of our study was small involving only single centre patients of acute ischemic stroke.

2. Owing to lack of long term follow up for our patients, we cannot comment whether platelet to lymphocyte ratio is a useful predictor of long term prognostic outcome in patients with AIS or not.
3. Our study was carried out in a tertiary centre where the cases are either serious or referred. Our study may thus be biased towards more serious cases.

Acknowledgement
Extremely grateful to principal and superintendent of Govt. Medical College, Kota for their extreme support. There has been no funding of any kind for this study.

References

Infer Table 5: Distribution of AIS patients according to clinical status in different NIHSS score group

<table>
<thead>
<tr>
<th>NIHSS score</th>
<th>Total no. of cases</th>
<th>Improved</th>
<th>Deteriorated</th>
<th>Static</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-4</td>
<td>28</td>
<td>17</td>
<td>6</td>
<td>5</td>
</tr>
<tr>
<td>5-15</td>
<td>47</td>
<td>26</td>
<td>11</td>
<td>10</td>
</tr>
<tr>
<td>16-20</td>
<td>15</td>
<td>9</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>21-42</td>
<td>10</td>
<td>4</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>Total</td>
<td>100</td>
<td>56</td>
<td>25</td>
<td>19</td>
</tr>
</tbody>
</table>

Table 6: Comparison of PLR according to clinical status in AIS patients at the time of admission and discharge

<table>
<thead>
<tr>
<th>Clinical status</th>
<th>No. of cases (n=100)</th>
<th>PLR (Mean±SD)</th>
<th>t value</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Improved</td>
<td>56</td>
<td>242.27±75.14</td>
<td>5.904</td>
<td>0.0001</td>
</tr>
<tr>
<td>Deteriorate</td>
<td>25</td>
<td>263.42±108.98</td>
<td>2.494</td>
<td>0.016</td>
</tr>
<tr>
<td>Static</td>
<td>19</td>
<td>181.35±105.40</td>
<td>0.057</td>
<td>0.955</td>
</tr>
</tbody>
</table>


Indian Expert Review on Use of Teneligliptin in patients with Diabetes and its Safety and Efficacy (INTENSE)

Subhankar Chowdhury1*, Manoj Chadha2, Sujoy Ghosh3, Anirban Majumder4, Debmalya Sanyal4, Soumik Goswami5, Debasis Giri6, Arjun Baidya7, PK Sahana8, Anirban Sinha9, Animesh Maiti9, Rana Bhattacharjee9, Ajitesh Roy10, Sambit Das11

Abstract

Introduction: Management of diabetes in India remains less than satisfactory despite a huge prevalence of type 2 diabetes (T2D). Associated obesity, inadequate lifestyle modifications and burden of treatment costs are certain major issues contributing to inadequate management of diabetes in India.

Aim: To evaluate the use of Teneligliptin in patients with diabetes and its safety, efficacy and cost effectiveness especially in Indian patients with T2D.

Methods: A detailed analysis of the best available scientific evidence (clinical trials, meta-analyses and real-world experience) was performed to create an evidence driven understanding of teneligliptin’s efficacy, safety and cost effectiveness. Fourteen leading endocrinologists contributed as experts and the modified Delphi process was followed. Evidences and clinical questions were discussed over a series of web and in a live meeting. Final draft was created based on the opinions endorsed by the experts.

Results: Teneligliptin is the most commonly used gliptin in India and exhibits pharmacokinetic and pharmacodynamic advantages as well as greater cost effectiveness compared to other gliptins. It has been recognized as an efficacious and well tolerated antidiabetic agent both as monotherapy and in combination based on multiple clinical trials, meta-analyses and real world studies. Teneligliptin as add on therapy to other antidiabetic drugs (OADs) or insulin has provided significant reductions in HbA1c, fasting plasma glucose (FPG) and postprandial plasma glucose (PPG) levels and is generally well tolerated with low risk of hypoglycemia both in short term and long term. Studies have also proven its efficacy in ameliorating glucose fluctuations, reducing post prandial insulin requirement, increasing active incretin levels and improving pancreatic β cells function. Efficacy and safety has also been proven in all age groups, all stages of renal disease and mild to moderate hepatic disease. QT prolongation is not seen even with maximum recommended dose of 40 mg/day.

Conclusion: Teneligliptin has firmly positioned itself as a very important drug in the armamentarium for managing T2D. It offers efficacy, safety and cost-effective therapeutic choice in Indian patients with T2D.

Challenges and Unmet Needs in Indian Diabetes Care

Diabetes is a global health emergency of this century. There has been a rapid rise of diabetes in India, affecting more than 77 million Indians, according to International Diabetes Federation (IDF) data from 2019. What is worrisome is that India has the highest number of people with Diabetes still undiagnosed, and by 2045 we are expected to cross 134.2 million (108.5–165.7). What is also worrying is that though a lot has been said about India and its epidemic proportion of Diabetes incidence, and despite various National guidelines and standards of care for diabetes which are now available, the management of patients with diabetes in practice remains less than satisfactory. This will continue to be a serious economic burden on our country more so because of sheer numbers and number of youths affected. While managing Indian patients with diabetes, it is imperative to recognize that due to associated obesity and inadequate lifestyle modifications, only metformin along with lifestyle management may not just be enough in initial management of patients, at least in some of them. While choosing Oral Anti-Hyperglycaemic Agents (AHA), apart from risk of hypoglycaemia, it is important to also look into impact on weight, renal safety and possible beta cell preservation. Gliptins usage has recently increased considerably in India after introduction of Teneligliptin in the year 2015. One of the most important factors while choosing any anti-diabetic agent, is cost of therapy, keeping in mind that majority of patients in India are not covered by insurance and also due to other co-morbidities and other therapies as well.

It is these issues which were a precursor for 14 leading Endocrinologists, Diabetologists

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Received: 21.10.2019; Accepted: 25.02.2020
across India, to develop this Expert Consensus Statement to address the use of Teneligliptin in patients with diabetes and its safety and efficacy, especially the advantage due to its cost effectiveness in diabetes care which is a lifelong economic burden on patients. A detailed analysis of the best available scientific data, trials, and meta-analysis and real-world experience was performed, so that an evidence driven understanding of teneligliptin’s efficacy, safety, impact on cost of therapy and compliance could be created. The process followed was modified Delphi, wherein evidences and clinical questions were discussed over a series of web followed by a live meeting; based on the opinion endorsed by the experts, the draft was created.

DPP4 Inhibitors Place in Therapy

Recent statement of Standards of Medical Care in Diabetes by the American Diabetes Association (ADA), American College of Endocrinology/ American Association of Clinical Endocrinologist, and Indian clinical practice recommendations, by RSSDI (Research Society for the Study of Diabetes in India) has recommended initial treatment with metformin as monotherapy after inadequate life style modification, followed by sulfonylurea, thiazolidinedione, dipeptidyl peptidase-4 (DPP-4) inhibitor, sodium-glucose cotransporter 2 inhibitor (SGLT2-i), glucagon-like peptide 1 (GLP-1) receptor agonist and insulin alone or in combination. It is still challenging to find an anti-hyperglycemic agent with long-term glucose control, minimal hypoglycemia, no weight gain and a relatively affordable price.3

In many randomized trials DPP4 inhibitors have found to be effective for glycemic control by declining the HbA1c, FPG, and PPG and improving the function of pancreatic β cells. In addition to targeting glycemic control, DPP4 inhibitors have low risk of hypoglycemia with neutral effect on body weight with a favorable safety profile. Also cardiovascular safety of DPP-4 inhibitors is established in large clinical trials.

In the past 17 years, 17 gliptins have been launched globally, and in India gliptins which are available are Sitagliptin, Saxagliptin, Vildagliptin, Linagliptin, Teneligliptin and Evogliptin. The cost of therapy is one of the biggest drawbacks of this effective therapy, which becomes an economic burden to majority of Indian patients leading to their discontinuing the medications.

Teneligliptin, a third-generation4 new oral anti-diabetic received Indian regulatory approval in 2015. Teneligliptin, apart from its pharmacokinetic advantages has greater cost effectiveness in comparison to other DPP-4Is. Presently, Teneligliptin is the most commonly used gliptin in India. This has resulted in availability of effective Gliptins as a therapy, widely affordable and available, resulting in thousands of crores rupees saving in National Diabetes care expenditure. In Indian scenario this is a vital aspect, as the financial burden of diabetes and its treatment is borne by patients themselves.

Teneligliptin – PKPd advantage translated to Clinical benefits

All DPP-4 inhibitors differ considerably in terms of pharmacokinetic and pharmacodynamic profiles. Teneligliptin, a 3rd-generation DPP-4 inhibitor, acts as a competitive reversible inhibitor of DPP-4 and decreases the degradation of GLP-1, consequently stimulating insulin secretion and suppressing glucagon secretion in a glucose-dependent manner.4 An interaction of DPP-4 inhibitors with S1 and S2 is considered to be the fundamental interaction required for DPP-4 interaction. Teneligliptin, a novel DPP-4 inhibitor, has a unique structure which binds to S1, S2 and S2 extensive subsite of DPP-4 enzyme leading to enhanced potency and selectivity. Teneligliptin belongs to Class 3 of the DPP-4 inhibitor, along with Sitagliptin, having additional binding to S2 extensive site apart from S1 and S2 sites imparts stronger inhibitory, action on DPP-4 enzyme. Moreover, Teneligliptin has been reported to have five-fold higher activity than Sitagliptin due to J-shaped anchor-lock domain, strong covalent bonds with DPP-4 and more extensive S2 extensive binding than Sitagliptin.5 Its elimination half-life in plasma is 24.2 and 20.8 h in 20 and 40 mg doses, respectively, with resulting DPP-4 inhibition through the day. More importantly, teneligliptin is effective and well tolerated in patients with type 2 diabetes (T2D) with renal impairment, or even end-stage renal disease, without dose adjustments.6

Teneligliptin – Efficacy

Teneligliptin has shown its efficacy and safety, in various trials. In a recently published 2018 meta-analysis (n=2119 T2D patients from 10 trials) by Xiao Xuan Li, et al; Teneligliptin improved blood glucose levels and β-cells function with low risk of hypoglycemia in patients with T2D. Teneligliptin produced absolute reductions in glycated hemoglobin A1c (HbA1c) levels [weighted mean difference (WMD) 0.82%, 95% confidence interval (CI) [−0.91 to −0.72], p < 0.00001] compared with placebo. Teneligliptin led to greater decrease of fasting plasma glucose (FPG) level (vs. placebo, WMD −18.32%, 95% CI [−21.05 to −15.60], p < 0.00001), significant decrease in the 2 h post-prandial plasma glucose (2h PPG) (WMD −46.94%, 95% CI [−51.58 to −42.30], p < 0.00001) and area under the glucose plasma concentration-time curve from 0 to 2 h (AUC0−2h) for PPG (WMD −71.50%, 95% CI [−78.09 to −64.91], p < 0.00001) compared with placebo. There was (0.96 risk ratio (RR), 95% CI [0.87, 1.06], p = 0.06). The risks of hypoglycemia were not significantly different between Teneligliptin and placebo (1.16 RR, 95% CI [0.59, 2.26], p = 0.66).6

Hong S, Park CY, et al. assessed 24-week efficacy and safety of Teneligliptin in Korean patients inadequately controlled with diet and exercise, in a multicenter randomized, double blind, placebo-controlled, parallel-group, phase III study. Incidence of hypoglycemia and adverse events were not significantly different between two groups.7

Kadowaki T, Marubayashi F et al. analyzed data from two Phase III clinical trials and concluded that long term use of Teneligliptin as monotherapy or combination therapy was evaluated to be well tolerated and effective as per the evidence generated from two trials.8

In a study by Tsuchimochi W. et al evaluated the effects of Teneligliptin on 24 hr. blood glucose control and gastrointestinal hormone responses to meal tolerance test and to investigate the glucose-lowering mechanisms of Teneligliptin. It was observed that Teneligliptin improved 24 hr. blood glucose levels by increasing active incretin levels and early phase insulin
secretion, reducing the post prandial insulin requirement and reducing glucagon secretion and concluded even short-term Teneligliptin treatment may offer benefits for patients with T2D.9

Kurozumi A, Okada Y, et al. compared the effect of Teneligliptin and sitagliptin with respect to glucose fluctuation and effect on GLP-1 in T2D where daily dose of Teneligliptin improved AUC for plasma glucose at evening after meal tolerance test and it also significantly increases the GLP-1 activity after the meal test.10

Experts comment:

Diabetes is manifested with various other health complications caused by blood glucose fluctuations. Teneligliptin shows potent and sustained effects on glycemic control without concern of hypoglycemia. It has a unique structure with J-shaped anchor-lock domain responsible for its action on 52 extensive subunit of DPP-4, which ultimately leads to its enhanced potency and selectivity. A long t1/2 of 24.8 hours with unique pharmacokinetic advantages allows its convenient once daily administration. As it has dual mode of elimination via renal and hepatic route, it can be administered safely in renal impairment patients, along with no dose adjustment requirement in mild to moderate hepatic impairment. It also shows promising beta-cell preservation potential along with an added advantage of cost-effectiveness in comparison to other anti-glycemic agents. Potential differences in pharmacodynamic and pharmacokinetic characteristics between teneligliptin and other DPP-4 inhibitors, marks its underlying first-rate potency and sustained effect in diabetes management.

Teneligliptin Effective as Monotherapy

Teneligliptin has been systematically evaluated in T2D as monotherapy with diet and exercise and in combination with metformin, glimepiride, pioglitazone, and insulin in short-term (12 weeks) and long-term (52 weeks) studies. These studies have reported a reduction in HbA1c of 0.8%–0.9% within 12 weeks of therapy.11

In a randomized, double-blind, placebo-controlled, parallel-group study, on 99 T2D patients inadequately controlled with diet and exercise by Eto T, et al; once daily Teneligliptin (10 or 20 mg) administration showed significantly smaller 2-h PPG, 24-h mean glucose and FPG values than the placebo group. Once-daily teneligliptin improved blood glucose levels over 24h without hypoglycemia.12

In a randomized, double-blind, placebo-controlled, parallel-group study by Kadowaki T, patients (n = 324) were randomized to receive teneligliptin 10, 20 or 40 mg, or placebo, once daily before breakfast for 12 weeks. Teneligliptin showed significantly greater reductions in HbA1c and FPG than the placebo group, across all the dose range studied and was well tolerated in Japanese T2D patients.13

Kutoh et al. explored the glycemic and non-glycemic efficacies of Teneligliptin in drug naïve T2D patients, and concluded that Teneligliptin was efficacious and safe as an initial therapy for newly diagnosed T2D, where glycemic efficacy was obtained by activating beta cell function as well as decreasing insulin resistance.14

Similarly, in an Indian study (multicentric, double-blind, placebo-controlled, Phase 3) by Suryawanshi et al, teneligliptin 20 mg daily in drug naïve T2DM patients, resulted in a significant reduction in HbA1c (-0.55%, P = 0.0043) and 2h-PPG (-25.8 mg/dl, P = 0.0070) in comparison to placebo. Similarly, higher percentage of patients achieved the target HbA1c levels (<7%) in teneligliptin arm (43.4% vs. 27.3%, P = 0.026) in comparison to control arm, and “overall” the drug was well tolerated (Table 1).

Teneligliptin as an add-on Therapy

Teneligliptin as an add-on to Metformin

Teneligliptin is efficacious and well tolerated as an add-on treatment with oral antidiabetic drugs (OADs) or insulin, in T2D patients on monotherapy with inadequate control. In an Indian study, Chatterjee AK reported that teneligliptin as an add-on therapy resulted in a significant reduction of HbA1c, FPG and PPG after 12-week treatment in patients inadequately controlled on monotherapy with OADs or insulin.16

In 2015, Kim MK conducted a 16-week, randomized, double-blind, placebo-controlled phase III trial, aimed to evaluate the efficacy and safety of Teneligliptin in combination with metformin in Korean T2D patients. It was concluded that Teneligliptin once daily add-on to metformin was effective and generally well tolerated.17

Similarly, Bryson A. Jennings PE et al evaluated the efficacy and tolerability of Teneligliptin (5, 10, 20 or 40 mg) co-administered with metformin in T2D inadequately controlled with Metformin (> 1000 mg/day). 447 patients from 55 European centers were enrolled in this study, and were treated for 24 weeks. It was observed that teneligliptin (5 to 40 mg) add-on to metformin demonstrated a dose-related and statistically significant reduction in HbA1c (-0.30 to -0.63% placebo adjusted). At 40 mg -0.63% reduction in HbA1c was observed at week 24. Noticeably, the decrease in HbA1c levels in teneligliptin arm was greater at week 24 (-0.58 to -0.91%, p=0.003 to <0.001; placebo -0.28%) than in Week 12. It was concluded that teneligliptin was well tolerated for 52 weeks, with a 2.3% incidence level of hypoglycemia.18

Teneligliptin as an add-on with Sulfonylureas

Kadowaki T and Kondo K (2014) conducted a study where 194 patients were randomized to either teneligliptin 20 mg or placebo once daily while continuing stable glimepiride therapy. It was concluded that Teneligliptin was effective and generally well tolerated in Japanese patients with T2D inadequately controlled with glimepiride monotherapy, and the improvements in glycemic control were maintained for up to 52 weeks.19

Teneligliptin add-on with pioglitazone

In 2013 Kadowaki T and Kondo K evaluated the efficacy and safety of Teneligliptin add-on with pioglitazone in Japanese T2D patients (n = 204), and they concluded that teneligliptin add-on therapy was effective and generally well tolerated in T2D

Table 1: Teneligliptin Effective as Monotherapy

<table>
<thead>
<tr>
<th>Author</th>
<th>Treatment</th>
<th>No. of Patients</th>
<th>Placebo-subtracted LSM change from BL to study end</th>
<th>% of patients with target HbA1c ≤7% or &lt;6.8% or &lt;7.3%</th>
</tr>
</thead>
<tbody>
<tr>
<td>T. Kadowaki, 2013</td>
<td>TEN 20 mg</td>
<td>79</td>
<td>-0.9**</td>
<td>-56.8**</td>
</tr>
<tr>
<td>TEN 40 mg</td>
<td>81</td>
<td>-1.0**</td>
<td>-58.6**</td>
<td>-20.0**</td>
</tr>
<tr>
<td>M. Goda, 2013</td>
<td>TEN 20 mg</td>
<td>99</td>
<td>-0.79**</td>
<td>-44.7**</td>
</tr>
</tbody>
</table>

BL baseline. FPG fasting plasma glucose. HbA1c glycated hemoglobin. LSM least-square mean. NR Not recorded. NA Not applicable. PL placebo. PPG postprandial plasma glucose. TEN teneligliptin. **p < 0.001 p < 0.01. Post-prandial glucose values after breakfast. Studies also included Teneligliptin 10 mg arm but results are not tabulated here it is not recommended dose; b and c NGS units (National Glycohemoglobin Standardization Program). In Japan, HbA1c (Japan Diabetes Society) values <6.5 and <7.0% are equivalent to HbA1c<6.8 and <7.3% in NGS units.
Teneligliptin add-on with Insulin Therapy

Effect on Glucose variability when added to Insulin therapy
Tanaka S et al. added Teneligliptin in Japanese diabetes patients with insulin therapy to examine whether Teneligliptin ameliorated glucose fluctuation in hospitalized Japanese patients with T2D receiving insulin therapy with or without other antidiabetic drugs and using continuous glucose monitoring (CGM). It was concluded that addition of Teneligliptin to insulin therapy led to a significant improvement in diurnal glycemic control and significant reductions in glucose fluctuations in 24 hr. periods without increasing hypoglycemia.23

Yajima T, et al. also used Teneligliptin in addition to insulin therapy in T2D on hemodialysis and observed that the insulin dose reduced from 18U to 6 U (p<0.0001). The incidence of asymptomatic hypoglycemia on hemodialysis day detected by CGM was greater in the C+T group (-0.94%; P < 0.001). No incidence of hypoglycemia was reported, and a comparable adverse event rate between both the groups was observed (55.8% and 49.4% in the C + T and C + P groups, respectively). FPG, body weight and the proinsulin/C-peptide ratio were significantly lower in the T+C group than in the T+P group. Teneligliptin added to ongoing canagliflozin monotherapy improved glycemic control and was well tolerated in patients with inadequately controlled T2D.21

This same study was carried for 52 weeks for long term safety and efficacy of canagliflozin as add-on to Teneligliptin therapy in T2D. The mean changes in HbA1c, FPG and body weight were -0.99% (95% confidence interval [CI] -1.12 to -0.85), -38.6 mg/dL (95% CI -43.4 to -33.9) and -3.92% (95% CI -4.53 to -3.31), respectively suggesting the long-term co-administration of canagliflozin with Teneligliptin is well tolerated and effective in T2D who have inadequate glycemic control on Teneligliptin alone22 (Table 2).

Teneligliptin add-on with canagli/flozin

Kadowaki T et al., evaluated the efficacy of teneligliptin add-on therapy (20 mg for 24 weeks) in T2D patients already on canagliflozin (100 mg) for ≥12 weeks (C + T group), in comparison to placebo (C + P group). The reduction in HbA1c levels at week 24 from baseline was greater in the C+T group (-0.94%; P < 0.001). No incidence of hypoglycemia was reported, and a comparable adverse event rate between both the groups was observed (55.8% and 49.4% in the C + T and C + P groups, respectively). FPG, body weight and the proinsulin/C-peptide ratio were significantly lower in the T+C group than in the T+P group. Teneligliptin added to ongoing canagliflozin monotherapy improved glycemic control and was well tolerated in patients with inadequately controlled T2D.21

This same study was carried for 52 weeks for long term safety and efficacy of canagliflozin as add-on to Teneligliptin therapy in T2D. The mean changes in HbA1c, FPG and body weight were -0.99% (95% confidence interval [CI] -1.12 to -0.85), -38.6 mg/dL (95% CI -43.4 to -33.9) and -3.92% (95% CI -4.53 to -3.31), respectively suggesting the long-term co-administration of canagliflozin with Teneligliptin is well tolerated and effective in T2D who have inadequate glycemic control on Teneligliptin alone22 (Table 2).
Table 2: Summary of Teneligliptin Trials

<table>
<thead>
<tr>
<th>Author name</th>
<th>Study design</th>
<th>Dose</th>
<th>Baseline values</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eto T, Inoue S et al. 2012 Nov 1</td>
<td>Randomized, double blinded, placebo controlled, parallel study (n=99)</td>
<td>Teneligliptin 10 mg (n=34), 20 mg (n=33)</td>
<td>HbA1c - 8.3% FPG - 162.1 mg/dL</td>
<td>DPP4 inhibition rate at 24 hrs (E24 h) was 66.9% ± 4.17%</td>
</tr>
<tr>
<td>T. Kadowaki and K. Kondo, 2013 Sep</td>
<td>Randomized double blinded, parallel group study (n=324)</td>
<td>Teneligliptin – 10 mg (n=84), 20 mg (n=79), 40 mg (n=81)</td>
<td>HbA1c - 7.8% FPG - 145.7 mg/dL</td>
<td>After 12 weeks, HbA1c was 7% and FPG was 129.5 mg/dL</td>
</tr>
<tr>
<td>Kadowaki T, Sasaki K et al. 2018 Apr 1</td>
<td>Open labelled, phase 3 clinical trials (n=702)</td>
<td>Teneligliptin-20 mg, 40 mg</td>
<td>HbA1c - 7.5% FPG - 147.6 mg/dL</td>
<td>HbA1c levels in teneligliptin 40 mg dose were 8.57 ± 0.77% at week 0, 7.93 ± 0.69% at week 28 and 7.85 ± 0.85% at week 52:</td>
</tr>
<tr>
<td>Kadowaki T, Haneda M et. Al. 2018 Jan 22</td>
<td>Interim analysis (n=10,532)</td>
<td>Teneligliptin-20 mg/day</td>
<td>HbA1c - 7.57% FPG - 147.6 mg/dL</td>
<td>Overall ADRs: 3.46% and most common ADRs were Hypoglycemia (0.32%) and constipation (0.27%)</td>
</tr>
<tr>
<td>Ito R, Fukui T et. Al. 2015 Sep 1</td>
<td>Open label clinical study (n=13)</td>
<td>Teneligliptin – 20 mg (n=8)</td>
<td>HbA1c - 8.3% FPG - 142.5 mg/dL</td>
<td>HbA1c significantly decreased from 8.3 ± 0.4% at baseline to 6.3 ± 0.2% after 12 weeks of teneligliptin treatment</td>
</tr>
<tr>
<td>Kutoh E, Hirate M et al 2014 Aug</td>
<td>Project of Monitoring the effects of oral hypoglycemic drugs in T2D patients (n=31)</td>
<td>Teneligliptin – 20 mg (n=31)</td>
<td>HbA1c – 10.34% FPG - 211.3 mg/dL</td>
<td>Homeostasis model assessment β-cell (HOMA-β) significantly increased from 24.04 ± 31.14 to 40.23 ± 40.98</td>
</tr>
<tr>
<td>Kusunoki M, Sato D et al 2015 Oct</td>
<td>Study to investigate the effects of Teneligliptin on HOMA-R and insulin resistance (n=9)</td>
<td>Teneligliptin – 20 mg (n=9)</td>
<td>HbA1c-6.6% HOMA-R-2.5</td>
<td>After 14 week treatment with Teneligliptin, HbA1c value was decreased to 5.9% and HOMA-R was 1.6</td>
</tr>
<tr>
<td>Tanaka S, Suzuki k et al 2014 Dec 1</td>
<td>Prospective, non blinded, pilot study (n=26)</td>
<td>Teneligliptin – 20 mg, (&lt;26)</td>
<td>HbA1c – 10.8% Mean glucose levels – 148.8 mg/dL</td>
<td>Significantly decreased both fasting and postprandial glucose levels on Days 5 – 7, significant decrease in 24-hour mean glucose levels</td>
</tr>
<tr>
<td>Kurozumi A, Okada Y et al 2018 Mar 1</td>
<td>Randomized, cross over study (n=14)</td>
<td>Teneligliptin – 20 mg (n=7) Sitagliptin – 50 mg (n=7)</td>
<td>-</td>
<td>Teneligliptin once daily improved the plasma glucose and also resulted a significant increased in GLP-1 level at 30 minutes after the meal load</td>
</tr>
<tr>
<td>Kim Y, Kang ES et al 2018 Oct 26</td>
<td>Phase 3, randomized, double blind, non inferiority study (n=201)</td>
<td>Teneligliptin – 20 mg (n=103) Sitagliptin – 100 mg (n=98)</td>
<td>HbA1c – 8.11%</td>
<td>At 24 weeks, reduction from baseline in HbA1c: Teneligliptin: -1.03 ± 0.10% Sitagliptin: -1.02 ± 0.10%</td>
</tr>
<tr>
<td>Bryson A, Jennings PE et al. 2016 Jul 2</td>
<td>Multicenter, randomized single blind, placebo controlled study (n=447)</td>
<td>Teneligliptin – 5 mg, 10 mg, 20 mg, 40 mg</td>
<td>HbA1c - 7.89% FPG - 162.39 mg/dL</td>
<td>Greatest reduction in HbA1c was seen with Teneligliptin at 40 mg (-0.63) at week 24.</td>
</tr>
<tr>
<td>Kadowaki T, Inagaki N et al 2018</td>
<td>Multi center, randomized, double blinded, placebo controlled, phase 3 clinical trials (n=154)</td>
<td>Teneligliptin – 20 mg (n=77) Canagliflozin – 100 mg (n=77)</td>
<td>HbA1c – 8.18% Men glucose levels – 173.9 mg/dL</td>
<td>Teneligliptin showed significant improvements in glycemic control, including HbA1c, FPG and PPGs, compared with placebo</td>
</tr>
<tr>
<td>Kadowaki T, Kondo K, 2013 Nov 1</td>
<td>Double blinded, placebo controlled, parallel group study (n=204)</td>
<td>Teneligliptin – 20 mg (n=103)</td>
<td>HbA1c-8.1% FPG – 150.7 mg/dL</td>
<td>Significant reduction in HbA1c and FPG were observed with Teneligliptin treatment</td>
</tr>
<tr>
<td>Otsuki H, Kosaka T et al 2014 Feb 1</td>
<td>Bi center, prospective, non randomized study (n=43)</td>
<td>Teneligliptin – 20 mg (n=14)</td>
<td>HbA1c – 6.4%</td>
<td>Blood glucose level decreased 21.60 mg/dL at 28 weeks after Teneligliptin administration GA dropped 1.7-2.5% by 28 weeks and HbA1c fall 0.3-0.8% by 28 weeks</td>
</tr>
<tr>
<td>Tanaka K, Okada Y et al 2016 Dec 1</td>
<td>Randomized crossover study (n=13)</td>
<td>Teneligliptin – 20 mg, Linagliptin – 5 mg</td>
<td>HbA1c – 6.7% eGFR (ml/min/1.73 m2) – 28.2</td>
<td>Teneligliptin and Linagliptin significantly reduced the 24-h mean glucose levels and AUC(180) but did not increased the incidence of hypoglycemia</td>
</tr>
<tr>
<td>Hashikata T, Yamaoka-Tojo M et al 2016 Aug 1</td>
<td>Single center, pilot study (n=27)</td>
<td>Teneligliptin – 20 mg, 40 mg</td>
<td>HbA1c – 7.5% LVEF -63.7% E/e-13.4</td>
<td>Teneligliptin improves left ventricular diastolic function and endothelial function in patients with diabetes</td>
</tr>
<tr>
<td>Patel DK, Sharma RT et al. 2016 Dec 28</td>
<td>Randomized, double blinded, placebo controlled, parallel comparative study (n=240)</td>
<td>Teneligliptin – 40 mg (n=59), 160 mg (n=59) Moxifloxacin – 400 mg (n=62)</td>
<td>HbA1c – 7.5% FPG – 148.4 mg/dL</td>
<td>Teneligliptin was not associated with significant QT interval prolongation at 40 mg dose and QT prolongation was observed at 160 mg</td>
</tr>
<tr>
<td>Suryawanshi SY, Bhargava A et al 2016 Aug 1</td>
<td>Multicentric, double blinded, placebo controlled, phase 3 clinical trials (n=237)</td>
<td>Teneligliptin – 20 mg (n=58)</td>
<td>-</td>
<td>Treatment with once-daily Teneligliptin led to statistically significant and clinically meaningful reductions in HbA1c and PPG, and was well tolerated in Indian nationals with T2D</td>
</tr>
</tbody>
</table>
Glucose fluctuation using CGM: No significant difference

Teneligliptin significantly improved:
Plasma glucose (≥ 140 mg/dl) after supper (20:00-24:00)
GLP-1 level at 30 minutes after the meal load area under curve was better with Teneligliptin

No serious adverse effects, other than asymptomatic hypoglycemia.

**Fig. 1: Teneligliptin in comparison to Sitagliptin**

**Fig. 2: Teneligliptin: Real World Evidence In Indian Patients- TREAT India Study**

**Expert comments:**
Although TREAT-INDIA is the largest real-world data in India but longer follow-up is needed to evaluate the long-term benefits and risks of teneligliptin. Also, trials are needed to be conducted to assess the therapeutic effect of teneligliptin by comparing the effects with other DPP4 I. Another important issue here is to observe 24 h glucose fluctuations. Large fluctuations may increase the risk of complications, such as CV disease, so it is better to evaluate post-prandial glucose fluctuations over the entire 24 h dosing interval.

**Subgroup analysis** was also performed across three age groups (<65; 65 to 75 and >75 years). These interim results showed that Teneligliptin was well
tolerated and effective in long term therapy and improved hyperglycemia.28

RUBY Surveillances conducted in Japan, showed that teneligliptin in long term was well tolerated in all age groups with low incidence of adverse events and reduced blood glucose levels and glycated hemoglobin. It is also well tolerated in all stages of renal disease and mild to moderate hepatic disease. It has no harmful effects on cardiovascular system at the recommended clinical doses.

**Teneligliptin Safety**

**Efficacy and safety of high dose (40mg) of Teneligliptin**

Kadowaki T, et al. examined the treatment response when Teneligliptin dose was increased from 20 to 40 mg in post hoc pooled analysis of data from two 52 week open-label, phase III clinical trials where 204 patients received increased Teneligliptin dose from 20 to 40 mg/day at 28 week and then observed for another 24 weeks (28-52 weeks). In both studies, the dosage of teneligliptin was titrated to 40 mg once daily during weeks 28–40 for
those patients who met the criteria for dose increase (HbA1c > 7.3% in Study 3000-A8; > 7.4% in Study 3000-A14) and for whom there were no safety concerns as judged by the investigator. Out of 204 patients, 108 (52.9%) showed a response to teneligliptin 40 mg (HbA1c change < -0.1% during weeks 28–52) and had mean (± SD) HbA1c reduction of 0.50 ± 0.44%. Of patients showing re-elevation of HbA1c during treatment with teneligliptin 20 mg, 89/143 (62.2%) achieved HbA1c reduction after dose increase to 40 mg. It was concluded that increasing the dosage of Teneligliptin from 20 to 40mg/ day had a potential as a well-tolerated and effective option for treating T2D. However, the study did not specifically look and analyse the effect on QT prolongation with higher dose despite a serious concern about this issue. Though the incidence of Adverse Drug Reactions were not about this issue. Though the incidence of Adverse Drug Reactions were not.

Teneligliptin – Renal Safety

The anti-diabetic efficacy of Teneligliptin has also been found to be effective in diabetic patients irrespective of CKD predisposition, and Diabetic Nephropathy (DN) is said to be a frequently occurring microvascular complication of T2D. Diabetes has been the major aetiological factor of kidney failure in nearly 45% of patients undergoing dialysis. Out of all the cases, ~25-30% patients may develop end-stage renal disease (ESRD), which may make the conditions more difficult to manage.

The advantageous use of DPP-4 inhibitors has long been emphasised upon. Observational studies demonstrated potential increase in estimated glomerular filtration rate (eGFR). However, this observational renal benefit was not corroborated by any dedicated phase 3 renal outcome data.

Halabi et al, evaluated the pharmacokinetics of teneligliptin in renally impaired (mild to end-stage) and healthy subjects. The results suggested that the Cmax following single dose administration of teneligliptin (20 mg) was unaffected by mild, moderate and severe renal impairment. Post-dialysis ESRD patients displayed a higher Cmax and AUC in comparison to healthy patients. An important conclusion of the study was the fact that the plasma protein binding (PPB) capacity in renally impaired studies was <80%, which is in accordance with the FDA guidelines stating; drugs with low extent of PPB (<80%), alterations in protein binding is likely to be small in relative terms. It was concluded that single 20 mg dose of teneligliptin is well tolerated by healthy subjects and subjects with renal impairment or ESRD, so teneligliptin given predialysis, 90% CI for AUCmax was within the no effect boundaires and upper limit of 90% CI for Cmax, is also below 125% which indicates, teneligliptin can be given before dialysis without dose adjustment.

This confirmed the fact that dose adjustment of Teneligliptin in case of renally impaired patients is not required. This comes as an advantage for diabetic patients as the drug regimen can be followed by the patients in the same dose, even in the light of renal impairment.

Teneligliptin effect in CKD

Otsuki H et al, conducted a prospective study to assess the utility of Teneligliptin for diabetic patients undergoing hemodialysis. It was concluded that Teneligliptin 20 mg is well tolerated, and significantly improves glycemic control in diabetic patients with ESRD. Teneligliptin 20 mg once daily was found to be more potent than voglibose 0.2 mg t.i.d. or vildagliptin 50 mg qd.

Wada N et al, evaluated the efficacy and safety of teneligliptin in Type 2 DM on haemodialysis by CGM and concluded that this drug improves blood glucose AUC on both HD day (p=0.004) and NHD day (p=0.004) with significant reduction in glycated albumin (GA), HbA1c, FPG without severe hypoglycaemia.

Fifteen patients with diabetes and CKD undergoing hemodialysis were treated with Teneligliptin 20 mg in Homma K et al, study. Teneligliptin significantly reduced plasma levels of RLP-C (Remnant-like particle cholesterol), FPG and HbA1c in

![Fig. 3: Results- Teneligliptin: Real World Evidence In Indian Patients- TREAT India Study](image)
patients with CKD and undergoing hemodialysis.

Haneda M et al, published a data from Ruby surveillance regarding the safety and efficacy of Teneligliptin in impaired renal function patients. Where it was concluded that Teneligliptin was effective and well tolerated in patients with any stage of renal impairment from normal to end stage disease, including those on dialysis and improved glycemic control.

Kitada M, Ogura Y et al, observed the effect of switching to Teneligliptin from other DPP-4 inhibitors on glucose control and renoprotection in T2D patients with diabetic kidney disease. The plasma DPP-4 activity was significantly reduced after 24 weeks (0.57 ± 0.26 nmol/min/mL, P = 0.012, vs baseline), compared with baseline (1.49 ± 1.73 nmol/min/mL), without any significant change in HbA1c, FPG and UACR values. Switching to Teneligliptin from other DPP-4 inhibitors for 24 weeks reduced the DPP-4 activity, which was associated with non-significant reduction of albuminuria (r value=0.3038, p value=0.1588 ns).

**Expert comments:** Teneligliptin in high doses (40mg/day) is well tolerated without any significant safety concerns, both at 24 and 52 weeks, and is an effective option for treatment of T2D. But the limitations of the study was that effect on QT prolongation has not been systematically studied at this dose.

Teneligliptin is well tolerated in impaired renal function patients and in patients undergoing hemodialysis with significant reduction in glycaated Albumin, HbA1c, FPG, RLP-C (Remnant Lipoprotein Cholesterol) levels without severe hypoglycemia. Teneligliptin is well tolerated in all stages of renal impairment and no dosage adjustment required.

**Teneligliptin – Hepatic Safety**

Teneligliptin is unlikely to cause conspicuous drug interactions or changes in its pharmacokinetics in patients with hepatic impairment, due to a balance in the elimination pathways. Halabi A et al, studied the pharmacokinetics of Teneligliptin in 3 groups of 8 subjects assigned according their degree of hepatic impairment (mild, moderate or matched healthy subjects). The lower mean total clearance in subjects with mild (9.79 L/h) or moderate (8.57 L/h) hepatic impairment resulted in longer mean half-lives (27.9 and 30.9 hours, respectively) than in healthy subjects (clearance: 13.11 L/h, half-life: 24.8 hours). It was concluded that Teneligliptin was well tolerated by subjects with mild to moderate hepatic impairment and was indicated that caution will be needed when administering Teneligliptin in patients with hepatic impairment. However, data on hepatic safety is small and based on a very small population. There is no clinical experience of Teneligliptin use in severe degree hepatic dysfunction patients.

**Teneligliptin and Cardiovascular Safety**

Cardiovascular events are commonly associated with T2D and the incidences are said to be frequent and often severe. Additionally, incidences of dyslipidaemia are also linked to T2D. The overall scenario as such highlights the gravity of the fact that even with glycaemic control, adverse effects of the disease tend to progress and aggravate. Hence, selecting the optimal therapy for individuals with T2D necessitates careful retrospective vis-à-vis cardiovascular safety and concurrent antidiabetic therapy. In all published randomized controlled trials, no serious cardiac events have been attributable to teneligliptin. The important cardio-vascular and effects of Teneligliptin provide an alternative and safer mode of anti-diabetic care. However, no dedicated phase-3 cardiovascular outcome trial was done to establish the safety of this drug beyond doubt among diabetics with overt cardiovascular disease or heart failure. Therefore, more data for long-term effects on cardiovascular events are needed as rightly pointed out by Li X in a systematic review and meta-analysis of randomized controlled trials on teneligliptin.

**Teneligliptin: QT prolongation**

Reported evidences suggest that QT prolongations were not observed with teneligliptin 40 mg daily dose. However, mild and transient QTc prolongation was observed only at a supraclinical dose of 160 mg/day which is 8 times the daily dosage of teneligliptin. To confirm the effect of teneligliptin on QT prolongation a randomized, double-blind, placebo and moxifloxacin controlled, parallel-group comparative study was conducted in 240 healthy adult male and females to investigate the effect of multiple-dose administration of teneligliptin (40, 160 mg) on QTc intervals. Placebo, teneligliptin (40 mg and160 mg) were administered orally once daily for 4 days. In the moxifloxacin group (positive control group), placebo was administered orally once daily for 3 days and moxifloxacin 400 mg on day 4. QTc interval prolongation was observed only time points near tmax after administration of teneligliptin. No clinically significant QTc interval prolongation was observed at 40 mg. It was observed that teneligliptin was not associated with QT interval prolongation at clinically relevant dose (maximum recommended dose 40 mg) in healthy individuals. However, teneligliptin should be used with caution when co-administered with drugs known for QT prolongation like class IA or class III antiarrhythmic drugs. There is scarcity of data regarding effect of teneligliptin on QT prolongation and the above findings on QT prolongation were not corroborated by other similar study.

A study was conducted by Erande et al, involving 66 uncontrolled T2D patients, with HbA1c >7.0 % and were glitpit naive at two dose of Teneligliptin (20 mg or 40 mg). The results showed significant reduction in FPG (p<0.002), PPG (p<0.001) and HBA1C (0.69%, p<0.001) with no effects on QT / QTc interval prolongation by Teneligliptin at both doses.

**Expert comments:**

Teneligliptin should be used with caution in patients with mild to moderate hepatic impairment. QT prolongation is seen only with higher doses (160mg/day) but not with maximum recommended dose of 40 mg/day, however caution should be exercised when Teneligliptin is co-administered with drugs known to cause QT prolongation such as class IA or class III anti-arrhythmic agents. There have been no reports of QT prolongation in India so far. Teneligliptin in Type-2 DM patients resulted in improvement of systolic and diastolic function at 3 months with increase in adiponectin levels making Teneligliptin a useful drug in cardiac and renal patients.

**Teneligliptin: non-glycaemic Benefits**

**Cardiovascular benefits:**

Teneligliptin: Effect on LV function

Hashikata T et al, evaluated whether Teneligliptin (3 months treatment) affects Left ventricular (LV) function in patients with T2D (n=29). There was a decrease in HbA1c levels (7.6 ± 1.0 % to 6.9 ± 0.7 %, p < 0.01) after the treatment, whereas the 5-anhydro-D-glucitol levels increased (9.6 ± 7.2 μg/mL to 13.5 ± 8.7 μg/mL, p < 0.01) significantly. The systolic and diastolic functions got significantly improved (LV ejection fraction, 62.0 ± 6.5 % to 64.5 ± 5.0 %, p = 0.01; peak early diastolic velocity/basal
septal diastolic velocity (E/e’) ratio, 13.3 ± 4.1 to 11.9 ± 3.3, p = 0.01]. It was noticeable that teneligliptin could have beneficial effects on the cardiac pump but needs to be replicated in a study of longer duration with large population for further validation.41

**Teneligliptin: Effect on Cardiovascular Markers**

In a study, Okuda Y et al, assessed the effects of Teneligliptin on serum cardiovascular risk markers including soluble P-selectin (sP-selectin), platelet-derived microparticles (PDMPs), plasminogen activator inhibitor 1 (PAI-1), soluble E-selectin (sE-selectin), soluble vascular adhesion molecule 1 (sVCAM-1), and adiponectin in HD and non-HD patients with T2D. Teneligliptin therapy significantly reduced plasma levels of sP-selectin, PDMPs, and PAI-1 compared to baseline levels, while significantly increasing adiponectin levels. sE-selectin and sVCAM-1 levels were significantly decreased only at 6 months. The reduction in sP-selectin, PDMPs, and PAI-1 was more significant in hemodialysis patients than in non-hemodialysis patients. Interestingly however, the improvement in adiponectin levels was unchanged with hemodialysis. By modulating PDMPs or PAI-1, teneligliptin showed an anti-atherothrombotic effect that may be beneficial in the long run in the primary prevention of CVD in patients with T2D on hemodialysis.42

**Teneligliptin Positive Effect on Oxidative Stress and Endothelial Function**

Sagara M et al., compared the efficacy of Teneligliptin and Sitagliptin on oxidative stress and endothelial function in T2D patients with CKD. Reactive hyperaemia peripheral arterial tonometry was used to assess peripheral endothelial function. Endothelial dysfunction was defined as Reactive Hyperaemia Index (RHI) <0.670. T2D patients with CKD (n=45) receiving Sitagliptin for at least 12 months were randomized to receive either Teneligliptin (n=22) or continue therapy with Sitagliptin (n=23) for 24 weeks.

This study showed Teneligliptin to be equivalent to Sitagliptin with regard to effects on HbA1c, eGFR and urinary albumin excretion. Only Teneligliptin, significantly improved reactive hyperaemia index values (1.49±0.32 to 1.55±0.29, p<0.01), reduced levels of 8-hydroxy-2’-deoxyguanosine, [oxidative stress marker (7.1±4.9 to 5±2.9 ng/m Cr, p<0.05)] and urinary liver type fatty acid binding protein (L-FABP) (p<0.05). Improvements in urinary L-FABP levels have been associated with beneficial outcomes for patients at high risk of renal disease and Atherosclerotic Cardiovascular Disease (ASCVD), in published literature.43

**Teneligliptin: Effect on Lipids**

As per study of Kusunoki M, et al, on the effectiveness of treatment with Teneligliptin (20 mg/day) given for 14 weeks in T2D patients (n=9) based on the HOMA-Ratio, an indicator of insulin resistance, and serum lipid profile, suggested that Teneligliptin not only improve blood glucose control, but also improves insulin resistance and serum lipid profile in T2D patients.44

**Expert comments:**

Teneligliptin has anti-atherothrombotic effect that may be beneficial in the primary prevention of cardio-vascular disease in patients with T2D on hemodialysis. Teneligliptin significantly improved reactive hyperaemia index values showing positive effect on oxidative stress and endothelial function, along with HOMA-R and serum lipid profile in T2D patient’s after 14 weeks of treatment. Teneligliptin also improved the histopathological appearance of NAFLD affected liver in mouse models with down regulation of hepatic lipogenesis related genes. Teneligliptin, a novel DPP-4 inhibitor may have anti-oxidant properties and protects endothelial cells exposed to high glucose levels, but not yet well established in randomized controlled trial.

**Teneligliptin Effect in Non-Alcoholic Fatty Liver Disease (NAFLD)**

A distinct hepatic condition, NAFLD is higher in prevalence amongst obese individuals and patients with T2D. Teneligliptin has been shown to improve the hepatic histopathology and decreased intrahepatic triglyceride levels in an NAFLD model mouse. This improvement was associated with AMPK activation and the subsequent down regulation of hepatic lipogenesis-related genes.45

**Teneligliptin: Other Pleiotropic Effects**

The vascular endothelium plays a crucial role in maintaining vascular integrity and function. Chronic exposure to high glucose generates oxidative stress leading to endothelial dysfunction. Considering the potential protective action of Teneligliptin in endothelial cells exposed to high glucose, Pujadas G et al (2017), published a study showing Teneligliptin as novel dipeptidyl peptidase-4 inhibitor in terms of its antioxidant properties and has the potential of inducing a good metabolic memory. Human umbilical vein endothelial cells were cultured under normal (5 mmol/L) or high glucose (25 mmol/L) during 21 days or at high glucose during 14 days followed by 7 days (normal glucose), to reproduce the high-metabolic memory state, using different concentrations of Teneligliptin (0.1, 1.0 and 3.0 μmol/L) or Sitagliptin (0.5 μmol/L). RNA and protein expression were assessed for antioxidant response, proliferation, apoptosis and endoplasmic reticulum stress markers. Teneligliptin, was superior to Sitagliptin in counteracting reactive oxygen species production, inducing a robust antioxidant response and reducing endoplasmic reticulum stress. This study shows that.46

**Conclusion**

Challenges and gaps in diabetes care concerning Indian patients can be summarized as inadequate lifestyle management, early onset, cost of therapy, lack of uniform access to proper care and ever-growing problem of obesity, which at times is compounded by anti-diabetic agents. Teneligliptin a truly 3rd generation, gliptin has firmly positioned itself as a very important drug in the armamentarium of physicians managing diabetes, especially in Indian patients. Teneligliptin is the most commonly used DPP IV inhibitor option for diverse diabetic profiles in India. This can be attributed not only to its positive effect in controlling the Glycaemic parameter, but also to its efficacy and safety at very low cost in a developing country like India where diabetes is a major health care burden. Diabetes can be a very expensive disease; wherein incomplete control can lead to multiple complications adding to the cost of monthly therapy cost. Teneligliptin offers efficacy along with safety and cost-effective therapeutic choice especially in Indian T2D patients.

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Real Time Flash Glucose Monitoring: Now a Reality in India

Ranjit Unnikrishnan¹, Viswanathan Mohan¹, Jothydev Kesavadev², Mangesh Tiwaskar³, Banshi Saboo⁴, Shashank Joshi⁵

Abstract
Tight glycemic control has been recognised as the cornerstone of modern diabetes management. Until recently, glycated hemoglobin (HbA1c) was the only reliable tool for measuring glycemic control, but it is not an ideal metric as it is retrospective, unable to pick up hypo- and hyperglycemic excursions and prone to interference by conditions such as anemia and hemoglobinopathies. The advent of continuous glucose monitoring systems is a giant leap in diabetes management as it enables visualisation of glucose trends over periods of time, helping in identification of hypo- and hypoglycemic events and enabling appropriate treatment decisions to be made. The recent launch of the real-time patient CGM in India is a further step in the right direction as it will empower patients to take control of their diabetes by providing them information on their glucose levels and trends in real time.

tight glycemic control, aiming for blood glucose levels as close to normal non-diabetic levels as possible, has been shown to reduce the risk of both micro- and macro-vascular complications of diabetes.¹² For nearly 50 years since the concept of tight glycemic control was first introduced by Joslin, its achievement remained elusive, primarily due to the absence of a convenient and reliable marker of long-term glycemia. This deficiency was overcome, to a large extent, by the advent of glycated hemoglobin (HbA1c) testing, and maintaining HbA1c at target levels is now part of all established guidelines for diabetes care.³

However, the use of HbA1c as a tool to measure glycemic control is not without its disadvantages, some of which are listed below.⁴

1. HbA1c represents the average glycemia over the preceding 2 to 3 months and does not provide information on hypo- and hyperglycemic excursions.
2. HbA1c fails to identify the magnitude and frequency of intra- and inter-day glucose variation
3. The relationship between HbA1c and average glycemia may not be exactly the same in all individuals, such that certain individuals demonstrate an inappropriately high or low HbA1c for their degree of glycemia.
4. HbA1c can be affected by several non-glycemic factors such as altered RBC lifespan, hemoglobinopathies, renal insufficiency and (non-diabetes) medication use.

Therefore, relying solely on the HbA1c to assess an individual’s glycemic control does not provide a comprehensive picture of the clinical situation, and may also lead to erroneous treatment decisions. This realization has led to the development of alternative methods of assessing glycemic control that can supplement the HbA1c. The most widely used among these is self-monitoring of blood glucose (SMBG). SMBG is relatively easy to perform, but has the disadvantage that it is operator (patient)-dependent, often leading to data not being available for time periods of interest to the physician to adjust medicine doses. It is also difficult to draw inferences about glycemic trends from the (often disjointed) data generated from SMBG. In other words, the SMBG provides ‘Snapshots’ of glucose levels at the times when the patient chooses to test providing no idea about the time in between.

Continuous glucose monitoring (CGM)
CGM is a robust technique for assessing the day to day fluctuations and medium-term glycemic trends in patients with diabetes. One can therefore compare the SMBG to ‘still photography’ and CGM to a ‘video’. (Figure 1A and 1B).

CGMS has been in clinical use for more than 20 years now. The traditional

Fig. 1: (A) SMBG measurements do not show trends in glucose; (B) CGM/FGM shows trends of glucose

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CGM systems suffered from various drawbacks such as short duration of recording, requirement for fingerstick calibration, cumbersome sensors and high cost. The advent of flash glucose monitoring (FGM) devices over the last 5 years has revolutionized the field of diabetes monitoring worldwide. Two variants of this system were launched—one meant for patient use, which is a real time FGM and the other meant for use by healthcare professionals. In India, the professional model was made available in 2015. In contrast, in many other regions such as Europe and UK, the patient model was introduced first. Table 1 lists the differences between the professional and patient FGM system.

Both these systems consist of a sensor which is inserted subcutaneously (usually over the upper arm) and a reader that collects data from the sensor when placed close to the sensor (“intermittent scanning”). Both these systems offer considerable advantages when compared to the earlier (non-flash-based) systems. The sensors for both these systems work for a period of 14 days, as compared to 7 days for the older systems. They are factory-calibrated, and hence there is no need for calibration with fingerstick glucose values. The sensor is unobtrusive and its insertion is virtually painless. The system is also less expensive as compared to the earlier traditional CGM systems. Indeed, if one takes into account the number of times the glucose can be tested, it works out to be cost effective. It is also much less cumbersome and practically painless compared to SMBG.

These systems provide their reports in the form of an ambulatory glucose profile (AGP). The proprietary AGP software collapses all CGM data from several days or weeks into a single 24-h period. This helps in providing insights into the glycemic trends for the preceding 2 weeks, which can then be used to predict the patterns for the next 2 to 3 months with a reasonable degree of confidence. The software also calculates such variables as the glucose management indicator (GMI), time in-, above and below range and glycemic variability. This is of immense help to clinicians in adjusting therapies, and in assessing the effects of such adjustments. In view of these advantages, it is probably not surprising that the flash glucose monitoring systems have become popular in India and are widely accepted by clinicians. Consensus Guidelines have also been published on the use of CGM in India.

Recently, an International Panel of experts convened by the Advanced Technologies & Treatments for Diabetes (ATTD) Congress, published guidelines for the reporting of CGM metrics. As per these guidelines, the most important metric derived from CGM is the “time-in-range” (TIR). TIR is defined as the proportion of time (usually expressed as a percentage) that an individual spends with his/her blood glucose levels within a prespecified target range (usually defined as 70 to 180 mg/dl). TIR is rapidly emerging as an important complement to HbA1c as a measure of glycemic control and may even replace HbA1c in the future. A recent study from India demonstrated close alignment with TIR in accordance with the International Consensus on TIR for A1c between 7 and 9 %. Higher TIR has been shown to be associated with lower odds of developing severe retinopathy, as well as lower risk of cardiovascular disease and all-cause mortality.

Table 2 shows the differences between HbA1c and TIR. While it is possible to calculate TIR from SMBG data, its accurate measurement requires the use of CGM and flash glucose monitoring systems.

In a study from multiple diabetes clinics across India, 2536 individuals who had unsatisfactory control of diabetes (HbA1c >7%) were initiated on the professional FGM system and compared with 2536 age, sex and HbA1c-matched individuals who were not put on FGM, after a period of 6 months. Individuals who were initiated on FGM showed greater reduction in HbA1c levels compared to those who were not, even after adjusting for age, gender, body-mass index, systolic blood pressure, time to follow-up A1c, and medication use.

The patient FGM system is meant for patient use and requires the patient to purchase the reader as well as the sensor. It permits the patient to view the glucose trends and levels in real time. The professional model is meant for use by healthcare professionals for detecting trends and tracking patterns and glucose level excursions above or below the desired range, facilitating therapy adjustments. The patient usually purchases only the sensor, while the reader remains in the physician’s office, and can be used to

| Table 1: Differences between ‘Retrospective’ and ‘Real Time’ flash glucose monitoring systems |
|-----------------------------------------------|-----------------------------------------------|
| Type of device                              | Retrospective flash glucose monitoring         |
| Sensor applied by patient                   | Real time flash glucose monitoring             |
| Sensor wear duration                        | Personal use                                   |
| Real-time readings                          | Professional use                               |
| How to get glucose readings?                | Up to 14 days                                  |
| Fingerstick calibration                     | No (Retrospective)                             |
| On-the-body equipment                       | Yes, with a scan of the sensor                 |
| Reader                                       | The sensor needs to be brought to the          |
|                                               | clinic for reading                             |
|                                               | Patients can scan the sensor by themselves at |
|                                               | each time and get real time readings          |
|                                               | Sensor applied by patient to the back of the   |
|                                               | patient’s arm; worn for up to 14 days         |
|                                               | Sensor applied by patient to the back of his/ |
|                                               | her own arm; worn for up to 14 days           |
|                                               | • HCP owned and stays in the office/clinic    |
|                                               | • One reader can be used for multiple patient |
|                                               |                                               |

<table>
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<tr>
<th>Table 2: Differences between HbA1c vs. TIR</th>
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<tr>
<td>Glycated hemoglobin (HbA1c)</td>
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<tr>
<td>Retrospective measure of average glucose</td>
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<td>Provides data on control</td>
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<td>over preceding 3 months period</td>
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<td>ranging from 3 – 14 days</td>
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<td>Does not capture hypo- or hyperglycemic</td>
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<td>excursions</td>
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<td>Immediate effects of therapy changes</td>
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<td>Bad correlation to Patient reported</td>
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<tr>
<td>outcomes (PROs)</td>
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<td>High susceptibility to interference</td>
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<td>(method and lab-dependent, anaemia,</td>
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<td>hemoglobinopathy, etc.)</td>
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<tr>
<td>Good correlation to clinical endpoints,</td>
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<td>many long-term studies</td>
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Recent studies have demonstrated close alignment with TIR in accordance with the International Consensus on TIR for A1c between 7 and 9 %. Higher TIR has been shown to be associated with lower odds of developing severe retinopathy, as well as lower risk of cardiovascular disease and all-cause mortality. 

Some other important metrics derived from CGM can also be measured. These include daily glucose variability (VGI), continuous glucose variability (CGVI), and time spent within specific glucose ranges (TIR range).

In conclusion, CGM systems offer considerable advantages over traditional SMBG methods. They are easy to use, convenient, and provide real-time glucose readings. The professional model is meant for use by healthcare professionals, while the patient model is designed for patient use. Both these models provide valuable insights into glycemic control and can help in adjusting therapies. However, they require a higher financial investment compared to SMBG. Therefore, clinicians should consider the benefits and drawbacks of these systems before deciding on the appropriate device for their patients.
scan the sensors of multiple patients. However, the professional model suffers from the disadvantage that even if the patient purchases the reader separately, it does not provide real-time glucose values, necessitating the use of capillary glucose meters for immediate diagnosis of hypo- or hyperglycemic events. The advent of the patient model of FGM in Europe and France, showed that use of FGM was significantly reduced in HbA1c over the 1 year of use. Individuals reported fewer episodes of hypoglycemia, less absenteeism from work and scored better on quality of life scores and lower on perceived disease burden scores after FGM use.

The advent of flash glucose monitoring represents a significant advance in diabetes care in India. Patients who use the system are able to obtain a real time glucose reading, a trend indicator and history of glycemic excursions over the preceding 8 hours, each time they scan their sensor. The patient is also able to visualize daily trends, the time in range and hypoglycemic episodes. However, the sheer magnitude of data generated by the system may feel overwhelming to some patients. Should patients therefore be given appropriate education on how best to interpret the data provided by their monitoring system and how to utilize it to make the most appropriate decisions. It is hoped that the HbA1c of our patients in India will further improve after introduction of these devices, which represent a big step forward in personalized or precision diabetes monitoring.

References
Peripheral Gangrene in a Rare Scleroderma Overlap Syndrome

Ramadoss Ramu¹, Vivek Arya², Ashish Sharma¹, Randeep Rana³

A 48-year-old woman, a known case of systemic sclerosis and interstitial lung disease, presented with complaints of pain and blackish discoloration of the toes of both feet for 1 month (Figure 1). There was no history of fever, muscle pain, weakness, skin rash, joint pain or bleeding from any site. On examination, the patient had a pulse rate of 90/minute which was regular and the pulse volume was low in the left brachial and radial arteries. Dorsalis pedis pulse was not palpable on both sides. There was a difference of 30 mmHg between the right and the left arm in systolic blood pressures. Musculoskeletal examination showed auto amputated fingers of both hands, telangiectasia, calcinosis cutis and skin thickening (Figures 2 and 3). Dry gangrene was present in both feet (right > left). Investigations showed raised ESR and CRP and positive ANA and anti-centromere antibodies. Radiographs of both hands showed acro-osteolysis, erosions and joint space narrowing at proximal interphalangeal joints (Figure 4). Arterial Doppler of both lower limbs was reported as showing features of small vessel disease. CT aorta angiogram revealed focal stenosis of branches of the aorta which was suggestive of type V Takayasu arteritis (Figures 5, 6 and 7). Since our patient had progressive gangrene, an active vasculitic process was thought of. The patient was treated with pulse methyl prednisolone followed by oral Prednisolone because of extensive gangrene in both feet. Since there was no improvement in the peripheral gangrene even after a month, she was given a cyclophosphamide pulse. However, the patient succumbed to a respiratory infection 3 weeks later.

Scleroderma is a debilitating autoimmune connective tissue disorder affecting the skin, lung, pulmonary artery, renal artery and the alimentary tract. Diffuse microangiopathy, inflammation due to autoimmunity, and visceral and vascular fibrosis are the cardinal pathophysiology features of scleroderma. Raynaud phenomenon is present in almost all patients with scleroderma. It can lead to digital pitting, ulceration and gangrene.¹

Overlap syndrome is a well-known entity among rheumatological diseases. Scleroderma overlap syndrome can present with other connective tissue disorders like polymyositis, systemic lupus erythematosus and rheumatoid arthritis etc.² Typical vasculitis with inflammatory infiltrates damaging blood vessels has rarely been reported in patients with Scleroderma.³

Takayasu arteritis is a chronic large-
vessel arteritis that predominantly affects the aorta, its major branches, and the pulmonary arteries. Segmental stenosis, occlusion, dilatation, or aneurysm formation may occur in the vessel wall during the course of the disease. Various signs and symptoms such as constitutional features (fever, malaise, anorexia, and weight loss), extremity pain, claudication, lightheadedness, bruits, absent or diminished pulses and reduced blood pressure can be present according to the vessel involved. Several reports describe skin lesions such as erythema nodosum, malar rash or erythema induratum associated with Takayasu arteritis. But peripheral gangrene is rare and only a few case reports are available.

Very few cases of scleroderma overlap syndrome with Takayasu arteritis were reported in the literature. Four cases of Takayasu arteritis in the setting of SSC have been reported. These patients were females with age ranging from 29 to 68 years. Three of them had diffuse skin thickening. Computed tomographic angiography in all cases showed stenosis of various aortic branches.

Our case highlights the importance of being aware of a possible overlap syndrome when clinical features do not fit into one rheumatological disorder.

References


Pseudo Tachycardia

A Shaheer Ahmed¹, Mondithoka Sukumar²

A 75-year-old male had presented to the emergency with history of fall from a motor cycle. Evaluation by the orthopedics team revealed fracture neck of left femur and was planned for surgery. He did not have any previous known cardiac ailments or any cardiac symptoms. As part of routine preoperative evaluation electrocardiogram was done. It showed broad regular QRS complexes in the limb leads and multiple p waves in the chest leads with around 3:4:1 atrioventricular conduction (one QRS complex for 3-4 p waves) (Figure 1), which on first look appeared to be some sort of tachyarrhythmia. The limb leads and chest leads gave the perception of ventricular tachycardia and atrial tachycardia/atrial flutter respectively. However, on meticulous analysis of the electrocardiogram we were convinced that it was an artifact based on few features. The patient was asymptomatic, hemodynamically stable and had a normal heart rate. Lead II didn’t show any abnormal QRS complexes (Sinus Sign), which is not possible in case of tachycardia. In the limb leads there were distinct narrow QRS complexes in the midst of wide complexes (Spike sign). Typical counterclockwise atrial flutter will have positive p waves in lead V1 but negative p wave in lead V6, which is not the case in our ECG. Atrial tachycardia arising from left atrium will have a positive p wave in lead V1, but again has a negative p wave in lead V6 as the vector of p wave is directed away from lead V6. The patient was having Parkinson’s disease with tremors more prominent in left arm and right leg, perhaps explaining normal QRS complexes in lead II. Artifacts produced as a result of electromagnetic interference tends to have a higher frequency and will be seen in all the leads. An occasional patient with Parkinson’s disease might have a deep brain stimulator implanted, which also can artefact in all 12 leads. Precordial leads also show artefactual changes since wilson’s central terminal is produced by connecting the negative pole of limb electrodes. Patient underwent surgery with uneventful hospital stay. Benign ECG artefacts tend to masquerade as life threatening arrhythmias. It is of utmost importance to promptly recognize the correct diagnosis by systematically analyzing the ECG, which in turn helps in both preventing unnecessary shocks/antiarrhythmics and timely management of life threatening arrhythmias.

References


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Abstract
Pregnant women are one of the most important groups who need special attention during this Covid-19 pandemic. Women's physiological changes in the immune system during pregnancy put them and their neonates at increased risk of adverse outcomes due to COVID-19. Available literature indicates that intrauterine exposure to SARS-CoV-2 infection does not affect the immune function in term babies. However, biased expression of inflammatory response may occur spontaneously or in presence of comorbidities which may be an indicator of complications as in adults. Therefore, it is important to accumulate knowledge about outcomes of COVID-19 infected pregnancies, which include the possibility of vertical transmission, potential complications during pregnancy, in foetus and in neonate. We report one of the first cases of cytokine storm in neonate born to asymptomatic SARS-CoV-2 infected mother although the neonate harboured IgG antibodies to SARS-CoV-2.

Case report
A 28 years old female, third gravida with two live issues was admitted at 37 weeks+4 days period of gestation in which she was diagnosed as having asymmetrical FGR. Thereafter she visited the hospital twice in which no significant growth was observed on serial sonography. All blood pressure records were normal during this period. Her screening with SARS CoV-2 antibodies was done (in view residential area in containment zone) which was positive with value of 39.52 Au/ml (normal < 1.0 Au/mL) at 37 weeks+2 days period of gestation. Her RT/PCR for SARS-CoV-2 was negative at the same time. Past obstetric history was unremarkable.

She was induced with two doses of dinoprost (PGE2) gel and augmented by oxytocin but she developed severe foetal distress in latent labour and was taken up for caesarean section, which was uneventful. Male baby of birth weight 1658 grams, with APGAR score 5 and 8 at 1 and 5 minutes respectively, was delivered and required bag and mask ventilation for 15 seconds. Her placenta was small with calcifications. Baby had external congenital anomalies viz. left ear malformation, left cheek skin tag, left undescended testis and hypospadias. In view of low birth weight, baby was shifted to neonatal intensive care unit (NICU) for further observation. Initial vitals were stable with no respiratory distress and SpO2 maintained >95% at room air. At 24 hours of life, baby was noted to have petechial rash and tachypnoea. Intravenous antibiotics and oxygen support were initiated with a provisional diagnosis of early onset sepsis. Blood reports revealed thrombocytopenia (platelet count 62000/mm3, Hemoglobin 18.4g/dl, TLC 10820/mm3) and deranged coagulation profile (INR 2.7). Platelets and fresh frozen plasma were given. In view of worsening respiratory distress, baby was put on CPAP and antibiotics were upgraded. Further blood reports showed deranged KFT (Blood urea 18.3mg/dL, serum creatinine 1.0mg/dL, serum calcium 7.3mg/dL) and LFT (bilirubin 10.9mg/dL, albumin 3.3g/dL, globulin 1.1g/dL, SGOT/SGPT 74/14 IU/L). A repeat CRP done was 0.6mg/dl, less than the cut off guidelines to classify as positive screen for sepsis. Blood culture was sterile and baby’s RT-PCR for SARS-CoV-2 was negative. SARS CoV-2 IgG antibodies were positive (46 Au/ml) and IL-6 was elevated (53.5pg/ml; Normal:<7.0 pg/ml). A simultaneous CPK and LDH

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Transplacental COVID Antibodies and Cytokine Storm in Newborn: Presence of Antibodies does not Indicate Protection Always!

Introduction
Pregnant women require special attention in the COVID pandemic, since physiological changes of the immune system during pregnancy put them and their neonates at increased risk of negative outcomes of COVID-19 infection but the data is still scarce to comment upon. A case of asymptomatic SARS-CoV-2 infected mother and its effect on neonate is reported. This is the first case where the evidence of cytokine storm in neonate has been demonstrated in the presence of transplacental acquired IgG antibodies.
sent were also very high [CPK 358 U/L (Normal:26-192 U/L), LDH 3796 IU/L (Normal:135-214 IU/L)]. A possibility of cytokine storm reaction leading to multiorgan dysfunction was kept. Baby’s condition further deteriorated and was put on ventilatory support. Baby succumbed on day 4.

Discussion

In the SARS epidemic in 2004, SARS-CoV was associated with higher rates of miscarriage, preterm delivery and FGR. However, there is no conclusive opinion in this regard. There is still lack of data on effects of COVID-19 on the pregnancy and neonatal outcome. Current case shows that despite presence of COVID IgG antibody in newborn, cytokine storm occurred as evidenced by raised IL-6 with subsequent development of multiorgan dysfunction and neonatal death. This cytokine storm occurred in the absence of active COVID infection in mother and neonate. It is well known that new-borns in the first few weeks are immature to generate immunity and are protected by the maternal antibodies. The potential effect of maternal inflammatory response on development and immunology is still unknown. IL-6 is the most reported cytokine in COVID-19 patients and has been shown to be associated with high morbidity and mortality in these patients. One of the studies have shown that IL-6 >25 pg/ml was associated with very severe disease and mortality in adult patients. No such level has been proposed for newborns. In our baby IL-6 level was 52 pg/ml. Cytokine storm is the main factor in determining the extrapulmonary organ involvement as well which was evidenced in this case by raised liver enzymes and creatinine on second day.

Placental regulation of cytokines is an important component for the maintenance of appropriate intrauterine milieu to avoid fetal rejection. IL-10, an anti-inflammatory marker, the main component of these cytokines is secreted from placenta in significant amount starting from early pregnancy and this secretion decreases at the time of parturition. It can be postulated that in late trimester infection, the critical balance between proinflammatory (IL-6) and anti-inflammatory markers (IL-10) was maintained due to the placental production of IL-10. But after delivery, withdrawal of IL-10 from circulation led to imbalance between these markers leading to cytokine storm in already compromised baby, in this case. The similar type of effect has been shown from the study in China where 1/51 neonates who was RT-PCR negative, IgG positive with very high IL-6 level (109.42 pg/ml) developed necrotizing enterocolitis later. Rest of the neonates who did well, had median IL-6 level of 10.82 (3.37-8.01) pg/ml and with low level of IgG (<15 g/L).

Patient had raised antibody titre against SARS CoV-2 with negative COVID-19 RT/PCR at 37 weeks pregnancy suggesting that the patient had an asymptomatic COVID-19 infection in late third trimester. Vertical transmission is unlikely, as mother was RT-PCR negative at time of delivery. The available data also hints at negligible evidence of vertical mother-to-baby transmission of COVID-19 infection. Exaggerated response in this patient might be due to presence of increased ACE2 receptors in the placenta, as SARS CoV-2 uses ACE2 receptor for cell integration. In a hypertensive rat model, induced by a saline diet, expression (mRNA) and significant enzymatic activity of the ACE2 receptor was observed in the uterus and the placenta in late gestation. Our patient being hypertensive may have increased ACE2 receptor. Thus, the possibility of placental infection and therefore a potential passage to the foetus of infection and/or antibodies cannot be ruled out. As the maternal antibodies were very high, it can be anticipated that viraemia must be high during antenatal infection which went unnoticed. FGR can be associated with this viraemia if we anticipate that it has occurred 8-10 weeks back. In one of the study where placenta was studied in 7 COVID patients, it was demonstrated that when the patient had infection in first trimester, there were no changes in the placenta but in presence of infection in the third trimester (2/7 patient) extensive fetal thrombotic vasculopathy with sharply demarcated zones of avascular fibrotic villi were found and both these pregnancies had FGR, oligohydramnios and small for gestational age neonate. The incidence of FGR has been found to be as high as 10% in COVID-19 positive mothers.

The presence of minor external anomalies can be a mere coincidence as the possibility of this infection appears to be remote in first or early second trimester. Association or causation will be resolved with future studies. The important thing which needs to be emphasized here is that all neonates of pregnant females who may have suffered from COVID-19 in the third trimester, can pass on the antibodies to the neonate and trigger a cytokine storm, and one needs to be aware of this possibility. Neonatal IgG antibody titre and the interleukin levels can help arrive at the diagnosis.

Patient consent

Informed written consent was taken from mother of neonate

References

Hypokalaemic Paralysis Associated with COVID-19 Infection

Atul Kaushik¹, Anish Garg¹, Brinder Mohan Singh², Ashok Kumar Agarwal³, Showkat Nazir Wani⁴

Abstract

Introduction: COVID-19 is a pandemic affecting mainly respiratory and gastrointestinal system. Severe acute respiratory syndrome coronavirus-2 (SARS-COV-2) binds angiotensin converting enzyme 2 (ACE-2) of renin-angiotensin system (RAS) resulting in hypokalaemia. We hereby report the a of hypokalaemic paralysis induced by COVID-19.

Case: A 56 years old male with no co-morbidities presented with fever (2 days), weakness in bilateral lower limbs (1 day). His had severe hypokalaemia with serum potassium of 2.05 mEq/L. RT-PCR of nasopharyngeal swab for SARS-CoV-19 was positive. He was diagnosed as a case of hypokalaemic paralysis induced by COVID-19 infection.

Conclusion: We suggest that during this pandemic era if a COVID-19 patient presents with paralysis, hypokalaemia induced paralysis should be kept in the differential diagnosis.

What is known: COVID-19 infection leads to hypokalemia.

What is new: Hypokalaemic paralysis as a manifestation of COVID-19.

Introduction

Severe acute respiratory syndrome–coronavirus2 (SARS-CoV-2) is a positive strand RNA virus that causes severe respiratory syndrome in humans.¹ In December, 2019, an outbreak of a novel coronavirus SARS-CoV-2, previously 2019-nCoV started in Wuhan, China, and has since become a global threat to human health. ² 2019-nCoV infection may be associated with cellular immune deficiency, respiratory injury, coagulation activation, myocardial injury, hepatic injury, and kidney injury.³

Case Report

A 56-year-old male patient presented to emergency department in our hospital with complains of fever 2 days, weakness in bilateral lower limbs for 1 day.

There was no history of nausea, vomiting, diarrhoea, shortness of breath, chest pain, loss of consciousness, abnormal body movement or bowel or bladder involvement. Patient had no co-morbidities like diabetes mellitus, Thyroid dysfunction. There was no history of diuretics, laxatives or insulin intake.

In the emergency room, patient was conscious, alert and oriented to time place and person. His vitals included pulse- 90/min, blood pressure-136/86mmhg, respiratory rate- 22/min, SpO2 of 98% at room air and temperature of 98.8°F. General physical examination was unremarkable. Neurological examination revealed GCS of 15/15, no cranial nerve involvement. Motor examination revealed flaccid paralysis of both lower limbs with normal bulk. Hypotonia and power of grade 1 while upper limbs muscle power was normal (grade 5). There was no sensory involvement in any limbs. Deep tendon reflexes were attenuated (1+) but symmetrical in all limbs. Cerebellar and meningeal signs were negative. There was no focal tenderness over spine. The abdominal, respiratory and cardiovascular examinations were unremarkable.

NCCT head was unremarkable as shown in Figure 1. ABG revealed severe hypokalemia with K+ of 2.05 mmol/L while rest was within normal limits. The initial laboratory investigations were done as shown in Table 1 which confirmed hypokalemia with serum K+ level of 2.0 mEq/L. ECG revealed T- wave flattening seen in leads II, III, aVR, aVL, aVF and U waves are seen in lead V2 and V3 as shown in Figure 2. Chest x-ray PA-view was within normal limits.

Fig. 1: NCCT head- No significant abnormality was detected
Patient was diagnosed as a case of hypokalaemic paralysis associated with COVID-19 and was managed with oral potassium supplements, multivitamins, hydroxychloroquine, favipiravir and ivermectin. Patient improved and was discharged after negative RT-PCR for COVID-19 on day 10.

**Discussion**

According to the study by Chen et al., there is high prevalence of hypokalaemia (37%) among patients with COVID-19 and the positive association of hypokalaemia with the severity of COVID-19. They also suggested that hypokalaemia was more attributable to renal loss of K+ than gastrointestinal loss.

In our case we ruled out other causes of sudden onset paralysis like Guillain barre syndrome, transverse myelitis, cerebrovascular accident (CVA), trauma, thyroid dysfunction, etc with thorough history, clinical examination and relevant investigations as discussed.

The response to IV and oral potassium supplementation also goes in favour of hypokalaemia induced paralysis. As the patient was COVID-19 positive with and no history of gastrointestinal symptoms were present, it is likely that he developed renal loss of potassium due to COVID-19.

Virus invades human cells by binding ACE-2 on a cell membrane which is widely distributed in many human vital organs like liver, heart, kidney lungs. ACE is principle counter regulatory mechanism for the main axis of RAS system which plays a vital role in control of blood pressure and electrolyte balance. SARS-CoV-2 binds ACE-2 and enhances its degradation. This leads to increased reabsorption of water and sodium thus leading to rise in blood pressure and potassium excretion which leads to hypokalaemia.

Thus, we suggest that during this pandemic era if a COVID-19 patient presents with paralysis, hypokalaemia induced paralysis should be kept as the differential.

**Abbreviations**

COVID-19, Coronavirus disease 2019; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; ACE2, Angiotensin-converting enzyme 2; RAS, Renin angiotensin; CBC, complete blood count; LFTs, Liver function Tests; KFT, Kidney Function Tests; CVA, Cerebrovascular accident.

**References**


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**Table 1:** Demographic profile, clinical profile and laboratory findings of the patient

<table>
<thead>
<tr>
<th>Age</th>
<th>56 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td>Male</td>
</tr>
<tr>
<td>Medical history</td>
<td>No History of Hypertension, Diabetes, Thyroid dysfunction</td>
</tr>
<tr>
<td>Symptoms at COVID-19 onset</td>
<td>Fever 2 days</td>
</tr>
<tr>
<td>Day of onset of paraplegia after initial symptoms</td>
<td>1 days</td>
</tr>
<tr>
<td>Haemoglobin</td>
<td>13.9 g/dl</td>
</tr>
<tr>
<td>White cell count</td>
<td>10,830/mm3</td>
</tr>
<tr>
<td>Differential count</td>
<td>---</td>
</tr>
<tr>
<td>Neutrophil</td>
<td>9205/ul</td>
</tr>
<tr>
<td>Lymphocytes</td>
<td>758/ul</td>
</tr>
<tr>
<td>Platelet Count</td>
<td>1,48,000/ mm3</td>
</tr>
<tr>
<td>Albumin</td>
<td>4.2 g/dl</td>
</tr>
<tr>
<td>Globulin</td>
<td>3.5 g/dl</td>
</tr>
<tr>
<td>Alanine aminotransferase</td>
<td>127 U/L</td>
</tr>
<tr>
<td>Aspartate aminotransferase</td>
<td>60 U/L</td>
</tr>
<tr>
<td>Alkaline phosphate</td>
<td>81 U/L</td>
</tr>
<tr>
<td>Bilirubin (total)</td>
<td>0.41 mg/dl</td>
</tr>
<tr>
<td>Creatinine</td>
<td>1.2 mg/dl</td>
</tr>
<tr>
<td>Urea</td>
<td>42 mg/dl</td>
</tr>
<tr>
<td>Uric acid</td>
<td>7.3 mg/dl</td>
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<tr>
<td>Sodium</td>
<td>143 mEq/L</td>
</tr>
<tr>
<td>Potassium</td>
<td>2.0 mEq/L</td>
</tr>
<tr>
<td>Chloride</td>
<td>107 mEq/L</td>
</tr>
<tr>
<td>Serum Calcium</td>
<td>10.2 mg/dl</td>
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<tr>
<td>Phosphorus</td>
<td>2.6 mg/dl</td>
</tr>
<tr>
<td>TSH Total</td>
<td>3.51 uIU/ml</td>
</tr>
<tr>
<td>Thyroxine T4</td>
<td>9.75 ug/dl</td>
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<tr>
<td>Thyroid stimulating hormone</td>
<td>0.37 mg/dl</td>
</tr>
<tr>
<td>Triiodothyronine (T3)</td>
<td>1.76 ng/ml</td>
</tr>
<tr>
<td>Thyrotrypsin</td>
<td>0.143 ng/ml</td>
</tr>
<tr>
<td>Tridot (HV 1.2, Hepatitis B Surface antigen HbsAg, Anti Hepatitis C card)</td>
<td>All non reactive</td>
</tr>
<tr>
<td>Urine Routine and microcopy</td>
<td>Within normal limits</td>
</tr>
<tr>
<td>Blood Culture &amp; Sensitivity</td>
<td>No growth after 72 hrs</td>
</tr>
<tr>
<td>ESR</td>
<td>25mm/hr</td>
</tr>
<tr>
<td>CRP</td>
<td>Positive 96 mg/L</td>
</tr>
<tr>
<td>Rapid Malaria Antigen test</td>
<td>Negative</td>
</tr>
<tr>
<td>Dengue IgM, IgG and NS1Ag</td>
<td>All negative</td>
</tr>
<tr>
<td>ECG</td>
<td>Within normal limits</td>
</tr>
<tr>
<td>Nasal and Throat swab for RT PCR for COVID-19</td>
<td>Positive</td>
</tr>
</tbody>
</table>

Fig. 2: ECG at presentation: T-wave flattening seen in leads II, III, aVL, aVF and U waves (marked with arrows) are seen in lead V2 and V3

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Palade, Claude & Cell Biology

Jayant Pai-Dhungat

George Emil Palade (1912-2008) was born in Jassy, Moldavia, the eastern province of Romania. He studied medicine at the University of Bucharest and earned a medical degree in 1945. After WW-II, he immigrated to USA for further studies in 1946. Palade worked as a visiting investigator at New York University, but soon received an appointment to the Rockefeller Institute to work under Albert Claude and his research group.

Albert Claude (1888-1983) a Belgian immigrant was a pioneer in electron microscopic cell functioning by fractionation (ultracentrifugation) process.

Claude and his colleagues had published their seminal paper on study of tissue Culture Cells by Electron microscopy in 1945 with a first electron micrograph of an intact cell. Claude also discovered the existence of an extensive ‘lace-like reticulum’ using centrifugation techniques, Claude had also succeeded in obtaining sub cellular fractions, including one containing tiny particles he called ‘microsomes’, but whose precise origin was yet to be determined.

Palade soon became another pioneer in the use of the electron microscope to unlock sub-cellular secrets during his long and productive career (1946-1973). He began his string of innovations and discoveries

In 1953, Palade first described the internal structure of mitochondria, including the unfolding of the inner membrane, which he called ‘cristae mitochondriales’, and in 1954, with Porter, described the invariable presence of the ‘endoplasmic reticulum’ (ER), in various cell types. The lace-like system of interconnected tubular or cisternal cavities bound by a membrane had been first observed in intact cultured cells by Claude.

Soon Palade made the momentous discovery of the ribosome the protein-synthesizing organelle (earlier called microsome by Claude). He recognized that ribosome exist free in the cytoplasm or is attached to the ER membranes.

George Palade virtually founded the discipline of modern cell biology while developing numerous innovations in electron microscopy and discoveries in cell fractionation.

1950s witnessed a period in which pioneering electron microscopists, including Claude, Palade and Porter, feverishly endeavored to improve preparation, procedures applicable to solid tissues that could yield the ultra-thin sections required for electron microscopy. During this period, Palade and Porter were unrivalled in the number of important new observations they made with the electron microscope.

Palade’s genius, however, was his masterful combination of electron microscopy cell fractionation and biochemical analysis enabling him to integrate structural and functional information which lead to molecular biology. He became naturalized citizen of the United States in 1952, and was appointed Professor of cytology at Rockefeller Institute in 1958. Palade then joined Yale University Medical School (1973-1990) to direct studies in cell biology. In 1990, Palade moved to the University of California, San Diego (UCSD) School of Medicine, where he acted as Dean for scientific affairs. He also served as professor of Medicine, and established cell biology program. Post-retirement (2001), he continued as Professor emeritus.

Palade was awarded the Nobel Prize in Physiology or Medicine in 1974, which he shared with Albert Claude and Christian de Duve, “for their discoveries concerning the structural and functional organization of the cell”. He also received numerous other awards. Palade died in October 2008 at the age of 95.
Antithrombotic Therapy in COVID-19 – A Scientific Position Statement by Heart Disease Management Program, National Health Mission, Government of Tamil Nadu

Justin Paul Gnanaraj1,2, Anne Princy S2,3, Cecily Mary Majella5, Prabhakar Durairaj4, Ravichandran Edwin5, Kumaresan Kannan6, Veeramani Ramachandran7, Nambirajan Jeyabalan8, Nandakumaran Mohanan9, Senthilraj Krishnan2, Shanmugasundaram Somasundaram10

Introduction

The understanding and treatment of COVID-19 has changed more often than the months of COVID-19. According to the largest clinical data published (n=72,314 persons), 81% had mild infection, 14% had severe infection and 5% had critical infection with respiratory failure, septic shock or multiorgan dysfunction. Clinical severity grading suggested in the version 3 of the clinical management protocol: COVID-19 by the Director General of Health Services, Ministry of Health and Family welfare, Government of India as given in Table 1, is used in the current statement. As we continue to traverse the uncharted territory of COVID-19 management, antithrombotic management has withstood the test of time in the roller coaster ride for the successful drug treatment of COVID-19. We do not have enough evidences from randomised controlled studies to formulate anticoagulation guidelines for COVID-19. However with the available evidences, we have attempted to summarise briefly the need for and means of anticoagulation therapy in COVID-19.

Pathology and Pathophysiology

Venous thromboembolism (VTE) is one of the major cardiovascular hazards noted in about more than 20% of critically ill COVID-19 persons, which is 3-4 fold higher than the critically ill viral pneumonia patients. When surveillance venous ultrasonography was performed, the frequency of VTE was as high as 69%. Autopsy studies had shown nearly 88% had widespread thromboembolic disease. Small arteries (<1mm) had fibrin thrombi in 87%.

The initial damage in persons prone for severe infection occurs in the alveoli evoking an inflammatory response and microvascular thrombi. There is a “bidirectional cross talk” between inflammation and thrombosis leading to a state of thrombo-inflammation. The inflammatory molecules released by the host cells following viral damage activate both the coagulation system and immune response of the host. As illustrated in Figure 1, dysregulated immune response, hypoxia and direct triggers contribute to the thrombotic milieu.

Significant endotheliopathy detected by increased levels of endothelial and platelet cell markers like von Willebrand factor, soluble P-selectin and soluble thrombomodulin are more likely associated with critical illness and death. Patients with moderate and severe COVID-19 often have elevated D-dimer and fibrinogen levels with low anti-thrombin levels. There is evidence of direct correlation between D-dimer levels and poor prognosis. Cases of pulmonary embolism were more likely to be associated with higher D-dimer levels.

Patients with severe COVID-19 had higher levels of IL-6, suggesting that the hypercoagulation status of COVID-19 patients may be related to the elevated levels of cytokines. COVID 19
coagulopathy has a partial overlap with four different coagulation disorders as shown in Figure 2.

“Sepsis induced coagulopathy” has distinctive laboratory features – lymphopenia, thrombocytopenia, elevated fibrinogen and elevated D-dimer, which are common in COVID-19. Antiphospholipid antibodies have also been detected during acute illnesses and in COVID-19, but rarely responsible for thrombotic events.

A registry on the prevalence of thromboembolic complications in COVID 19 following anticoagulation gave few important inferences. First, most thromboembolic events occur after the first 5-7 days following hospital admission. Second, systematic VTE prophylaxis reduced the incidence of VTE. Third, the central lines have been a significant source of thrombotic complications. Fourth, the bleeding rates were 2.7% in hospitalized patients.

**Anticoagulation Therapy**

Patients hospitalised with COVID-19 are at increased risk of VTE. High incidence of pulmonary embolism has been reported even among non-critically ill, hospitalised COVID-19 patients. As the understanding of COVID 19 increases, more cases of pulmonary embolism have been detected in the absence of deep vein thrombosis and the thrombi are located more in the peripheral pulmonary arteries. We discourage routine use of ultrasound to identify VTE in COVID-19 patients. Anticoagulation therapy has shown significant mortality benefit among ventilated COVID 19 patients in a single centre observational study of 2773 COVID-19 patients, without any significant increase in bleeding. LMWH within 7 days of ARDS has shown to reduce 7 day mortality by 48% and 28 day mortality by 37%.

In a series of 107 COVID-19 patients admitted in ICU from France, prophylactic dose of AC was inadequate in preventing VTE/PE in 20 of the 22 patients, who developed acute pulmonary embolism. Intermediate dose anticoagulation has been suggested and found to be helpful in VTE prevention and management during COVID. Hence it is important to ensure hospitalised patients get anticoagulation therapy at appropriate doses to prevent VTE. Most of the hospitalised COVID-19 patients will need some form of anticoagulation. Hospitalised patients with other medical, surgical and obstetric conditions who are positive for COVID-19 will also need anticoagulation therapy unless there are contraindications. Selected individuals with COVID-19 who are not admitted to hospital but with high thrombotic risk should receive thromboprophylaxis. Extended prophylaxis beyond discharge may be needed in some subgroup of high-risk patients. D-dimer as a routine to guide anticoagulation in COVID-19 is not beneficial and is not recommended. However monitoring of biomarkers like D-dimer, PTT, platelet count, and fibrinogen, can be used for risk stratification of COVID-19 patients. The optimal thromboprophylaxis is unclear considering the paucity of data. The following sections aim to throw some light in this area, with the available evidence in literature as of now.

**A. Risk Scoring and anticoagulation**

It is important to consider the thrombotic risk and bleeding risk of the patient, while planning anticoagulation therapy. We recommend the use of risk scoring to decide on the intensity and duration of anticoagulation therapy (Table 2). Numerous scoring systems are available for assessing VTE risk, like the PADUA model, CAPRINI Risk assessment model and the IMPROVE score.

**Assessment of VTE risk**

Numerous scoring systems are available like the PADUA model, CAPRINI Risk assessment model and the IMPROVE score. We recommend the use of PADUA model, a comprehensive, yet simple and a validated VTE risk scoring tool in COVID-19. A patient with a total score of ≥ 4 is considered to be at high risk for VTE.

**Assessment of bleeding risk**

It is important to assess the baseline bleeding risk of the patient before initiating anticoagulant therapy. We suggest the use of HAS-BLED score. A patient with a score of 0 or 1 is considered at low risk, and 3 or more is considered as high risk for bleed.

**Scoring for DIC risk**

We recommend the use of ISTH-DIC score in sick patients admitted to ICU. Elevated ISTH-SIC score ≥ 5 has been shown to be associated with high likelihood of death due to thrombotic events in COVID-19 patients. In case
ISTH scoring cannot be done due lack of facility of FDP estimation, use clinical high-risk features like increasing oxygen requirement, and increasing high risk markers like D-Dimer, CRP, ferritin etc.

**B. Anticoagulants used in COVID-19**

Parenteral anticoagulants

**Table 3: Dose of parenteral anticoagulation during COVID-19**

<table>
<thead>
<tr>
<th>Dose</th>
<th>LMWH [Enoxaparin]</th>
<th>Unfractionated Heparin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prophylactic</td>
<td>40 mg once a day</td>
<td>5000 IU subcutaneous bid</td>
</tr>
<tr>
<td>Intermediate</td>
<td>60 mg once a day</td>
<td>5000 IU subcutaneous tid or as IV infusion [target aPTT 50-70 sec]</td>
</tr>
<tr>
<td></td>
<td>40 mg twice a day</td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.5 mg/kg twice a day</td>
<td></td>
</tr>
<tr>
<td>Therapeutic</td>
<td>60 mg / kg twice a day or 1 mg/Kg twice a day</td>
<td>IV infusion [target aPTT 70-110 sec]</td>
</tr>
</tbody>
</table>

(LMWH), unfractionated heparin (UFH) and fondaparinux are the available parenteral anticoagulants. Heparins, with their anti-coagulant activity, anti-inflammatory property and ability to decrease thrombin generation, can modify the onset and course of DIC. Though widely available and economically friendlier, use of unfractionated heparin has concerns like, the frequent need of aPTT monitoring for dose titration, time taken to achieve a therapeutic aPTT, inability of aPTT to adequately reflect the anticoagulant activity of heparin during COVID-19 and associated greater occupational exposure of health care workers. Anti Xa level is superior to aPTT, in monitoring efficacy of UFH for appropriate anticoagulation in COVID-19. LMWH is often preferred for use in COVID-19 due to its improved pharmacodynamic, pharmacokinetic properties, predictable anticoagulant response, more favorable side-effect profile, and lack of need for monitoring anticoagulant activity. Enoxaparin is the preferred LMWH in most of the available literature. However, other LMWH in equivalent doses can be used.

In patients with anticipated invasive procedures and in those with impaired renal function[creatinine clearance less than 30 ml/min] UFH is preferred over LMWH. In obstetric patients, UFH is appropriate if delivery is expected within 24 hours as faster discontinuation of anticoagulation activity may be necessary. The recommended dose of UFH and LMWH is shown in Table 3.

Fondaparinux in a dose of 2.5 mg subcutaneous once a day, is an
alternative for thromboprophylaxis, particularly in patients with heparin induced thrombocytopenia.\textsuperscript{22,26}

Dose modification in renal failure:

- UFH: Preferred anticoagulant with creatinine clearance < 30 ml / min
- Enoxaparin: Generally avoided with creatinine clearance < 30 ml / min. If needed, can be used at a reduced therapeutic dose of 1 mg / kg once a day with creatinine clearance between 15-30 ml/min.\textsuperscript{26}
- Fondaparinux: Reduce therapeutic dose to 1.5 mg SC once a day with creatinine clearance 20-50 ml/min\textsuperscript{22}

Oral Anticoagulants: This includes Vitamin K antagonists and Directly acting oral anticoagulants [DOACS]. Vitamin K antagonists (VKA) are potent anticoagulant drugs, which require periodic monitoring of INR for dose titration. Dietary and drug interactions interfere with the anticoagulant activity of VKAs. Compared to VKAs and Heparins, DOACS have equal antithrombotic efficacy, proven safety and ease of use in both therapeutic and preventive indications without need for monitoring. Hence, DOACS are often the preferred option in patients who need outpatient prophylaxis or extended post discharge prophylaxis. Apixaban and Rivaroxaban have been successfully used in therapeutic management of COVID induced VTE.\textsuperscript{22}

DOACS have significant interaction with drugs that are often administered for COVID-19 like ritonavir and lopinavir, azithromycin, dexamethasone etc. DOACS have a longer half-life than UFH or LMWH, which is a disadvantage, when urgent invasive procedures are required. Hence whenever possible, the patients who are already on VKA or DOACS can be switched to LMWH or UFH. For patients on prosthetic valves and certain other high thrombogenic conditions who are already on VKAs, it may be safer to continue VKAs, as more complications have been documented around the bridging period. Since the INR is labile during COVID-19, more frequent monitoring of INR is advocated. The suggested dose of DOACs in given in Table 4.

Therapeutic dose of apixaban is reduced to 2.5 mg bid\textsuperscript{28} if the patient has two of the three risk factors [age ≥ 80 years, a body weight < 60 kg, or a serum creatinine level above 1.5 mg%].\textsuperscript{34}

Contraindications to anticoagulation therapy: Anticoagulation is contraindicated in patients with active bleed or recent bleed\textsuperscript{27,28} and patients with platelet count is less than 25,000 per microliter.\textsuperscript{26} We advocate caution while choosing to use anticoagulation with platelet count less than 50,000 per microliter.

C. Anticoagulation therapy recommendation for COVID-19 patients

The suggested anticoagulation therapy according the clinical severity of COVID-19, adjusted based on the thrombotic and bleeding risk of the patients is illustrated in Figure 3.

1. No anticoagulation: The following patients do not need anticoagulation.

Ambulant COVID-19 patients with or without constitutional / respiratory symptoms.\textsuperscript{35}

Patients with mild or moderate COVID and high bleeding risk

Abnormal PT / aPTT alone need not be a contra indication for anticoagulation, when necessary.\textsuperscript{29}

Clinical judgement is advocated and treatment may be individualized based on the risk and benefit.

2. Prophylactic anticoagulation dose: The following patients can be given prophylactic anticoagulation dose

Hospitalized mild COVID-19, with evidence of lung involvement, without high bleeding risk.

Patients hospitalized with moderate COVID-19 with low VTE risk and low bleeding risk

Patients with severe COVID-19 with high bleeding risk and low VTE risk / low ISTH- DIC score

3. Intermediate anticoagulation dose: Following patients can be given intermediate anticoagulation dose

Hospitalized moderate COVID-19 patients with high VTE risk and low bleeding risk

Hospitalized severe COVID -19 patients with low VTE / low ISTH-DIC score and low bleeding risk.

4. Therapeutic anticoagulation dose: Following patients can be given therapeutic anticoagulation dose

Patients with documented thrombotic events like DVT, acute pulmonary embolism, device thrombosis etc.\textsuperscript{19,33,36}

Patients with high suspicion of thrombotic events, when imaging is not possible.\textsuperscript{19,33,36}

Patients with pre-existing clinical indications for therapeutic anticoagulation like AF, Prosthetic valves etc

Patients receiving RRT or those on ECMO\textsuperscript{28}

Patients with severe COVID-19 with low bleeding risk and high-risk features / high ISTH- DIC score

5. Thrombolytic Therapy for Pulmonary embolism

In patients with definite indications for anticoagulant therapy, but with contraindications for anticoagulation, methods of mechanical thromboprophylaxis like pneumatic compression are encouraged

D. Extended anticoagulation for COVID-19 patients post discharge

Routine anticoagulation prophylaxis for all COVID-19 patients at discharge is not recommended.\textsuperscript{19,33}

Patients who were on anticoagulation before COVID-19 hospitalisation for other indications (AF, prosthetic valve etc) have to be specifically advised to continue anticoagulation as before.

COVID-19 patients with documented VTE, should continue post discharge anticoagulant therapy for 3 months. This duration can be reduced in patients with high bleeding risk.\textsuperscript{19,33,38}

Non ambulant patients who are discharged home, because of bed shortages or discharged to rehabilitation centres will need prophylactic anticoagulation.

Patients with no documented VTE, but at high VTE risk and with low bleeding risk: Extended anticoagulant therapy may be considered for 6 weeks.\textsuperscript{30}

Patients with no documented VTE, but with high VTE risk and high bleeding risk: Extended anticoagulant therapy can be considered up to 2 weeks based on clinical judgment.

LMWH up to 14 days and
Rivaroxaban up to 6 weeks can be considered for extended prophylaxis.\textsuperscript{36,37} Apixaban can be used as an alternative to rivaroxaban.

**E. Anticoagulation for COVID-19 patients managed as outpatient**

Anticoagulation should not be given as a routine to COVID-19 patients managed as outpatients.\textsuperscript{36}

Selected patients with COVID-19 who are not admitted to hospital, with very high thrombotic risk but low bleeding risk can be given prophylactic dose for 4-6 weeks.

**Antiplatelet Therapy**

Antiplatelets have no role in thromboprophylaxis for patients with COVID-19. They are not recommended as a routine in these patients.\textsuperscript{19} A small retrospective study in 412 COVID-19 patients suggests that aspirin use is associated with decreased mechanical ventilation, ICU admission, and inhospital mortality in hospitalized patients with COVID-19.\textsuperscript{29} However, larger data is needed before this can be recommended.

Patients with acute and chronic coronary syndromes and percutaneous coronary interventions, who are already on antiplatelets may continue the same unless contraindicated.\textsuperscript{36}

In patients with perceived elevated bleeding risk, regimens with clopidogrel, which has lesser bleeding risk can be considered.

**Anticoagulation in Special Situations**

**Prosthetic Heart Valves**

COVID-19 patients with mechanical prosthetic heart valve constitute a category which is at a very high risk of VTE.\textsuperscript{26,28} Potential interaction of antiviral drugs with VKAs, potential of liver / renal involvement in COVID-19 and the consequent labile INR, add to the complexity in managing the patients. Further during the COVID pandemic, many patients choose to continue on VKAs without adequate monitoring of INR to avoid a potential chance of infection. This can pose a great thrombotic / bleeding risk to this subset of patients.

Some patients have developed VTE even with therapeutic INR levels.\textsuperscript{31} Hence maintaining INR levels in therapeutic range is challenging in these patients. Current guidelines do not include a definite recommendation for bridging therapy in COVID-19 patients with a mechanical prosthetic heart valve. We recommend that all patients with mechanical prosthetic heart valves, including those who are pregnant, may preferably be continued on VKAs with frequent [once in 3-6 days] INR and clinical monitoring.\textsuperscript{30} However, bridging anticoagulants can be considered for hospitalized patients on antiviral therapy and in patients with significant fluctuations in INR.\textsuperscript{40}

**Atrial Fibrillation**

Atrial fibrillation [AF] was found in 19% of all COVID patients and in 36% of patients with COVID and underlying cardiovascular disease and it was more common in patients who did not survive.\textsuperscript{39} Mild COVID patients who are already on DOACs for AF, can be allowed to continue DOACs, with watchful pharmacotherapy avoiding drug interactions. For other hospitalized COVID-19 patients with AF, heparin [UFH and LMWH] is the anticoagulant of choice. New onset AF patients are considered for long term anticoagulation, guided by CHA\textsubscript{DS\textsubscript{2}}-VASc Score.\textsuperscript{45,46} Chronic AF patients are switched back to the prehospitalization anticoagulation therapy, at discharge.

**Pregnancy and Postpartum**

Antenatal patients requiring anticoagulation for pre-existing clinical conditions will need to continue anticoagulation during COVID. LMWH is appropriate if delivery is not expected within 24 hours and after delivery. Pregnant women who may need a faster discontinuation of anticoagulation may be placed on UFH. DOACs are not proven to be safe during pregnancy. Anticoagulant therapy should be continued for four to six weeks postpartum for all COVID-19 patients, and for at least three months in those with documented VTE.\textsuperscript{34} Thrombolytic therapy in acute pulmonary embolism is not altered by pregnancy.

**Thrombocytopenia**

COVID-19 can lead to thrombocytopenia in about a third of the patients by a variety of postulated mechanisms which include direct viral suppression of the bone marrow, immune mediated platelet destruction, platelet aggregation in lung and reduced efficacy of thrombopoietin.\textsuperscript{46,47} A rapid fall in platelet count >50% over 24-48 h or a platelet counts of <20,000 point to an immune aetiology. Anticoagulation therapy is unsafe when platelet count is less than 25,000-50,000.\textsuperscript{26,28} Fondaparinux is useful when heparin induced thrombocytopenia is suspected.\textsuperscript{23,26} Dose of concomitant antiplatelet therapy needs to be adjusted with thrombocytopenia. Dual antiplatelet therapy required for other indications [eg Post-PCI] can be continued if platelet count is ≥50,000, reduced to single antiplatelet therapy if platelet count is between 25,000 to 50,000, and discontinued if platelet count is less than 25,000.\textsuperscript{30}

**Liver Disease**

COVID-19 patients with advanced liver disease have to be considered as patients with very high risk of VTE as both these conditions are associated with a hypercoagulable state.\textsuperscript{44} Data from 853 cirrhosis with portal hypertension patients on anticoagulation therapy has demonstrated no excess of bleeding events.\textsuperscript{49} Thromboprophylaxis with LMWH, should be standard of care for all patients with cirrhosis.\textsuperscript{30}

**Kidney Disease and COVID-19**

CKD patients are at a high risk for bleeding and thrombotic complications and need close monitoring. Renal specific anticoagulation recommendation includes, LMWH with targeting a systemic anti-factor Xa level of 0.25 to 0.35 IU/ml or UFH at 10 to 14 unit/kg per hour targeting an activated partial thromboplastin time (aPTT) of 60 to 90 seconds. Argatroban has been proposed as an alternate strategy.\textsuperscript{51} In the absence of contraindications, patients with COVID-19 should receive anticoagulation during RRT by systemic anticoagulation with UFH / LMWH or by regional anticoagulation using UFH / citrate.

**Conclusion**

As our understanding of COVID coagulopathy unfolds, our approach to anticoagulation continues to evolve. Precise mechanism behind the increased thrombogenicity of COVID-19 is still incompletely understood, and further research is needed. In a large registry of COVID-19 patients given thromboprophylaxis, the overall rate of thrombotic events was comparable with other similar patients receiving thromboprophylaxis in Pre-COVID times.\textsuperscript{16} This gives hope that with appropriate anticoagulation, the coagulopathy associated with COVID-19 can be managed well. As such anticoagulation in this vulnerable population should be considered with utmost care, with special emphasis in
balancing associated co-morbidities, thrombotic risk, bleeding risk, and potential drug interactions.

References


Diet in Thyroid Disorders: Myths and Facts

Rudrajit Paul¹, Jyotirmoy Pal²

¹Ex-Associate Professor, Department of Critical Care Medicine, IPGMER and SSKM Hospital, Kolkata, West Bengal, ²Professor, Department of Medicine and Special Adviser to Government of West Bengal, RG Kar Medical College, Kolkata, West Bengal

Sir,

Doctor, I have thyroid disorder. Some neighbour/friend has told me to avoid certain food products. Can I eat all vegetables?

This is a question faced by physicians almost every day. But physicians often are at a loss to answer this question correctly. There are a lot of myths surrounding this topic and people (including physicians) are often misled by the junk pseudoscientific articles available online and in various sensational “health magazines”.

This correspondence is a small attempt to put the facts straight in this regard.

First of all, it must be stressed that there is no special diet for thyroid diseases and patients with hypo-or hyperthyroidism can have the same meal as others. However, one myth, which is widely prevalent in the Indian society, is that concerning vegetables of the Brassica family, like cauliflower, cabbage, Brussels’s sprouts and broccoli. In various discussions, they are often referred to as “goitrogen”. Probably, this myth started in the scientific community after publication of the reports by Chesney et al in 1928, where it was said that rabbits fed on fresh cabbage developed goitre. In 1936, another report was published where it was shown that rats fed on Brassica seeds also developed goitre. This led to the conclusion that humans were also susceptible to goitre after eating these food items. In the early days, this was even given a name: Cabbage Goitre. Much has changed in biochemistry and nutrition science after that; but somehow, this myth about goitre has endured.

Biochemical analysis has revealed that vegetables of the Brassica family contain sulphur compounds called glucosinolates. These may be converted to bioactive isothiocyanates inside the human body. This compound may inhibit thyroid hormone (T4) synthesis, leading to hypothyroidism. But conversion of glucosinolate to isothiocyanate requires an enzyme called myrosinase, which is also present in the same vegetable. Good cooking will completely destroy this enzyme and thus the conversion of Glucosinolate and subsequent effect on thyroid function will be absent. So, properly cooked vegetables of Brassica family are not banned in patients with hypothyroidism. If someone consumes raw cabbage (e.g. in salad or burger) there is hypothetically a risk of generation of isothiocyanates. But the amount, in occasional consumption, is too small to be of any significance.

There are, however, some other food items which can have a substantial effect on the thyroid gland function. One of them is seaweed like kelp. This contains excess iodine. This is mainly an ingredient of Chinese food but recently, many restaurants in our country have also started offering this in their menu. If someone consumes kelp in excess, thyroid hormone synthesis may be inhibited by the Wolff-Chaikoff effect (especially if that person is borderline iodine deficient). Similarly, in Grave’s disease patients, such seaweed consumption may cause thyrotoxicosis by Jod-Basedow phenomenon.

Soy beans are another group of products which may have some effect on the thyroid. It contains Flavonoids. In large doses, these chemicals may inhibit the Thyroperoxidase enzyme. For euthyroid patients this may be negligible but those patients who are living in iodine deficient areas and are subclinically hypothyroid, excess flavonoid intake may precipitate clinical hypothyroidism. Similar effects have also been observed with excess Green tea consumption.

Thus, in conclusion, most food items are safe for all patients with dysfunction of the Thyroid gland. Only a few items like Soya bean may be used with caution, especially in areas where iodine intake is insufficient. Generally speaking, if iodized salt is consumed by everyone, then these dietary effects on thyroid can be totally ignored. But there are some places in India where environmental iodine content is low (and thus, vegetables grown in those areas are also deficient in Iodine) and there are many people who have recently developed a fad for “Rock Salt”. In such populations, these dietary factors may become significant.

One more caveat which the authors would like to point out is biotin supplementation and laboratory testing for thyroid hormones. Biotin does not affect the thyroid gland function, but it interferes with the in vitro tests and causes biochemical anomalies. Thus, thyroid profile testing should not be done in someone on biotin supplementation.

References


Looking Beyond Thyroid in a Thyroid Disorder Patient

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Sir,

Thyroid disorders are very common in India. Prevalence of hypothyroidism (overt & subclinical) and hyperthyroidism (overt & subclinical) in India is 13.3% and 2.9% respectively¹. These two disorders are usually associated with various psychiatric disorders like depression, anxiety, mood disorder and others². Many times, patients with thyroid disorders continue to suffer from nonspecific symptoms like fatigue, giddiness, anorexia, weight loss and muscle weakness even when their thyroid function test have become normal. There are many reasons for this like D2 deiodinase polymorphism, selenium deficiency, tissue hypothyroxinemia, depression and other diseases associated with thyroid disorders. Primary care physician (PCP) often diagnose thyroid disorder patient with these non-specific symptoms as a
case of depression and/or poor physical fitness. But certain diseases which are associated with thyroid disorder patients remain undiagnosed. Here we are reporting two thyroid disorder cases which were suffering from nonspecific symptoms even when their thyroid function test (TFT) had become normal.

Case 1

A 40-year-old female was diagnosed 2 years back as a case of primary hypothyroidism (TT4=3 mcg/dl, TSH=68mIU/ml, Anti TPO=200 IU/ml) by her PCP and was put on levo-thyroxine (100 mcg/day). She was quite well initially but since the last 6 months, she has started feeling nonspecific symptoms like fatigue, muscle pain, giddiness and anorexia. She was given supportive treatment but was not relieved. Two weeks ago, she developed nausea and vomiting, for which she was admitted and diagnosed as a case of gastroenteritis and hypotension. She improved on supportive treatment but her nonspecific symptoms persisted and for this she was referred to us. On examination there was hypotension (BP=90/60 mmHg), hyperpigmentation and diffuse goiter. She was suspected as a case of Addison’s disease. Laboratory test showed hyponatremia (Na=125 mEq/l), hyperkalemia (K=5.5 mEq/l), hypocortisolism (morning serum cortisol=3.4 mcg/dl) and raised ACTH (86 pg/ml). TFT, blood glucose, LFT and KFT were normal. Plasma renin activity, aldosterone and markers of autoimmunity (21 hydroxylase Ab, GAD Ab, IC Ab, Ttg Ab) were not done due to paucity of money. Patient was diagnosed as a case of Autoimmune Polyglandular Syndrome (APS) type 2. She was put on hydrocortisone and fludrocortisone along with thyroxine.

We report these two cases where diseases associated with thyroid disorder are often missed. Initially both patients were diagnosed as depression along with thyroid disorder which was not the case. First one was suffering from Addison’s disease along with thyroid disorder and second from hypokalemia along with thyroid disorder. So, if a patient of thyroid disorder shows persistence of nonspecific symptoms in spite of normal TFT, we should suspect other associated conditions like Addison’s disease, hypokalemia, diabetes mellitus, hypoparathyroidism and others.

References


Aluminium Phosphate Poisoning Causing Intravascular Haemolysis in G6PD Deficient Individual

Meenaxi Sharda, Bhimsain Goyal, Nitesh Kumar Baudh, Devendra Ajmera, Pravin Kumar

Aluminium phosphate (celphos) is commonly encountered poisoning in north Indian rural population because of its rampant use in agriculture as a fumigant. Common clinical manifestations of poisoning are nausea, vomiting, diarrhoea, resistant hypotension, shock, arrhythmia, myocarditis, pericarditis, pulmonary edema and acute hypoxic encephalopathy. Hematological manifestations do not occur per se. We are reporting a rare case of intravascular hemolysis in aluminium phosphate poisoning who was subsequently found to be G6PD deficient.

A thirty year old farmer male came to emergency department with nausea and recurrent vomiting after alleged history of ingestion of unknown amount of aluminium phosphate powder 8 hours prior to hospitalization. On examination he was conscious, well oriented with pulse rate (116/minute), respiratory rate (22/minute) and blood pressure 120/70 mm of Hg. Rest of the general physical and systemic examination was unremarkable.

Routine lab investigations on day second of hospitalization shows hemoglobin (12.5 g/dl) and normal blood counts however his liver function tests revealed raised serum bilirubin levels (2.6 mg/dl) with predominately indirect (1.8 mg/dl) hyperbilirubinemia and elevation of SGOT (551IU/L), LDH(561IU/L) but normal SGPT (343IU/L) suggestive of intravascular hemolysis. Cardiac biomarkers TropI (<0.04 ng/ml) and CKMB (221IU/L) were normal, suggestive of no cardiac toxicity and arterial blood gas analysis did not show metabolic acidosis with normal pH (7.43) and HCO₃⁻ (24 mEq). Patient was admitted to medicine ICU and was treated with intravenous magnesium sulphate and other supportive treatment. His Tachycardia and tachypnea settled after 24 hours of admission and he remained normotensive throughout. On the third day of admission, icterus was noted and his investigations showed rising indirect bilirubin (3.5 mg/dl) and serum LDH (2252IU/L) with fall in hemoglobin (9.2 g%). There was no history of bleeding from any site. His direct coomb’s test was negative, however his G6PD level (3.89 U/g of Hb) was found to be low (normal range: 5.5-20.5 U/g of Hb). Review of treatment did not reveal the administration of any offensive drug which can cause hemolysis in presence of G6PD deficient state. Patient was managed conservatively and his jaundice and investigations normalized over next 5 days as mentioned in Table 1.

When aluminium phosphate comes in contact with gastric acid and water after ingestion Active ingredient phosphine gas (PH₃) is liberated. This phosphine is absorbed through gastric mucosa and causes tissue hypoxia by inhibiting cytochrome c oxidase enzyme in mitochondria leading to overproduction of reactive oxygen species giving rise to oxidative stress, intracellular lipid peroxidation and...
vascular wall disintegration ultimately resulting in cardiotoxicity and multi organ failure.

In red blood cells the role of G6PD is critical because it is the only source of NADPH, which via glutathione defends these cells against oxidative stress.

The reason for intravascular hemolysis in aluminium phosphide poisoning is not known, however Srinivas R, et al (2007) and Farangh F, et al (2013) postulated it to be either due to the direct toxic effects or generation of free radical oxygen species causing oxidative stress.

**References**


**Favipiravir Induced Nephrotoxicity in Two Patients of COVID-19**

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Sir,

Kidney is reported second major organ affected after lungs in severe coronavirus disease 2019 (COVID-19) and is associated with poor outcome.1 The pathophysiology of acute kidney injury (AKI) in COVID-19 is unclear and may be multi-factorial; virus-host complex immune interactions, hemodynamic alterations, effect of therapies like invasive mechanical ventilation on renal blood flow and/or nephrotoxic drugs.2 We report two cases of AKI with favipiravir induced nephrotoxicity.

Patient 1: 38-year male, confirmed reverse transcriptase polymerase chain reaction positive (RT-PCR) positive for Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) and moderate pneumonia was given hydroxy-chloroquine (HCQ) 400 mg BID followed by 200 mg BID for 10 days and favipiravir at 1600 mg BID for 5 days. There was progressive rise in creatinine with good urine output from day three of starting favipiravir. The favipiravir was stopped, creatinine showed a progressive decreasing trend in 48 hours and reached baseline in five days.

Patient 2: 51-year male RT-PCR positive, severe COVID-19 was started on HCQ and favipiravir at same dose as in patient one along with methylprednisolone 40 mg BID for days and enoxaparin 40 mg subcutaneous once daily. His serum creatinine started increasing 48 hours after favipiravir with non-oliguria. The respiratory failure showed improvement in four days. The patients favipiravir was stopped and renal functions improved over three days (Figure 1).

**Table 1: Day wise laboratory parameters during the course of illness**

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Day 2</th>
<th>Day 3</th>
<th>Day 6</th>
<th>Day 8</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hb (g%)</td>
<td>12.5</td>
<td>9.2</td>
<td>9.5</td>
<td>10.1</td>
</tr>
<tr>
<td>Total bilirubin (mg/dl)</td>
<td>2.6</td>
<td>4.6</td>
<td>0.6</td>
<td>0.5</td>
</tr>
<tr>
<td>Indirect bilirubin</td>
<td>1.8</td>
<td>3.5</td>
<td>0.4</td>
<td>0.3</td>
</tr>
<tr>
<td>SGOT (IU/L)</td>
<td>55</td>
<td>36</td>
<td>14</td>
<td>17</td>
</tr>
<tr>
<td>SGPT (IU/L)</td>
<td>38</td>
<td>31</td>
<td>38</td>
<td>29</td>
</tr>
<tr>
<td>ALP(U/L)</td>
<td>165</td>
<td>158</td>
<td>162</td>
<td>197</td>
</tr>
<tr>
<td>LDH(IU/L)</td>
<td>561</td>
<td>2252</td>
<td>735</td>
<td>431</td>
</tr>
<tr>
<td>Total bilirubin (mg/dl)</td>
<td>2.0</td>
<td>1.8</td>
<td>0.6</td>
<td>0.5</td>
</tr>
<tr>
<td>Indirect bilirubin</td>
<td>0.6</td>
<td>0.4</td>
<td>0.4</td>
<td>0.3</td>
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<tr>
<td>SGOT (IU/L)</td>
<td>1.8</td>
<td>3.5</td>
<td>0.4</td>
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<tr>
<td>SGPT (IU/L)</td>
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<tr>
<td>LDH(IU/L)</td>
<td>1.8</td>
<td>3.5</td>
<td>0.4</td>
<td>0.3</td>
</tr>
</tbody>
</table>

In conclusion, we believe as many repurposed drugs are being used for COVID-19 on experimental and compassionate basis without well conducted research, the clinicians need to be very careful of any new adverse event. The AKI like in any other patient needs comprehensive review for all possible etiology before linking it to COVID-19.

**References**


*Fig. 1: Trend of serum creatinine and its relation to Favipiravir. Hollow arrow: Start of favipiravir. Solid arrow: stop of favipiravir*
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