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COVID-19 and Kidney

Niteen D Karnik¹, Mayuri Trivedi²

The Severe Acute respiratory syndrome Coronavirus 2 (SARS-CoV-2) causes a severe acute respiratory illness but also has a major crosstalk with other organs. Amongst these; the kidney is described as a major target for the infection related acute complications with even a pre-existing abnormal kidney function becoming a risk factor for severe infection and adverse outcomes.

Acute Kidney Injury (AKI) and COVID-19

The incidence of AKI in COVID-19 infections has been described as 5-40% in studies from around the world.² The postulated mechanisms includes haemodynamic alterations secondary to altered gas exchange in the lungs, volume overload, cytokine storm and volume depletion.³,⁴ The Angiotensin converting enzyme 2 (ACE-2) serves as the binding site of the virus in the lung. It is also expressed in large concentrations on the renal tubular epithelium cells, where it serves as a binding site for the virus particles and possibly contributes to acute worsening of renal function.¹

The other renal abnormalities which have been described include significant proteinuria, pyuria and haematuria.³ Renal biopsy reports by Kudose et al from critically ill patients with COVID-19 infections and AKI reveal a variety of glomerular and tubular diseases including collapsing glomerulopathy, immune mediated glomerular diseases and acute tubular injury.⁴ Rossi et al have described evidence of viral inclusion bodies on electron microscopy studies of the kidney biopsy, indicating a direct entry and replication within renal tubular epithilium. But absence of the viral cytopathic effect (cell detachment and death) argues against a causal relationship.⁴,⁵ Despite the exact mechanism of renal injury still being elusive, its presence definitely portends a poor prognosis. Hirsch et al in their study of 5449 patient with COVID-19 described 1993 patients (36.6%) with AKI. The AKI occurred early in the disease course with a temporal relationship with the respiratory failure (89.7% in ventilated patients vs. 21.7% in non-ventilated patients) and a poorer overall outcome with a mortality of 35% amongst those with AKI.²

Chronic Kidney Disease (CKD) and COVID-19

Patients with pre-existing CKD including ESRD (End stage renal disease) are at a higher risk of severe COVID-19 infections and have a 14-16 times higher mortality due to this infection with one-third of these patients succumbing to the illness.⁶ In an initial report from India by Trivedi et al describing 37 ESRD patients with COVID-19, the mortality was 38% which is almost 10 times the mortality of general population with the infection.⁷ In another study from Bronx describing ESRD patients with COVID-19, Fisher et al (n=114) found a mortality of 28%.⁸ In these patients, an existing pro-inflammatory state with maladapted innate and adaptive immunity results in higher risk of infections including COVID-19 and frequent visits to the dialysis centres leads to an increased exposure to the virus. In addition, presence of concomitant underlying co-morbidities like diabetes and hypertension or various immunosuppressive drugs (post transplantation or glomerular diseases) further elevate the risk of the infection.⁶

Management: Therapy and Hurdles

The therapy of COVID-19 remains elusive even in those with kidney involvement with lack of literature specifically targeting the drugs in these patients. In the RECOVERY Trial, Dexamethasone, which modulates inflammation mediated acute lung injury in severe COVID-19, has proven to be beneficial when used at 6mg daily for 10 days and may be used without any dose modifications in those with underlying kidney involvement.⁹ Data regarding the use of Tocilizumab, an Interleukin-6 antagonist, in severe COVID 19 is limited. However it may be used in these patients with no special dose modifications or reported unique adverse effects.¹⁰ Remdesvir, an antiviral nucleotide analog that inhibits RNA-dependant RNA polymerase has shown a promising result in reducing the median time of recovery in patients. SBECD, the vehicle used for the intravenous preparation of the drug, is associated with renal tubular obstruction on prolonged use and is eliminated with dialysis. The limited duration (5-10 days) and relatively low dose of 100mg per day of the drug used in COVID-19 infections suggests that the benefits outweigh the risk even on patients with eGFR <30/ml/min/m².¹¹ Favipiravir, yet another nucleotide inhibitor, is an oral anti-viral drug which is available for use in stable non hypoxic patients. Though this drug is renal eliminated and its plasma levels are 3-5 times higher in patients with eGFR <50 ml/min/1.73m², these levels do not appear to be nephrotoxic and hence can be used without dose modification.¹² As we await the results of the multicentric randomised control trial from Indian council of Medical Research (ICMR), on the effectiveness of plasma therapy in severe COVID-19 infections, the available data on the use of convalescent plasma therapy has shown no increased adverse events in patients with kidney diseases and may be safely prescribed.¹³ It should be acknowledged that all the above described therapies have been approved only on compassionate grounds and need a consent for use.

The patients of CKD are considered to be a burden to the already ailing healthcare system. The onset of the

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pandemic in India saw a rapid closure of dialysis centres especially the stand alone centres, overwhelming the existing dialysis facilities. COVID-19 infections amongst the dialysis staff, shortage of drugs and dialysis consumables, lack of transportation due to the nationwide lockdown combined with the social stigma of this disease resulted in long intervals of skipped haemodialysis in ESRD patients. The ensuing chaos resulted in an increased load of emergency presentations of the patients with fluid overload, lung shadows mimicking COVID-19 and metabolic emergencies. The compulsion of COVID-19 testing to segregate the COVID and Non COVID cases further delayed the required dialysis.

CKD patients with COVID-19 infection die more due to non availability of dialysis rather than due to the infection itself. This observation made over a span of time prompted the setting up of an Expert Task force committee of both the Central and State governments with a dedicated nephrologist who formulated and streamlined protocols for running efficient dialysis services during the pandemic. Simple steps like dialysing COVID positive patients in the last shift of the day, keeping a separate set of dialysis staff for each shift, effective sanitisation in between shifts and standardising a pre dialysis clinical screening protocol for patients and care takers were some of the effective protocols suggested by the task force for overcoming the hurdles. Another effective patient friendly initiative, was taken up by the Brihanmumbai Municipal Corporation (BMC) in association with a team of Nephrologists and IT professionals, by starting a dedicated web page (www.covidialysis.in) which allotted dialysis beds to the covid-19 positive patients on dialysis across the city in dedicated COVID centres. This project was launched under the name of ‘Project Victory’ and substantially stream-lined the process of dialysis for the patients.

Lung and Kidney are the two major determinants of outcomes in covid-19. The ARDS of COVID-19 lung is much feared and tends to overshadow the renal complications. Acknowledging the need to evaluate and effectively manage patients with renal complications in COVID-19 may increase the chances of patient survival in this dreaded pandemic.

References


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Abstract
COVID-19 has emerged as a pandemic of significance with potential to cause significant morbidity and mortality worldwide. Elderly with or without following comorbidities i.e Diabetes, hypertension, cardiac disease, chronic respiratory illnesses, chronic liver disease, CKD, malignancy and immunocompromised hosts are at increased risk of developing complicated course. Hemodialysis population hence are at increased risk for contracting the infection due to patient characteristics, environmental characteristics and procedural lapses. The current study was aimed at describing prevalence and characteristics of COVID19 in hemodialysis population across different HD centers across Mumbai. We found a prevalence rate of COVID19 in 6.4%, with 9 patients (12%) died during the study period. A fair proportion of Non covid HD patients (1.5%) also died due to lack of access to dialysis. At baseline, mean age of presentation was 54.5 years. On routine test 80% were asymptomatic at presentation. Patients with COPD, requiring ICU care and those on ventilation fared poorly. Contrary to assumption patients with underlying cardiovascular disease didn’t show poor outcome. Total of 4.1% health care workers turned positive during the study period with mean age of 31 years and median of 28years. Out of them 5 (45.4%) were symptomatic. All recovered from the illness without any sequelae. Seventy two percent of healthcare workers were on Hydroxy-chloroquine chemoprophylaxis didn’t reach statistical significance in preventing the infection. In our study elderly age with comorbidities had poor prognosis. We proposed extra healthcare measures to be taken in the dialysis unit presuming all as COVID suspect in the resource limited settings.

Introduction
ARS COV-2 is a subset of corona virus first isolated from Wuhan, China was declared pandemic by WHO in the month of March 2020. Patients with comorbid conditions including diabetes, hypertension, heart ailments, chronic respiratory illnesses, chronic liver disease, chronic kidney disease, cancer patients or individuals with compromised immune status are at higher risk for complications.¹

The Chinese center for Disease Control and Prevention recently published the largest COVID-19 case series, which includes 44,672 cases. This study shows an overall mortality rate of 2.3%. Besides age (1.3% mortality in the 50–59 age group, 3.6% in the 60–69 age group, 8.0% in the 70–79 age group, and 14.8% in the greater than 80 age group), the main risk factors are the presence of cardiovascular diseases (10.5% mortality), diabetes (7.3% mortality), chronic respiratory diseases (6.3% mortality), high blood pressure (6% mortality), and cancer (5.6% mortality).²³

CKD Stage 5 D patients on Haemodialysis usually have multiple comorbidities like diabetes, hypertension, hyporesponsive immune status, malnutrition besides underlying heart ailment. These group of patients are also at high risk of contracting the COVID-19 infection due to exposure to adverse environment i.e they need to attend dialysis unit intermittently either twice or three times a week. This renders them more susceptible to risk of exposure to covid 19 when compared to the general population ⁴

Most of hemodialysis patients are asymptomatic due to low immune status and manifest severe disease later which lead to increase mortality and morbidity 12 to 14% vs 2 to 4% when compared to general population.⁵

It is advisable to screen those patients closely and stringent protocol should be executed for detection of COVID-19 infection early in the course and should be followed up closely. In absence of effective treatment options and vaccines it is widely accepted by all that social distancing, proper cough etiquette practice, frequent hand washing and use of face mask in selected group of persons could curtail the spread of infection which usually spreads most often by droplets and through fomites. Not only Hemodialysis patients can get infected with COVID19 but healthcare workers can get infected from the patients they handled or vice versa, hence universal precaution practice should be practiced by both.

Our current study aimed at identifying the disease burden in our dialysis centers and impact of current hospital practice guidelines on outcome of dialysis patients during the COVID pandemic.
Review of Literature

Novel Coronavirus is a single stranded RNA virus renamed as SARS-CoV-2 and grouped in the same category of viruses like SARS & MERS. The disease it creates on entering into the human body is described as COVID-19 (Corona Virus disease 2019). Novel Corona virus SARS-CoV-2 can affect the individuals with varied type of symptoms. The individual to individual transmission is most commonly due to droplet infection. Novel Corona virus is uniquely differentiated from its cohorts like SARS and MERS as the incubation period can range from 3 days to 14 days. Hence although the person is infected it doesn’t show any signs or symptoms or mild symptoms but has the potential to transmit the virus unknowingly to healthy individuals. Hence R0 reproduction rate of the virus is high.

COVID-19 disease can be classified according to severity into mild, moderate, severe and critical according to new corona virus pneumonia prevention and control program (7th edition).5

Mild refers to patients who had mild clinical symptoms with- out manifestation of viral pneumonia on chest CT scans. Moderate refers to patients who had symptoms such as fever and respiratory tract symptoms, etc., with manifestation of viral pneumonia on chest CT scans. Severe refers to patients who met any of the following criteria: (1) respiratory rate greater than 30 breaths/min; (2) oxygen saturation less than 93% at rest state; and (3) arterial PO2/oxygen concentration less 300 mm Hg. Patients with pulmonary lesion progression greater than 50% within 24–48 hours on radiologic imaging were treated as severe cases. Critical refers to patients that met any of the following criteria: (1) occurrence of respiratory failure requiring mechanical ventilation; (2) presence of shock; and (3) other organ failure that requires monitoring and treatment in the intensive care unit.

As the patients on haemodialysis visit the hospital care set up frequently two or three times a week their chances of contracting the virus is higher.

1. Patient characteristics : Dialysis patients have low immunity resulting in incapability to defend the infection. Higher incidence of diabetes mellitus, ischemic heart disease, underlying malignancy, smoking, underlying chronic liver disease and failed kidney transplant recipients in this population increases their susceptibility as compared to general population. It has been observed in different studies that dialysis patients do not manifest symptoms, hence they manifest late in the illness and strong cytokine storm is usually absent in this group of patients. However these patients succumb to illness in short span of time in view of more comorbidity.

2. Health care facility characteristics: Hemodialysis is a procedure which requires multi disciplinary involvement i.e Nephrologist, dialysis medical officer, Dialysis Technicians, Nurses and ancillary staff. A dialysis patient is dependent on a dialysis unit to get the procedure done hence is more exposed to these health care providers.

3. Environmental factors: Environmental factors also contribute significantly towards spread of infection in dialysis patients. Clustered environment in the dialysis facility, using common facilities and travel in the public transport system also significantly contributes towards spread of infection in a pandemic. Some of these factors be controlled by interventions at hospital set up, patient education about the nature of virus, the routes of transmission and natural course of disease are essential to identify early and intervene accordingly.6

Any breach in the above steps will lead to spread of infection in the dialysis patients. Hence intervention strategies should be applied at multiple levels to effectively manage COVID-19 outbreak.

There are enough guidelines published both International as well as national level in each country to prepare standard operative protocol (SOP) and execute it. Here while preparing the SOP we have to incorporate the local standard practices to make it simple so that it can be implemented easily.7-10 (ISN guidelines, Indian society of Nephrology guidelines, Municipality guidelines, etc). CDC Guidelines, ASN guidelines.

The essential component of guidelines comprised of identifying the COVID-19 infected patients early by intermittent screening, isolation of patient, contact tracing, treating the dialysis patients as per SOP, quarantine the immediate contacts, use of chemoprophylaxis in healthcare workers as per local practices. Needless to say frequent hand washing, Social distancing, maintaining hygiene etc which were described earlier to be followed as per protocol.

The main aim is not only to protect our dialysis patients acquiring COVID-19 infection but also to protect our healthcare workers as well.

In case a dialysis patient or healthcare worker were to get infected with COVID-19, the SOP to be implemented included temporary closure of dialysis unit, with isolation/quarantine of exposed healthcare workers which resulted in rescheduling of dialysis treatments to large number of dialysis patients. Also the dialysis units which were functional were working with less manpower due to various factors which is beyond the reach of current discussion including lockdown, closure of public transport, logistic issues due to breakdown of supply chain etc. The resultant effect being inadequate delivery of services to the patients leading to increased morbidity and mortality during the current COVID-19 pandemic.11-13

Aims: To study impact of COVID-19 pandemic in Mumbai India on various aspects of management of patients on hemodialysis

Objective

1. To study clinical characteristics and outcomes of COVID-19 infection, both in terms of morbidity and mortality in patients on hemodialysis

2. Prevalence of COVID-19 in hemodialysis patient in centers with different modality of screening and routine vs symptomatic testing of COVID.


4. Impact of use of different levels of personal protection equipment on health care workers and rates of infections in patients.

5. Impact of duration of forced closure of dialysis units on non covid mortality due to non availability of dialysis

Material and Methods

The study is a non-interventional multicenter, retrospective,
observational study. It includes all hemodialysis patients who are receiving Hemodialysis from 1st February 2020. Data were captured from 27 Dialysis units by 9 Nephrologists working in those centers. The Dialysis units are heterogenous i.e some of these centers were functioning within tertiary care hospitals while few were standalone dialysis centers. Different dialysis centers had different strategies for screening and different levels of personal protection equipment (PPE) enumerated in the text. All dialysis centers had reduced the frequency of regular dialysis to twice a week for all patients on maintenance dialysis.

**Inclusion Criteria**

1. All patients on maintenance dialysis for 3 months
2. Health care worker defined as doctors, dialysis technician, nurses and house keeping staff involved in management of dialysis patients
3. COVID-19 positive is defined as positive throat swab by RT-PCR method with minimum 1 week of follow up

**Exclusion criteria**

1. Patients who has acute renal insufficiency
2. Patients having pneumonia of unknown etiology
3. Patients on peritoneal dialysis
4. Patients on home haemodialysis

A COVID-19 positive patient has been defined as having at least one of the two samples collected one week apart from both nose and throat swab. The method of detection would be by RT-PCR method.

A patient would be considered negative or cured when two samples would be negative one week apart, by RTPCR method

Methods of screening followed in different centers varied from

A. Temperature (By Non contact Infrared Thermometer/ Digital Thermometer)
B. Spo2 by pulse oximeter
C. Chest x-ray / HRCT chest
D. Declaration form with information on COVID19.

Personal protection equipment used by health care personnel would be categorized as level 1 to 4 according to CDC guidelines.

According to recommendation of ICMR- National task force on COVID-19 all asymptomatic health care worker were given prophylaxis with hydroxychloroquine (HCQ) at the dosage of 400mg twice a day on day 1 and then 400mg once a week for 7 weeks

According to guidance of the government all positive patients were transferred to designated COVID hospital with dialysis facility. We followed up all the patient and obtained the clinical data with their consent.

**Data Collection**

We collected information about exposure history, demographic data, clinical features, lab reports, chest CT scans, and treatment details for all patients with laboratory-confirmed COVID-19 between February 1 and 25th May, 2020, and reviewed the data. Written informed consent was waived because of the rapid emergence of this infectious disease, and verbal consent obtained. The date of disease onset was defined as the date when the symptoms were noticed. We obtained data by direct communication with patients or their families, attending doctors, and other health care providers if data were missing from the records or clarification was needed. All laboratory testing was performed according to the clinical care needs of the patient.

Treatment measures included antiviral or antibiotic therapy, corticosteroid therapy and was left to the discretion of attending Physician. All data entered into a computerized database on excel sheet and cross checked by four physicians (HT and CT).

**Statistical analyses**

Categorical variables were expressed in the form of frequency and percentage, and continuous variables were expressed as mean ± SD or median. Difference between survivors and nonsurvivors were assessed using chi-squared test or Fisher’s exact tests for categorical variables and unpaired t-test for continuous variables. A two sided probability (P) value of <0.05 was considered statistically significant. All analyses were performed using Jamovi software (Version 1.2).

**Results**

From 01 March 2020 till 25 May 2020 data were captured from dialysis centers. Out of 1113 patients on maintenance hemodialysis at 27 centers in Mumbai, 75 (6.74%) patients were detected positive for SARS-CoV-2 infection.

Basic clinical screening with a self declaration questionnaire was done for all patients. Seven centers practiced compulsory testing of patients by RT-PCR test at 7-14 days interval. After 19 May 2020, these 7 centers stopped compulsory testing due to government directives allowing for testing of only symptomatic patients. Level 1 PPE was used by HCW at 6 (22.2%) centers, level 2 PPE at 15 (55.6%) centers and level 3 PPE at 6 (22.2%) centers. As per government policy, if a patient was detected positive, then the center had to refer the patient for treatment at a COVID-19 designated hospital. The dialysis center had to suspend dialysis procedures temporarily for a variable time period for contact tracing, health care worker assessment and testing, and disinfection of dialysis center. In accordance with government policy and local infection control practices, forced closure of HD units happened in 13 (48.15%) out of 27 centers. Five (18.52%) HD centers had closure for more than 48 hours duration, 8 (29.63%) HD centers had closure for 48 hours or lesser duration, and 14 (51.85%) centers did not have any closure. Hemodialysis frequency and session length were changed by the centers to adjust the schedule after these closure events resulting in compromise in dialysis dose delivery.

Baseline characteristics of these 75 patients are described in Table 1. Mean age was 54.15 years and 57% were males. 60 patients (80%) were asymptomatic for COVID-19 and were detected positive on compulsory testing, whereas 15 (20%) were detected positive on symptomatic testing. Comorbidities in these patients included diabetes mellitus (52%), hypertension (73.33%), heart disease (29.3%) and chronic obstructive lung disease (5.33%). Of those 75 patients majority of them were getting HD through AV Fistula (70.6%) and rest through TCC. All patients had to be admitted in view of non-availability of OPD dialysis facilities.

Sixty patients (80%) were asymptomatic for COVID-19 and were detected positive on compulsory testing where as 15 (20%) were positive on symptomatic testing (Table 2).
six (88%) patients recovered from illness during the study period, 15 (20%) required ICU stay and 8 (10.6%) required ventilatory support. Majority of patients 81.3% were on HCQS as treatment where as 45.3% received Azithromycin along with it.

There were 9 (12%) deaths in 75 COVID-19 positive patients. On the other hand, 16 deaths were identified in 1038(1.5%) COVID-19 negative patients due to non-availability or lack of adequate dialysis. There were 13 deaths in centres closed for more than 48 hours and 3 deaths in centres closed for 48 hours or less in COVID-19 negative patients. Presence of underlying chronic obstructive lung disease, requirement of ICU care and ventilator support were significantly higher in nonsurvivors compared to survivors. There was no significant difference in age, sex, diabetes mellitus, hypertension, heart disease and use of hydroxychloroquine and azithromycin between survivors and nonsurvivors. Survivors included 6 patients who required ICU care and 2 patients who required ventilator support (Table 4).

Amongst 265 total HCW, 11 (4.15%) tested positive for SARS-CoV-2 in 7 (25.93%) centers and included 8 technicians, 1 nurse and 2 housekeeping staff. Three centers were using Level 3 PPE in which 6 HCWs tested positive on compulsory testing and 1 on symptomatic testing. Remaining 4 HCW were tested after development of symptoms (Table 3). Median age of HCW was 28 years (range 25-50 years) and 54.55% were females. None of the HCW had comorbidities, 72.72% were on HCQ prophylaxis, and none developed serious disease. There was no mortality in HCW. Dialyzer reuse was practiced at all 27 centers. Absenteeism due to travelling difficulties, HCW turning positive and quarantine after unwarranted, unprotected close contact with a patient or HCW, resulted in severe staff shortage during this period.

**Discussion**

The incidence of laboratory confirmed COVID-19 cases in CKD Stage 5D patients on maintenance hemodialysis in our study was 75/1113 (6.4%). In our study total of 9 patients died who were infected with COVID 19 (12%). In our analysis death due to COVID-19 dialysis population were less than Wuhan experience. However more striking feature in our dialysis population were death due to non availability of dialysis due to downtime of hemodialysis unit during the initial period 16/1038(1.5%). Out of these 13 deaths reported in centers who had more than 48 hours closure in comparison to 3 deaths in those centres where closure happened less than 48 hours. So we changed our strategies and in selected centers corrective strategies were implemented to keep a back up HD unit to dialyse the COVID-19 negative patients during downtime of main HD unit.

When compared with Wuhan our population were younger mean 54.1 yrs vs 63 yrs, had higher incidence of COVID-19 infection 6.4% vs 2.15%. There were more diabetics in our population.

Comorbidities in our patients included diabetes mellitus (52%), hypertension (73.33%), heart disease (29.3%) and chronic obstructive lung disease (5.33%). When compared to the severity of illness 15/75(20%) patients were severely affected who needed ICU care.

Baseline characteristics of these 75 patients in our study are described in Table 1. Mean age was 54.15 years and 57% were males. 60 (80%) were asymptomatic for COVID-19 and were detected positive on compensatory testing, whereas 15 (20%) were detected positive on symptomatic testing. Comorbidities in our patients included diabetes mellitus (52%), hypertension (73.33%), heart disease (29.3%) and chronic obstructive lung disease (5.33%). When compared to the severity of illness 23/75(30.66%) patients were severely affected who needed ICU care and 52/75(69.34%) were affected with mild to moderate severity. Out of 23 patients Fifteen (20%) required ICU care and 8 (10.67%) required ventilatory support. Hydroxychloroquine was given as part of treatment protocol to 61 (81.3%) patients and 34 (45.33%) patients received azithromycin. All patients had to be admitted in view of non-availability of OPD dialysis facilities. All patients received either regular hemodialysis or SLEDD (Slow low efficiency daily dialysis) according to their hemodynamic status. CRRT was not offered to most of the patents either due to non availability or due to financial constraints.

Level of PPE used by healthcare workers were level 1 in 6 centres, level-2 in 15 centers, and level-3 in 6 centers. 60 patients were covid 19 positive in centres using level 3 PPE where as 15 patients were covid positive in centers using level 1 or 2 PPE. This discrepancy is most likely as nonuniformity in testing practices.

There were approximately 9/75

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### Table 1: Baseline characteristics of dialysis patients turned COVID-19 positive (n=75/100%)

<table>
<thead>
<tr>
<th>S. No.</th>
<th>Characteristics</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Average age of patients</td>
<td>54.15 years</td>
</tr>
<tr>
<td>2</td>
<td>Gender</td>
<td>Male 43 (57%)</td>
</tr>
<tr>
<td>3</td>
<td>Comorbidities</td>
<td>Cardiovascular disease 39 (52%)</td>
</tr>
<tr>
<td>4</td>
<td>Mode of dialysis</td>
<td>Hemodialysis 75 (100%)</td>
</tr>
<tr>
<td>5</td>
<td>Dialysis access</td>
<td>Arteriovenous fistula 53 (70.6%)</td>
</tr>
<tr>
<td>6</td>
<td>Frequency of dialysis</td>
<td>Twice a week 75 (100%)</td>
</tr>
<tr>
<td>7</td>
<td>Dialyzer reuse</td>
<td>Yes 75 (100%)</td>
</tr>
</tbody>
</table>

### Table 2: Clinical characteristics of hemodialysis patients turned COVID-19 positive (n=75/100%)

<table>
<thead>
<tr>
<th>S. No.</th>
<th>Clinical characteristics</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>COVID-19 presentation</td>
<td>Symptomatic 15 (20%)</td>
</tr>
<tr>
<td>2</td>
<td>Outcome</td>
<td>Recovered 66 (88%)</td>
</tr>
<tr>
<td>3</td>
<td>ICU requirement</td>
<td>Yes 15 (20%)</td>
</tr>
<tr>
<td>4</td>
<td>Ventilator requirement</td>
<td>Yes 8 (10.6%)</td>
</tr>
<tr>
<td>5</td>
<td>Received HCQS treatment</td>
<td>Yes 61 (81.3%)</td>
</tr>
<tr>
<td>6</td>
<td>Received azithromycin</td>
<td>Yes 34 (45.3%)</td>
</tr>
</tbody>
</table>

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were sent to COVID designated centers which made data collection difficult, however significant effort was made to get relevant laboratory findings or events which lead to death.

Conclusion

To conclude from this study, we have found the following points of interest. There was no gender differentiation in the patients who get infected with COVID-19. Our findings indicate those patients who were elderly with more than 60 years of age with any of the associated comorbidities like Diabetes, Hypertension, IHD, COPD and CLD alone or in combination had poor outcomes. Our study did not find any significant correlation of more number of COVID testing with predicting outcome or improving management in COVID-19 dialysis patients. Rather it had an adverse effect over overall death rate due to closure of dialysis units. Those CKD stage 5D patients who require invasive ventilation do poorly during recovery. HCQ and or Azathioprine didn’t show any significant difference between survivors against non survivors.

We implemented universal PPE protection to our HCWs and recommended minimum proper hand hygiene and face mask for our dialysis patients. This made us rethink about scheduled testing in dialysis population in resource limited settings. We recommend that all patients should be treated as COVID suspect and HCW and patients should ensure social distancing, hand hygiene, cough etiquette and wear appropriate PPE. These will limit transmission of virus in the dialysis unit.

References

Preliminary Observations and Experiences of Physiotherapy Practice in Acute Care Setup of COVID 19: A Retrospective Observational Study

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Abstract

Background: The rapid outbreak of coronavirus disease 2019 (COVID-19), a public health emergency of grave concern, warranted hospital admissions with almost 90,000 cases in June 2020 in city of Mumbai. 3–10% of the patients with moderate to severe involvement required intensive care unit (ICU) admission with respiratory support. Patients admitted in ICU with an acute COVID event present with respiratory dysfunction and are more likely to have critical illness myopathy and neuropathy (CIMN). Physiotherapy services being integral part of non-pharmacological management of any ICU was implemented for patients with COVID 19; a novel viral disease.

Objectives: This retrospective study was undertaken to explore the physiotherapy practices that could be implemented in patients admitted with COVID 19 in the ICU and its effect on mobility and oxygen requirement as an outcome.

Methodology: Following ethical permission of institute, the data was extracted from electronic data record sheet in which daily parameters for physiotherapy intervention were recorded. Data from a single ICU and step down unit (SDU) from 5th June to 5th July 2020 was analysed. Records of patients diagnosed with COVID 19 and admitted in ICU or SDU were studied. Those in the age group of 18 to 90 years, of either gender were included. Demographic characteristics, disease severity, oxygen requirement, mobility status, physiotherapy intervention were studied.

Results: 278 record sheets (110 ICU and 168 SDU) were retrospectively analysed for demographics. 44.55% of patients improved with side lying position, 37.27% with prone position and 10.91% with quarter prone position. 4.55% of patients maintained oxygenation in propped up sitting. 2.73% could not be positioned. Chest physiotherapy techniques applied were deep breathing, ACBT, paced breathing and diaphragmatic breathing. Deep intercostal pressure on NIV along with vibrations was given to 12.72% of patients in the ICU. Group therapy sessions were conducted in SDU where 50.59% patients participated. ICU mobility score showed significant improvement on Wilcoxon Signed Ranks test status on day 7 in the ICU (z=-5.99, p=0.00) and SDU (z= 7.676, p=0.00) compared to day 1. Descriptive analysis showed a definitive reduction in oxygen support requirement

Conclusion: Most common form of physiotherapy interventions in patients with Covid 19 were therapeutic positioning, early mobilization and breathing exercises. Physiotherapy intervention appears promising in facilitating early patient ambulation and discharge. This study shows that it is safe and feasible to provide early physiotherapy treatment techniques in patients with COVID-19 using appropriate measures of infection prevention and cross contamination.

Introduction

The rapid outbreak of the coronavirus disease 2019 (COVID-19), a public health emergency of grave concern warranted hospital admissions with almost 90,000 cases in June 2020 in city of Mumbai. 3–10% of the patients with moderate to severe involvement require intensive care unit (ICU) admission with respiratory support. The primary presentation of COVID 19 patients in ICU is of Adult respiratory distress syndrome (ARDS), stroke, myocarditis, multi organ failure and sepsis.

Chest physiotherapy and early mobilization has a vital role in the management of patients in the ICU to reduce morbidity and mortality. Muscle wasting and weakness develops within days of ICU admission with effects on survival and physical functioning lasting for years post discharge. Patients admitted in ICU with an acute COVID event present with respiratory dysfunction and are more likely to have critical illness myopathy and neuropathy (CIMN). They may need greater psychological support than typical ICU patients because of higher levels of “survivors’ guilt” and post-traumatic stress disorder. Evidence from China and UK concludes that COVID 19 patients have neurological and respiratory after effects needing a complex and prolonged recovery. Therapeutic intervention amidst a clinical scenario of patients with minimal to no sputum, increased breathlessness and rapid desaturation on activity associated
with tachycardia provides a challenge in decision making.

Physiotherapy services being an integral part of non-pharmacological management of any Intensive Care Unit (ICU) was commenced for patients with COVID-19 with the goal of improving survival, reducing associated morbidity and gaining function. COVID-19 provides a challenging opportunity of doing things in a different manner. Safety and preventing cross infection are of utmost importance while administering physiotherapy intervention. Workforce organization and therapist training in donning and doffing about personal protective equipment (PPE) along with safe practices to minimize aerosol generation is extremely important. Guidelines and position statements for workforce planning, protection and implementation formed a framework to implement these practices.

The aim of this study was to explore and describe how COVID-19 patients received physiotherapy interventions in acute care setup of a tertiary hospital in Mumbai.

Materials and Methods

Study design

A retrospective cohort study was performed capturing the data from all consecutively admitted COVID-19 positive patients records in tertiary care hospital of Mumbai from 5th June to 5th July 2020. This study is reported as per STROBE guidelines. Ethical approval for this study was obtained from institutional ethics committee.

Table 1: Demographic details of the cohort receiving physiotherapy (N=278)

<table>
<thead>
<tr>
<th></th>
<th>ICU (n=110)</th>
<th>SDU (n=168)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean Age in yrs</td>
<td>54.82 ±13.09</td>
<td>51.71 ± 14.57</td>
</tr>
<tr>
<td>Males</td>
<td>79 (71.82%)</td>
<td>149 (88.69%)</td>
</tr>
<tr>
<td>Females</td>
<td>39 (35.45%)</td>
<td>24 (14.28%)</td>
</tr>
<tr>
<td>Stage I</td>
<td>71 (64.54%)</td>
<td>144 (85.71%)</td>
</tr>
<tr>
<td>Stage II</td>
<td>69 (62.72%)</td>
<td>102 (60.71%)</td>
</tr>
<tr>
<td>Mean resting Heart rate bpm</td>
<td>96.03 ± 15.7</td>
<td>93.92 ± 16.39</td>
</tr>
<tr>
<td>Mean resting SpO2%</td>
<td>91.93 ± 5.56</td>
<td>95.47 ± 3.61</td>
</tr>
<tr>
<td>Mean days of PT</td>
<td>6.4 (1-32)</td>
<td>8.8 (1-32)</td>
</tr>
<tr>
<td>Comorbidities present</td>
<td>69 (28.18%)</td>
<td>19 (11.31%)</td>
</tr>
<tr>
<td>Death</td>
<td>27 (24.54%)</td>
<td>0</td>
</tr>
<tr>
<td>Transferred</td>
<td>81 (73.63%)</td>
<td>4 (2.38%)</td>
</tr>
<tr>
<td>Discharged</td>
<td>2 (1.8%)</td>
<td>138 (82.14%)</td>
</tr>
</tbody>
</table>

Inclusion Criteria

1. All COVID-19 positive patients (age group of 18 years to 90 years) who were confirmed on laboratory diagnosis as COVID-19 positive and received Physiotherapy treatment between 5th June to 5th July 2020

2. COVID-19 patients admitted in the Intensive care unit (ICU) and a step down unit (SDU) of the hospital

Exclusion criteria

1. Incomplete documentation of physiotherapy practices in medical records
2. Those COVID-19 patients who were not referred for physiotherapy services
3. Metabolic acidosis
4. Severe hypoxaemia
5. Blood temperature above 38°C
6. Severe tachycardia
7. Comorbidities associated morbidity and gaining function

Statistical analysis: Data analysis was performed using software SPSS version 26. Patient characteristics were expressed as Mean ± Standard Deviation (SD) for continuous variables. Frequencies were expressed as percentages for categorical variables. Descriptive analysis was performed for evaluation of ICU mobility scores and oxygen support requirement on Day 1 and Day 7. Wilcoxon signed rank test was applied to study change in IMS from day 1 to day 7. All reported p-values are two-sided and a p-value of <0.05 was considered to indicate statistical significance.

Results

Total of 300 records; 124 from a single ICU and 176 from SDU from 5th June to 5th July were screened. 24 data record sheets (13 ICU and 7 SDU) with incomplete or missing data and
staging. Categorized as per clinical therapeutic of illness at the point of admission was predominant male ward. The severity the Covid ICU. The Covid SDU was a more predominant than females in 14.57 years respectively. Males were Mean age of the patients in ICU and Available data from 278 record sheets 2 below 18yrs of age were excluded.

### Table 2: Change in Median score and IQR of ICU mobility scale (IMS) from Day 1 to Day 7 (N=278)

<table>
<thead>
<tr>
<th>IMS</th>
<th>N</th>
<th>Mean</th>
<th>Std. Deviation</th>
<th>25th Percentiles</th>
<th>50th Percentiles (Median)</th>
<th>75th Percentiles</th>
<th>D7 - D1</th>
</tr>
</thead>
<tbody>
<tr>
<td>ICU (IMS 0-10)</td>
<td>D1</td>
<td>110</td>
<td>2.00</td>
<td>1.78</td>
<td>1.00</td>
<td>1.00</td>
<td>3.00</td>
</tr>
<tr>
<td>D7</td>
<td>110</td>
<td>4.27</td>
<td>3.31</td>
<td>1.00</td>
<td>4.00</td>
<td>8.00</td>
<td>Z = -5.997</td>
</tr>
<tr>
<td>ICU (IMS 5)</td>
<td>D1</td>
<td>103</td>
<td>1.65</td>
<td>1.11</td>
<td>1.00</td>
<td>1.00</td>
<td>3.00</td>
</tr>
<tr>
<td>D7</td>
<td>103</td>
<td>4.21</td>
<td>3.27</td>
<td>1.00</td>
<td>4.00</td>
<td>8.00</td>
<td>Z = -6.588</td>
</tr>
<tr>
<td>SDU (IMS 0-10)</td>
<td>D1</td>
<td>168</td>
<td>6.52</td>
<td>3.91</td>
<td>3.00</td>
<td>9.00</td>
<td>10.00</td>
</tr>
<tr>
<td>D7</td>
<td>168</td>
<td>9.32</td>
<td>1.69</td>
<td>10.00</td>
<td>10.00</td>
<td>10.00</td>
<td>Z = -7.676</td>
</tr>
<tr>
<td>SDU (IMS 5)</td>
<td>D1</td>
<td>55</td>
<td>1.40</td>
<td>1.24</td>
<td>1.00</td>
<td>1.00</td>
<td>3.00</td>
</tr>
<tr>
<td>D7</td>
<td>55</td>
<td>8.50</td>
<td>2.26</td>
<td>8.00</td>
<td>10.00</td>
<td>10.00</td>
<td>Z = -6.495</td>
</tr>
</tbody>
</table>

Wilcoxon Signed Rank Test. Significant p < 0.05

### Table 3: Descriptive statistics of ICU mobility scale (IMS) from Day 1 to Day 7 in ICU(N=110)

<table>
<thead>
<tr>
<th>Day 1</th>
<th>None</th>
<th>In Bed</th>
<th>Out Bed</th>
<th>Assisted walking</th>
<th>Independent walking</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Count</td>
<td>2</td>
<td>3</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Row %</td>
<td>40.0</td>
<td>60.0</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>Column %</td>
<td>33.3</td>
<td>6.5</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td></td>
<td>Count</td>
<td>4</td>
<td>39</td>
<td>25</td>
<td>15</td>
</tr>
<tr>
<td>Row %</td>
<td>4.3</td>
<td>41.5</td>
<td>26.6</td>
<td>16.0</td>
<td>11.7</td>
</tr>
<tr>
<td>Column %</td>
<td>66.7</td>
<td>84.8</td>
<td>100.0</td>
<td>78.9</td>
<td>78.6</td>
</tr>
<tr>
<td></td>
<td>Count</td>
<td>0</td>
<td>4</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>Row %</td>
<td>0.0</td>
<td>44.4</td>
<td>0.0</td>
<td>33.3</td>
<td>22.2</td>
</tr>
<tr>
<td>Column %</td>
<td>0.0</td>
<td>8.7</td>
<td>0.0</td>
<td>15.8</td>
<td>14.3</td>
</tr>
<tr>
<td></td>
<td>Count</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Row %</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
<td>50.0</td>
<td>50.0</td>
</tr>
<tr>
<td>Column %</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
<td>5.3</td>
<td>7.1</td>
</tr>
<tr>
<td>Total</td>
<td>Count</td>
<td>6</td>
<td>46</td>
<td>25</td>
<td>19</td>
</tr>
<tr>
<td>Row %</td>
<td>5.5</td>
<td>41.8</td>
<td>22.7</td>
<td>17.3</td>
<td>12.7</td>
</tr>
<tr>
<td>Column %</td>
<td>100.0</td>
<td>100.0</td>
<td>100.0</td>
<td>100.0</td>
<td>100.0</td>
</tr>
</tbody>
</table>

The baseline clinical and demographic characteristics are as shown in Table 1. Mean age of the patients in ICU and SDU was 54.82 ±13.09 and 51.71 ± 14.57 years respectively. Males were more predominant than females in the Covid ICU. The Covid SDU was a predominant male ward. The severity of illness at the point of admission was categorized as per clinical therapeutic staging.41 64.54% patients from ICU and 85.71% patients from SDU were in stage II b whereas 35.45% patients from ICU and 14.28% from SDU were in stage III. 24.54% of ICU patients succumbed to the illness and 73.63% were transferred to SDU. In SDU, 82.14% patients were discharged and 2.38% were transferred to ICU because of deteriorating clinical status. Comorbidities were present in 62.72% and 60.71% patients in ICU and SDU respectively.

Physiotherapy practices: The preferential position for saturation improvement in ICU as seen in Figure 1 were side lying and prone. 44.55% of patients improved with side lying position, 37.27% with prone position and 10.91% with quarter prone position. 4.55% of patient maintained oxygenation in propped up sitting. 2.73% could not be positioned. In SDU except for 13.69 % patients all were in prone position and practiced awake prone. Duration in therapeutic position ranged from 10 to 30 minutes.

Respiratory physiotherapy incorporated rational use of deep breathing exercises, paced breathing, active cycle of breathing technique (ACBT) and diaphragmatic breathing. Diaphragmatic recruitment was not possible in any of the patients on Non Invasive Ventilation (NIV). Patients on Non Rebreather Mask (NRM) could practice ACBT as airway clearance method and paced breathing. Incentive spirometry was given to 13.63% and 26.78% of patients in the ICU and SDU respectively. Deep intercostal pressure along with vibrations was given to 12.72% of patients on NIV in the ICU. Group therapy sessions were conducted in SDU where 50.59% patients participated.

Six minute walk test (6MWT), sit to stand could be conducted in 42 (25%) patients in SDU. A mean distance of 158.16 ± 58.36 metres (43-270 ) was covered on 6MWT. Mean repetitions on 30 second sit to stand test were 9 (6-13). The most common limiting factor was feeling of fatigue.

Mobility was scored on the ICU Mobility Scale (IMS). It provides a sensitive 11-point ordinal scale, ranging from nothing (lying/passive exercises in bed-score of 0) to independent ambulation (score of 10).12 Lower score indicated patient status as worst. As seen Table 2, Wilcoxon Signed Ranks test indicated significant improvement in mobility status on day 7 in the ICU (z=-5.997,p=0.00) and SDU (z= 7.676,p=0.00) compared to day 1.

On analysing those with poor mobility score of less than 5 separately, the median on day 1 was 1 (IQR 1-3) and on day 7 was 4 (IQR 1-8) in ICU. In SDU, the median was 1 on day1 (IQR 0-3) and on day 7 was 10 (IQR 8-10) indicating improvement in mobility scores on IMS.

Tables 3 and 4 shows the descriptive statistics for mobility progression from day 1 to day 7 in ICU and SDU respectively. 60% improved from none to in bed, 54.3% improved from in bed to out of bed and walking, 55.6 % improved from out of bed. 100% improved from nothing to mobility, 94.8% improved from in bed, 100% improved from walking with assistance to independent walking.

Oxygen requirement: Table 5 describes the amount of oxygen support needed from Day 1 to Day 7 in the ICU. 23.1% on face mask and nasal prongs were weaned to room air, 32.8% on NRBM were weaned to face mask and nasal prongs, 31.3% on NIV were weaned to NRBM or face mask. There was no change in intubated patients. 30.8% on face mask/nasal prongs, 18.8% on NRBM, 6.3% on NIV had increased oxygen requirement.

Table 6 describes the amount of oxygen support needed from Day 1 to Day 7 in the SDU. 57.6% of facemask/
Physiotherapy practices in COVID ICU setting were different from non-COVID ICU. The closed confined atmosphere with limited resources and manpower was a major hinderance in therapy and patient care. Working with personal protective equipment (PPE) was a new experience. Communication with the patient was difficult through the PPE as patients could not hear or lip read or see expressions and one had to speak very loudly. Hence use of self-illustrated posters in regional language eased the task of explaining the breathing exercise and basic mobility in patients. It was not possible to do elaborate evaluations of manual muscle testing or application of scales inside the COVID ICU with the given therapist-patient ratio and safety concerns. Family involvement which is an important component of ICU bundle of care\textsuperscript{13} was missing. COVID ICU, an isolation unit with shortage of manpower due to lockdown situation and absence of family support made it difficult to achieve ideal positions, feeding, facilitating cleaning after toilet activities or diaper change, and assist in mobility. Hence in the given context physiotherapeutic interventions had to be adapted and modified as per available resources as safety of therapist was of utmost importance along with patient safety.

The physiotherapy practices were targeted toward reducing the sequelae of bedrest, prevent deep vein thrombosis, augment recruitment of alveoli, reduce early airway closure, minimize critical care illness neuropathy and myopathy and improve long term function.\textsuperscript{14}

Amidst changing dynamics of patient’s clinical status, the physiotherapist had continuous updates and communication with the clinical unit faculty members. This aided in understanding the clinical condition to facilitate decision making for effective physiotherapy strategy. Factors such as age, co-morbidities, cognition, level of sedation, overall strength, ventilatory and haemodynamic status were crucial in decision making for physiotherapy intervention. Fear in the patients was associated with desaturation, inability to breathe and death which was aggravated on isolation. Physiotherapist-patient contact time of at least 15 minutes also provided as an opportunity for counselling and patient education. Compliance to mask along

---

**Table 4**: Descriptive statistics of ICU mobility scale (IMS) from Day 1 to Day 7 in SDU (N=168)

<table>
<thead>
<tr>
<th>Day 1</th>
<th>Day 7</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>In Bed</td>
<td>Out Bed</td>
</tr>
<tr>
<td>None</td>
<td>Count</td>
<td>2</td>
</tr>
<tr>
<td>Row %</td>
<td>13.3%</td>
<td>20.0%</td>
</tr>
<tr>
<td>Column %</td>
<td>40.0%</td>
<td>42.9%</td>
</tr>
<tr>
<td>In Bed</td>
<td>Count</td>
<td>2</td>
</tr>
<tr>
<td>Row %</td>
<td>5.1%</td>
<td>5.1%</td>
</tr>
<tr>
<td>Column %</td>
<td>40.0%</td>
<td>28.6%</td>
</tr>
<tr>
<td>Out Bed</td>
<td>Count</td>
<td>0</td>
</tr>
<tr>
<td>Row %</td>
<td>0.0%</td>
<td>7.4%</td>
</tr>
<tr>
<td>Column %</td>
<td>0.0%</td>
<td>28.6%</td>
</tr>
<tr>
<td>Assisted walking</td>
<td>Count</td>
<td>0</td>
</tr>
<tr>
<td>Row %</td>
<td>0.0%</td>
<td>0.0%</td>
</tr>
<tr>
<td>Column %</td>
<td>0.0%</td>
<td>0.0%</td>
</tr>
<tr>
<td>Independent walking</td>
<td>Count</td>
<td>1</td>
</tr>
<tr>
<td>Row %</td>
<td>1.2%</td>
<td>0.0%</td>
</tr>
<tr>
<td>Column %</td>
<td>20.0%</td>
<td>0.0%</td>
</tr>
<tr>
<td>Total</td>
<td>Count</td>
<td>5</td>
</tr>
<tr>
<td>Row %</td>
<td>3.0%</td>
<td>4.2%</td>
</tr>
<tr>
<td>Column %</td>
<td>100.0%</td>
<td>100.0%</td>
</tr>
</tbody>
</table>

---

**Table 5**: Descriptive statistics of Oxygen support at Day 1 and Day 7 of physiotherapy intervention in ICU(N=110)

<table>
<thead>
<tr>
<th>D1</th>
<th>D7</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>FM+NP</td>
<td>RA</td>
<td>FM+NP</td>
</tr>
<tr>
<td>Count</td>
<td>3</td>
<td>6</td>
</tr>
<tr>
<td>Row %</td>
<td>23.1%</td>
<td>46.2%</td>
</tr>
<tr>
<td>Column %</td>
<td>50.0%</td>
<td>19.4%</td>
</tr>
<tr>
<td>NRBM</td>
<td>Count</td>
<td>2</td>
</tr>
<tr>
<td>Row %</td>
<td>3.1%</td>
<td>29.7%</td>
</tr>
<tr>
<td>Column %</td>
<td>33.3%</td>
<td>61.3%</td>
</tr>
<tr>
<td>NIV</td>
<td>Count</td>
<td>1</td>
</tr>
<tr>
<td>Row %</td>
<td>3.1%</td>
<td>18.8%</td>
</tr>
<tr>
<td>Column %</td>
<td>16.7%</td>
<td>19.4%</td>
</tr>
<tr>
<td>Intubated</td>
<td>Count</td>
<td>0</td>
</tr>
<tr>
<td>Row %</td>
<td>0.0%</td>
<td>0.0%</td>
</tr>
<tr>
<td>Column %</td>
<td>0.0%</td>
<td>0.0%</td>
</tr>
</tbody>
</table>

---

nasal prongs were weaned to room air, 76.9% on NRBM were weaned to face mask/nasal prongs, 50% on NIV were weaned to NRBM and face mask. 2.5% on room air and 1.9% on NRBM showed increased oxygen demand.

**Barriers to physiotherapy intervention**: Figure 2 describes the various limitations to physiotherapy interventions. Haemodynamic instability, desaturation, fatigue, pain, weakness and shortage of manpower were the most prominent.

**Discussion**

In spite of thorough literature search, we could not identify a similar study at the international/national published literature. This is probably the first cohort study analysing various physiotherapy interventions for COVID-19 patients in acute care set up in India. Patients admitted with Covid 19 had pulmonary impairment of varying severity with hypoxia, multi organ dysfunction including ARDS and sepsis. The study identifies the involvement of physiotherapy in treating patients admitted with COVID 19 in the ICU and SDU. It also highlights judicious use of the services and physiotherapy practices that can be implemented in the given context. SDU provided a platform for inpatient rehabilitation, discharge planning, home programme and follow up considering residual involvement of fibrosis in the lung and associated sarcopenia and muscle wasting.
with alleviating fear and emphasis to maintain therapeutic position was crucial in all these patients.

Therapeutic positions were chosen based on saturation response, heart rate, chest x-ray and palpable rales. Inability to auscultate was a limitation. Though evidence-based practice recommends prone position for patients with severe involvement and ARDS as lung protective strategy, all patients did not show prone as the best position to improve saturation. Side lying followed by prone were two most applied therapeutic positions. Preference to side lying could be because of difficulty in going prone due to presence of NIV mask, IV lines, labour intensive process and more unilateral involvement of lung. Patients in SDU were more compliant to practice awake prone as they could comprehend the change in saturation improvement. Critical patients with multiorgan failure, who were intubated and sedated, received passive movements only as mode of physiotherapy intervention. The need of postural drainage, percussion and vibration was not justified as they did not have much secretion. These patients were very critical and haemodynamically unstable for any intervention. As all manoeuvres were aerosol generating, therapists’ fear of treating intubated patients could also be a limiting factor.16

Patients on 100% oxygen and PEEP > 10 cm of H2O had increased respiratory demands; the goal was to ventilate bases in normalized pattern and increasing the efficiency of diaphragm with minimal energy expenditure. Therapeutic positioning for better ventilation and oxygenation and deep intercostal pressure were applied to facilitate the diaphragm. Respiratory physiotherapy techniques included predominantly breathing exercises. Paced breathing and breathing control could be done in patients who were stable on NIV. Patients on Non rebreathing mask (NRBM) and facemask (FM) were better able to do diaphragmatic breathing exercises and ACBT.17

Incentive spirometer was an easily available, economical instrument for single person use which assisted sustained maximal inspiration in sitting, propped up or in recommended therapeutic position in selected patients and prior to discharge. Use of incentive spirometry was expected to help in recruiting alveoli and improve basal ventilation.18 It could be given in those who tolerated removal of facemask without desaturation below 90% or shifted to oxygen support through nasal prongs (NP). Though western guidelines do not recommend use of incentive spirometry, our patient population found it very beneficial.

Individually tailored mobilization program were based on patient cooperation, cardiorespiratory response and patients capabilities.19 As seen in Figure 3, it ranged from simple in bed activities of 1-2 METs, to out of bed, standing and walking up to 3 METS with oxygen titration as needed. Activity sufficient to elicit acute physiological effects to enhance ventilation, perfusion, circulation and countermeasures for venous stasis, deep vein thrombosis, dependent atelectasis and pressure sores was included.20,21 The mobilization was discontinued if saturation dropped more than 4% from resting or maximum of 86% and or if heart rate >30 beats from resting or maximum of 145 beats per minute. Rate of perceived exertion was measured on BORGs scale.22 To ambulate patients on NIV was not feasible due to various challenges. Posterior approach was used as far as possible and therapist

<table>
<thead>
<tr>
<th>D1</th>
<th>RA</th>
<th>FM+NP</th>
<th>NRBM</th>
<th>NIV</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>RA Count</td>
<td>77</td>
<td>0</td>
<td>2</td>
<td>0</td>
<td>79</td>
</tr>
<tr>
<td>RA Row %</td>
<td>97.5%</td>
<td>0.0%</td>
<td>2.5%</td>
<td>0.0%</td>
<td>100.0%</td>
</tr>
<tr>
<td>RA Column %</td>
<td>61.6%</td>
<td>0.0%</td>
<td>15.4%</td>
<td>0.0%</td>
<td>47.0%</td>
</tr>
<tr>
<td>FM+NP Count</td>
<td>19</td>
<td>14</td>
<td>0</td>
<td>0</td>
<td>33</td>
</tr>
<tr>
<td>FM+NP Row %</td>
<td>57.6%</td>
<td>42.4%</td>
<td>0.0%</td>
<td>0.0%</td>
<td>100.0%</td>
</tr>
<tr>
<td>FM+NP Column %</td>
<td>15.2%</td>
<td>51.9%</td>
<td>0.0%</td>
<td>0.0%</td>
<td>19.6%</td>
</tr>
<tr>
<td>NRBM Count</td>
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<td>13</td>
<td>11</td>
<td>1</td>
<td>52</td>
</tr>
<tr>
<td>NRBM Row %</td>
<td>51.9%</td>
<td>25.0%</td>
<td>21.2%</td>
<td>1.9%</td>
<td>100.0%</td>
</tr>
<tr>
<td>NRBM Column %</td>
<td>21.6%</td>
<td>48.1%</td>
<td>84.6%</td>
<td>33.3%</td>
<td>31.0%</td>
</tr>
<tr>
<td>NIV Count</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>NIV Row %</td>
<td>50.0%</td>
<td>0.0%</td>
<td>0.0%</td>
<td>50.0%</td>
<td>100.0%</td>
</tr>
<tr>
<td>NIV Column %</td>
<td>1.6%</td>
<td>0.0%</td>
<td>0.0%</td>
<td>66.7%</td>
<td>2.4%</td>
</tr>
<tr>
<td>Total Count</td>
<td>125</td>
<td>27</td>
<td>13</td>
<td>3</td>
<td>168</td>
</tr>
<tr>
<td>Total Row %</td>
<td>74.4%</td>
<td>16.1%</td>
<td>7.7%</td>
<td>1.8%</td>
<td>100.0%</td>
</tr>
<tr>
<td>Total Column %</td>
<td>100.0%</td>
<td>100.0%</td>
<td>100.0%</td>
<td>100.0%</td>
<td>100.0%</td>
</tr>
</tbody>
</table>

FM: Face mask, NP: Nasal prongs, NRBM: Nonrebreathing mask, NIV: Non invasive ventilation, RA: Room Air

![Fig. 2: Factors limiting Physiotherapy Intervention](image)
warranting a post COVID pulmonary physical and psycho social limitations at a risk of reduced participation, these patients appear to be without assistance.

With support and walking with or pumps, heel slides, single leg stance quadriceps, dynamic quads, ankle breathing exercises, static glutei, static Group therapy exercises included be easily monitored for desaturation.

Sitting on bed or standing and could to form groups of 8-10 patients either therapist exposure time. It was feasible providing peer support and reduced confidence.

Implementing group exercises in stable patients in SDU helped in providing peer support and reduced therapist exposure time. It was feasible to form groups of 8-10 patients either sitting on bed or standing and could be easily monitored for desaturation. Group therapy exercises included breathing exercises, static gluetei, static quardiceps, dynamic quads, ankle pumps, heel slides, single leg stance with support and walking with or without assistance. Upper extremity exercises coordinated with breathing and with ½ litre water bottles to give adequate resistance to the muscles to restore strength were added. Distance walked was gradually increased as part of mobilization protocol.

Quick screening for home programme recommendation was carried out using simple test such as maximum capacity on incentive spirometer, 30 second sit to stand and six minute walk test within the ward once patient was weaned off oxygen or when discharge was planned.

With 6MWD of less than 200 meters these patients appear to be at a risk of reduced participation, physical and psycho social limitations warranting a post COVID pulmonary rehabilitation. A number of factors limits physiotherapy intervention. Most important were patient related factors of fatigue, weakness, pain, haemodynamic instability and desaturation.

From the above data and experience we recommend following physiotherapy interventions. We have divided patients in four clinical levels based on oxygen support requirement and stability in order to prioritize and prevent cross infections.

Level 1- Patients that are critically ill, intubated, paralyzed and on high oxygen requirement with high probability of mortality

As the risk of aerosol generation is very high and accrued benefits minimal; physiotherapy implementation is limited to passive movements only. All chest physiotherapy manoeuvres such as postural drainage, percussion, vibration, suctioning including mobilization are aerosol generating and are to be used only where indicated as thick excessive secretions, not as routine. Hence it is important to weigh the benefits and use physiotherapy practices judiciously.

Level 2 - Patients on NIV varying form 100% oxygen requirement to 50% with PEEP 6-10. Physiotherapy practices implemented ranges from therapeutic positioning, breathing exercises, paced breathing and early mobilization.

Level 3 - Patients with reducing oxygen requirement on NRBM with increased degree of active participation.

Diaphragmatic recruitment along with paced breathing, ACBT, out of bed mobilization and standing and assisted walking can be initiated. Need for titration of oxygen to prevent desaturation should be looked into.

Level 4 - Patients on face mask or oxygen weaning trials

Patients with increasing mobility should be encouraged for group exercise participation and self - sustained maximal inspiration, positioning and self-monitoring. A pre discharge plan, quick assessment, home programme and need of pulmonary rehabilitation should be looked into at this level.

Physiotherapy as a non-pharmacological intervention was beneficial to the patients holistically as it helped in improving oxygen transport and preventing complications. It facilitated improved outcomes as seen in reducing need of oxygen support (Tables 5, 6) and progressive improvement in the patient mobility (Tables 3, 4).

Conclusion

COVID 19 proved to be a turning point in the history of physiotherapy with varied challenges. It appears promising in facilitating reduced oxygen requirement, early patient ambulation and discharge. Optimal use of resources, knowledge, and motivation lead to positive practices. Physiotherapy intervention was limited in critical patients who are intubated and sedated. Most common form of intervention were therapeutic positioning, early mobilization and breathing exercises. None of the staff or resident physiotherapy students treating patients of COVID 19 in the ICU or ward were infected over the three - month course since commencement of COVID services. This study shows it is safe and feasible to provide early physiotherapy treatment techniques in patients with COVID-19 using appropriate measures of infection prevention and cross contamination. The study is limited by its descriptive nature and data of only one month as the goal was to highlight the feasibility of physiotherapy intervention in improving outcome. Covid 19 patient care has proved a multidisciplinary approach with cooperation and collaboration from physicians and physiotherapist.

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Validation of Baveno VI Criteria for Screening of Esophageal Varices in a Cohort of South Asian Patients with Compensated Chronic Liver Disease

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Abstract

Objectives: A patient with liver stiffness by Vibration controlled Transient elastography (TE) <20 kPa and a platelet count >150,000/mm3 does not require screening endoscopy according to Baveno VI consensus. The Baveno consensus statement on esophageal varices screening has not been validated in the South Asian population. TE may not be widely available in resource limited areas. We tried to see whether easily available parameters could be used to predict high risk varices (HRV).

Method: A cross-sectional study evaluating patients with liver stiffness >10 kPa who had endoscopy within 6 months of TE evaluation.

Results: 375 patients who underwent TE and upper GI endoscopy over one year were included. Commonest etiology was...
HBV(42 %) followed by Hepatitis C(39%), NAFLD(9.1%) and alcohol(9%). 262 of the 266 patients satisfying Baveno VI consensus criteria for avoiding screening endoscopy did not have HRV. Sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) was 96 %, 90 %, 74% and 99 % respectively and (AUC = 0.91). By using MELD 6 or MELD < 8 and platelet >150000/mm3 criteria, 67% endoscopies could have been circumvented. Using Baveno VI criteria, 70% endoscopies could have been circumvented.

**Conclusion:** This study validates the Baveno VI consensus statement on esophageal variceal screening in cirrhosis, in a South Asian population. It also describes a new strategy using MELD 6 or MELD < 8 and platelet > 150000/mm3 in areas with limited resources where TE is not widely available.

**Background**

According to Baveno VI consensus in Patients with liver stiffness by TE < 20 kPa and platelet count >150,000/mm3 does not require screening endoscopy and can be followed up annually with platelet count and TE scan. If there is worsening in the TE score or Platelet count then should undergo UGI endoscopy. TE is costly and many patients cannot afford it in developing countries. It is also not widely available. It has not been validated in the South Asian population. The validity of the same among etiology other than viral hepatitis also is not widely tested. The aim of our study was to validate Baveno VI consensus statement regarding screening of esophageal varices in a cohort of South Asian patients and to look for alternate parameters without TE in ruling out high risk varices (HRV). We also attempted to validate Baveno consensus statement regarding esophageal varices screening among various etiologies of Cirrhosis, other than viral hepatitis.

**Gastroesophageal varices** occur as a consequence of portal hypertension. Variceal hemorrhage is a major complication of cirrhosis and it is associated with significant morbidity and mortality. First variceal hemorrhage can be prevented through the use of non-selective beta-blockers or endoscopic variceal ligation.\(^1\) However, not all patients with varices are candidates for the prevention of first variceal hemorrhage. Guidelines recommend prophylactic therapy in patients with high-risk varices (HRV), that is, those that are more likely to bleed, in other words patients with medium/large varices or patients with small varices with red wale marks on their surface or small varices occurring in Child C patients.\(^2\)

To determine the presence and size of varices as well as to look for red wale signs, Patients have to undergo screening Upper Gastrointestinal endoscopy (UGI endoscopy) which is an invasive and expensive procedure. Though rare, It is not completely free of risks. At present, most of the patients who are diagnosed to have cirrhosis in compensate state, undergo UGI endoscopy for detection of varices. Many of these patients do not have varices or they have small varices which do not need treatment. There is increased burden on the healthcare system as well as on the patient. Therefore, there is need for noninvasive markers to screen the patients to identify who requires an endoscopy.

Recently, transient electrography (TE) has become a widely used, noninvasive measure of liver stiffness and fibrosis. Studies have shown that TE is of potential benefit in the noninvasive diagnosis of varices, especially when it is combined with other markers such as platelet count.

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**Fig. 1: Study design**
and spleen size.\textsuperscript{3-5} The promising sensitivity and negative predictive value of TE, especially in combination with other non-invasive markers, means these investigations may be more effective tools at identifying low risk cirrhotic patients who can be safely ‘ruled out’ of needing an endoscopy.

Many studies have looked for non-invasive ways of determining the presence of HRV, so as to circumvent the need for screening endoscopy in some patients. Although a number of laboratory/imaging-derived markers have been proposed, the most significant being the platelet/spleen size ratio, these studies have combined patients with both compensated and decompensated cirrhosis.\textsuperscript{5} Finding non-invasive predictors of the presence of HRV is more relevant in patients that do not include TE would be desirable. Validation studies of Baveno VI in Asian population are very few. There is no study validating it in the South Asian population. There are only a few studies validating the Baveno VI consensus statement among various etiologies of cirrhosis. Ours is a novel attempt to validate the statement in a cohort of South Asian population and to validate the statement among various etiologies of cirrhosis.

### Aims and Objectives

Our study had two aims:

(i) The primary aim was to validate the Baveno VI Consensus statement regarding esophageal variceal screening in a cohort of Indians with cACLD

(ii) To determine whether alternate parameters (not including TE) would be equally or more predictive than the Baveno statement in ruling out HRV.

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**Materials and Methods**

This is a cross-sectional study. It included patients with chronic liver disease that attended the OP at the Department of Medical Gastroenterology, Government medical college, Trivandrum between September 2016 and August 2017 in whom TE was performed. This study was approved by the institutional ethics committee.

Patients were included in the study if they had a LSM (Liver Stiffness Measurement) ≥10 kPa and had laboratory tests and upper endoscopy performed within 6 months of TE. Exclusion criteria were decompensated cirrhosis (defined as the history or presence of overt ascites, overt encephalopathy or variceal haemorrhage and jaundice); portal or splenic vein thrombosis, history of splenectomy or liver transplantation. The the cutoff of 10 Kpa was kept because, according to Baveno VI. The probability of having cACLD is very low if LSM is <10 Kpa. Also, it mentions that patients with LSM in between 10 to 15 are likely to have cACLD. TE was performed using Fibroscan© (Echosens, Paris) after at least 4 hours of fasting by experienced practitioners (WHO had done more than 500 fibroscan). Mean value of two fibroscan reading in fasting in two different days were taken. LMSMs were performed in the right lobe of liver and 10 successful measurements were obtained in each patient and the mean value was taken.
Patients also underwent OGD scopy and grading of varices was done by standard criteria. All oesophageal varices described as grade 3 oesophageal varices, grade 2 varices with red wale markings, or gastric varices, were defined as HRV. Data pertaining to etiology, LFT, RFT, CBC, INR was noted for all patients.

Our first aim was to validate the Baveno definition (LSM <20 kPa and platelet count >150000/mm³) that is, its ability in ruling out the presence of HRV and to determine the number of endoscopies that would have been safely avoided by using this definition.

As our second objective, we first compared routine laboratory values between patients with and without HRV. Potential number of endoscopies which could have been avoided by both methods was calculated. Statistical analysis was performed using SPSS package v.22 (SPSS Inc., Chicago, IL, USA). Sensitivity, specificity, positive predictive value and negative predictive value was calculated. Comparisons between groups were performed using Mann-Whitney U test for non-parametric tests and Fisher’s exact test for proportions. AUROC was constructed for validation study.

**Results**

Among all patients who underwent Transient elastography at our centre between September 2016 and August 2017, 382 patients had LSM values > 10 Kpa. Of these, 7 patients were excluded because endoscopy report was not available (Figure 1). Demographic and clinical characteristics of these patients are shown in Table 1. 238 (63%) patients were male and 137 (37%) female. Main etiology of compensated cirrhosis was Hepatitis B (42%) followed by Hepatitis C (39%), NAFLD (9.1%) and alcohol (9%) in our study. In hepatitis B and C, TE was done before starting antivirals. Endoscopically, 246 (65.6%) patients had no gastroesophageal varices, 45 (12%) had small varices and 84 (22%) had medium/large varices (HRV). As shown in Table 1, 266 patients fulfilled Baveno criteria to rule out HRV i.e. they had LSM<20 Kpa and platelet count >150000/mm³. Among those, 262 did not have HRV while 4 patients had HRV. 109 patients were out of Baveno criteria and among those, 80 patients had HRV. The sensitivity, specificity, Positive predictive value (PPV) and negative predictive value (NPV) was 96%, 90%, 74% and 99% respectively. AUROC for compensated cirrhosis was 0.91(Figure 2).

**Study Design**

The second objective of our study was to determine whether alternate parameters (not including TE) would be equal to or more predictive than Baveno criteria in ruling out HRV.

For that, we first compared clinical and laboratory parameters between those patients who had HRV and those patients who did not have HRV. As shown in Table 1, bilirubin, INR, platelet count, LSM and MELD score were the parameters which significantly differed between patients with and without HRV. An alternative strategy excluding TE and including platelet count and MELD was also used. For the cutoff of platelet count, we decided to keep the one established by Baveno criteria (>150 000) because this cutoff has been established not only by Baveno but also by other studies. In our study, No patient with MELD of 6 showed HRV irrespective of platelet count. So, the sensitivity and NPV for MELD=6 is 100%. No patient with MELD=7 and platelet count > 150000/mm³ had HRV (sensitivity and NPV= 100%) while 1 patient out of 233 patients with platelet > 150000/mm³ had HRV whose MELD was 8. By using MELD=6 or MELD < 8 and platelet >150000/mm³ criteria. Among all the patients, 251(67%) screening endoscopies could have been circumvented, while using Baveno criteria 262 (70%) endoscopies could have been circumvented which is comparable.

**Discussion**

Identifying patients with a low probability of having high-risk gastroesophageal varices (i.e. those requiring prophylactic therapy) is important to be able to circumvent the performance of unnecessary screening endoscopies which can save time and cost and possible risks associated with the procedure. This is particularly relevant for patients with cACLD who have a low probability of having high-risk varices (HRV). For this, Baveno VI consensus defined patients having a low probability of having HRV as those with cACLD, a LSM <20 kPa and a platelet count >150 000/mm³.

We validated these criteria in our population with cACLD (defined as a liver stiffness ≥10 kPa and no decompensating events). Among our results, only 4 patients out of 266 who satisfied Baveno criteria had HRV needing treatment. (Sensitivity= 96%, NPV= 99%). Percentage of endoscopies that could have been circumvented by Baveno criteria were 70%, but it incorrectly classified 2% of patients. Thus, adherence to these criteria may delay clinically effective prophylaxis against variceal bleeding with non-selective beta-blockers in this small proportion of patients. Also, application of the guidelines would have excluded these patients from endoscopic surveillance. However, it is possible that these patients might be having other causes which can falsely elevate platelet count to high normal in the setting of cACLD like blood dyscrasias. Therefore, careful consideration must be given to comorbidities which may impact the validity of the proposed platelet cut-off. Reassuringly, only 4/266 (0.15 %) cases meeting BAVENO criteria had HRV, therefore the annual risk to a patient counselled in clinic based on a bleeding rate from varices of 15% per year would be just 0.3% (AASLD guidelines 2016). The guidelines however advise annual assessment of TE and TE count, followed by endoscopic surveillance of patients who move out of the low risk category. Like majority of the published studies which evaluated Baveno criteria to rule out HRV, our study also had patients mainly of viral etiology. But in contrast to the previous studies which had Hep C as most common etiology, the maximum number of patients with cACLD in our study were hepatitis B (42%) rather than Hep C (39%). Etiologically, applying Baveno criteria in Hep B patients had a sensitivity of 93% and NPV of 98% to rule out HRV. In patients with Hep C as etiology, Baveno criteria could rule out HRV with a sensitivity of 95% and...
NPV of 98%. Interestingly, in our study, patients with alcohol and NAFLD etiology had a sensitivity of 100% and NPV of 100%.

Our study suggests there is a role for non-invasive markers in identifying patients at low risk of having clinically significant varices who can safely avoid screening endoscopy. Our reported NPV of 0.98 is similar to the NPV of troponin, which is widely implemented to exclude the diagnosis of myocardial infarction.11 This presents an opportunity to reduce the burden of unnecessary endoscopies for patients who often face many invasive investigations through the course of their disease, but the poor PPV show these non-invasive tests cannot replace endoscopy in the diagnosis of varices and deciding which patients warrant treatment with primary prophylaxis. One of the factors to be considered here is that the cutoff limit of 20 Kpa is uniform for all etiologies by Baveno guidelines. But most of the data for TE comes from viral etiologies. Reassuringly in our small sub group of ALD and NAFLD cases no HRV were missed by the Baveno VI criteria. This finding also matches the findings suggested by Maurice et al.9 However, further research is needed to validate these non-invasive markers in other etiologies, particularly NAFLD and ALD.

The rationale for the Baveno VI guidelines comes from evidence in a number of studies demonstrating that non-invasive investigations such as TE and platelet count show promise in the diagnosis of varices, but generally perform better at excluding rather than diagnosing high risk varices. Similarly Stefanescu et al showed that TE combined with additional serological and radiological markers produced a NPV 1.0 and LR- 0.1 for high risk oesophageal varices.12 More recently Perezro et al focussed on TE and platelet count as in the Baveno VI guidelines in a prospective assessment 99 HCV cirrhotic patients (80% Child Pugh A, 63% female): 14% had HRV, all of which were appropriately classified by the Baveno VI criteria. Spleen stiffness did not improve the performance of TE and platelet count to identify low risk patients.13

Study by Maurice et al,9 which included 310 patients, The sensitivity and Negative predictive value of Baveno criteria to rule out HRV was 0.87 and 0.98 respectively which is comparable to our study.

TE is not widely available in India. Moreover wherever it is available, it is too expensive to be routinely prescribed for all patients. Therefore, we tried to develop strategy excluding TE and including platelet count and MELD which is simple, widely available and inexpensive. Our study shows that no patient with MELD of 6 showed HRV irrespective of platelet count. (sensitivity and NPV= 100%). No patient with MELD = 7 and platelet count > 15000/mm3 had HRV (sensitivity and NPV= 100%). Therefore, this criteria also can be used to determine patients who can safely avoid screening endoscopy. The number of endoscopies that could have been circumvented by this criteria using MELD=6 or MELD < 8 and platelet > 15000/mm3 was 67% which is comparable to the number of endoscopies that could have been circumvented using Baveno criteria (70%). Although MELD score has been explored as a predictor of varices, these studies have included a significant proportion of patients with decompensated cirrhosis. There are paucity of studies which show the value of MELD in predicting HRV in patients with compensated cirrhosis. We found that none of patients with HRV had a MELD score of 6. This finding matches those findings put forth by Jangouk et al.10

This study has some limitations. The retrospective design brings inherent limitations of bias. Moreover, using the presence of varices as an endpoint is limited by variable and subjective reporting of their size. However, in clinical practice, initiation of primary prophylaxis is based on the endoscopic evidence of high risk varices given the impractical nature of routinely measuring HVPG. Therefore, identifying non-invasive techniques to identify patients without varices is relevant. Moreover, other causes of chronic liver disease such as non-alcoholic liver disease are often poorly represented in this field of research, and the LSM criteria for cirrhosis in non-viral aetiologies is less well defined.

Conclusions

This study validates Baveno VI consensus statement for endoscopic screening of esophageal varices in a cohort of Indian population. The risk of misclassifying small proportion of patients can be minimized by careful assessment for co morbidities that may affect platelet count, and long-term follow-up with annual TE and platelet count to initiate timely endoscopic surveillance in suitable patients. The Baveno VI criteria holds good in ruling out HRV in NAFLD and ALD patients also. It also describes a new strategy with MELD 6 or MELD < 8 and platelet > 15000/mm3 which can be used when TE is not available to screen patient who can safely avoid endoscopy in resource constrained settings. Confirmation by prospective, longitudinal data collection will give further support to these recommendation.

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Assessment of Insulin Resistance Indices in Individuals with Lean and Obese Metabolic Syndrome Compared to Normal Individuals: A Population Based Study

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Abstract
Introduction: Obesity is associated with insulin resistance and measuring it in an apparently healthy population and correlating them with established risk parameters may identify predisposed individuals who may later develop diabetes or cardiovascular diseases.

Material and Methods: 405 participants from a rural area were investigated for various metabolic parameters and indices of insulin resistance. Insulin resistance indices were evaluated in the 3 different groups [Obese Metabolic Syndrome (MetS), Lean MetS and those without MetS]. Various anthropometric and metabolic parameters were compared. Lean MetS is defined as those having waist criteria below the region specific waist criteria and even then satisfying the definition of MetS as per the NCEP ATP-III criteria.

Results: The mean fasting insulin level was 7.69±4.38 uIU/ml in normal population, 10.40±5.65 uIU/ml in Lean MetS population and 13.71±6.63 uIU/ml in Obese MetS population (P<0.05). The HOMA-IR2 measured was 2.39±1.69 in normal population, while in the Lean MetS and Obese MetS were 3.99±3.40 and 4.04±2.53, respectively (P<0.05). The QUICKI level measured was 0.358±0.041 in normal population and 0.334±0.037 and 0.316±0.026 respectively in the Lean MetS and Obese MetS (P<0.05). McAuley index measured in normal population was 0.49±0.26 and 0.75±0.25 and 0.79±0.17 in the Lean MetS and Obese MetS population (P<0.05).TyG index measured was 8.51±0.46 in normal population and 9.27±0.56 and 9.06±0.49 respectively in the Lean MetS and Obese MetS (P<0.05).

Conclusion: Insulin resistance indices are elevated in MetS compared to the normal population but the indices in Lean MetS are not different from Obese MetS. The relevance of ethnicity specific waist circumference may need re-evaluation considering its little impact in influencing the level of insulin resistance.

Introduction

A significant proportion of an apparently healthy population is insulin resistant to an extent to develop a cluster of metabolic abnormalities leading to the development of metabolic syndrome (MetS), cardiovascular disease and diabetes later on in life. Therefore, it seems useful to obtain estimates of degree of insulin resistance in apparently healthy persons to assess their propensity to develop related diseases. However, specific quantification of insulin resistance, as assessed by measuring insulin mediated glucose disposal, is impractical in logistical sense at either a population or individual subject level. Plasma insulin concentrations in nondiabetic persons are significantly correlated with direct measures of insulin resistance, and measurements of plasma insulin concentration have been used to generate a number of indices to serve as surrogate estimates of insulin resistance. These various indices are similar in that they all contain a measure of plasma insulin concentration, but differ substantially in a number of ways; e.g. fasting versus post-glucose challenge insulin measurements, if post-glucose, what time-point(s) used, incorporation of additional measurements in the index, the nature of the relationship: insulin/glucose versus insulin x glucose, etc. These surrogate estimates are used frequently in large epidemiological studies aimed at evaluating links between insulin resistance and disease, effect of intervention on insulin resistance etc. At a clinical level, it would seem useful to identify those apparently healthy individuals whose degree of insulin resistance puts them at increased risk in order to initiate clinically appropriate interventions aimed at decreasing their likelihood of developing manifest disease.

We had undertaken a population-based study to assess the level of insulin resistance by these surrogate measures and correlate them with the presence of MetS, especially Lean MetS.

Fasting insulin was found to have a good accuracy in predicting the presence of insulin resistance in normoglycemic individuals. Therefore, many indices used to measure insulin sensitivity especially in normoglycemic individuals utilizes and includes fasting glucose as a part of the index, namely HOMA-IR, QUICKI, etc. In addition the variables (other than fasting glucose...
insulin) that best predicted insulin sensitivity were fasting triglycerides, aspartate transaminase (AST), waist circumference, and BMI.

The inclusion of triglyceride to a fasting insulin level to calculate a log transformed value increases the sensitivity significantly and maintains good specificity. This McAuley index, which has been compared with various other insulin resistance indices and has been found to identify insulin resistant individuals with a similar diagnostic accuracy as post-oral glucose challenge measures. The McAuley Index has been used in various population surveys, has proven itself to be a robust method especially suited for a population based epidemiological study.

In some recent studies a log transformed fasting glucose and triglyceride product index has attained the status of a simple surrogate measure for assessing insulin resistance with high sensitivity especially in asymptomatic normal individuals in population-based studies. This triglyceride and glucose (TyG) index has shown improved efficiency compared to other markers and has been demonstrated to predict development of diabetes, hypertension, cardiovascular disease, chronic kidney disease and cancer associated with insulin resistance.

We therefore estimated the insulin resistance by four different methods, namely, HOMA-IR, QUICKI, McAuley index and TyG index in all the three groups.

Material and Methods

A population-based observational study was undertaken to compare the parameters of metabolic health (anthropologic and biochemical) between tribal and non-tribal population in a rural area in the District of Birbhum, West Bengal, India in collaboration with Palli Sangathan Bibhagh (PSV), Sriniketan, Visva Bharati. The results presented herein are part of the data collected in the aforementioned study. Clearance from the Institutional Ethics Committee was obtained and the study was conducted in accordance with the guidelines of the Helsinki Declaration. We selected areas with high concentration of tribal population and continued consecutive sampling till 205 samples were collected from the tribal population though 200 samples were targeted initially. A sample of 200 consecutive populations from the same or neighborhood areas not belonging to the tribal population was also selected. Thus, 405 individuals including both the tribal and non-tribal population were included in the study to make it an appropriate representation of rural population of West Bengal. The sample size was chosen on the basis of available resources. A health camp was organised with prior information to all eligible healthy participants of the area within the age group of 18 to 60 years. The participants were explained about the study in the rural health camp. Individuals were included in the study only if they agreed to give informed written consent and did not have any evident or definite or documented chronic infective or inflammatory disorder. History of addiction, including tobacco and alcohol, was documented. Anthropometric data including height, weight, waist circumference and hip circumference were measured by trained personnel obeying the standard procedure of measurement as described below. Blood pressure was measured using standard methods in right arm sitting posture by an aneroid manometer. Height was measured (± 0.1 cm) in all included patients at baseline using a wall-mounted stadiometer. Body weight was measured (± 0.1 kg) with the individuals wearing light indoor clothing and without shoes, using an electronic calibrated scale. BMI was calculated as weight in kilograms divided by the square of height in meters (kg/m²). Waist circumference was measured at the end of a gentle expiration midway between the lower rib margin and iliac crest, with the patient standing with feet 23–30 cm apart. Hip circumference was measured at the level of maximum extension of the buttocks, at the same level all around the body with feet together. Waist to hip ratio (WHR) was calculated as a measure of the truncal obesity. Blood samples were collected for biochemical tests in overnight fasting state in camps to which participants came in the early morning hours. Part of the sample were allowed to clot and serum was separated by centrifuging on site and samples were immediately sent for biochemical examination at a NABL accredited laboratory (appropriately transported on dry ice) for measurement of fasting serum insulin, creatinine, lipid profile, uric acid, alanine transaminase (ALT), aspartate transaminase (AST), alkaline phosphatase, calcium, phosphate, iPTH and 25-hydroxy vitamin D3. Rest of the blood sample collected were anticoagulated with EDTA for fasting blood sugar (FBS), glycated hemoglobin (HbA1c). The samples were analyzed using standard laboratory procedure. Diabetes was defined as per the standard diagnostic criteria satisfying either FBS or HbA1c. The presence of MetS was ascertained using the consensus criteria by IDF along with AHA and NHLBI. Lean metabolic syndrome (Lean MetS) was defined as those having waist criteria below the region specific waist criteria (80 cm for females and 90 cm for males) and even then satisfying the definition of MetS as per the NCEP ATP-III criteria (at least 3 criteria). Obese MetS was similarly defined as those having satisfied the MetS criteria and also having the region specific waist criteria as defined in the IDF criteria.

The following insulin resistance indices namely HOMA, QUICKI, McAuley index and TyG index have been calculated using the formulae as noted below.

\[
\text{HOMA} = \frac{\text{insulin (mIU/L) \times [glucose (mmol/L)/22.5]}}{\text{calculated with the help of the software available from website https://www.dtu.ox.ac.uk/homacalculator/download.php (accessed on 08 August 2019)}}
\]

\[
\text{McAuley Index} = \frac{1}{\text{log insulin (mIU/L) + log glucose (mg/dL)}}
\]

\[
\text{McAuley Index} = \text{exp} \left[ 2.63 - 0.28 \ln (\text{insulin in mIU/L}) - 0.31 \ln (\text{triglycerides in mmol/L}) \right] (\text{the normal range is >5.80})
\]

\[
\text{TyG Index} = \ln (\text{fasting triglycerides (mg/dL)} \times \text{fasting plasma glucose (mg/dL)/2}) (\text{the normal range is <8.80})
\]

All analyses were conducted using SPSS (2012, version 21.0.0.0). Continuous data are presented as the mean ± standard deviation (SD, if normally distributed) or median (interquartile range, if skewed), and categorical variables are presented as proportions. Correlations were calculated by Pearson’s Correlation test for normally distributed data and by Spearman’s Correlation test for data
that were not normally distributed.

Comparison between multiple means was done by one-way ANOVA. Post-hoc analysis was done by LSD method.

**Results**

Four hundred and five individuals were included in the study, of whom 205 persons (50.62%) were from tribal population in distant rural areas and 200 persons (49.38%) were from rural/semiurban areas; of these 405 persons, 200 persons (49.38%) were from the tribal population studied.

Comparison was done by one way ANOVA; Note: Post-hoc analysis by LSD test showed that the McAuley Index was significantly different between Lean MetS and Obese MetS.

Comparison between multiple groups including between the Obese MetS and Lean MetS was not statistically significant (p=0.770). However, the fasting insulin level was significantly different between groups of Obese MetS and Lean MetS (p<0.05); Lean MetS was defined as those not clearly having the waist circumference the region specific waist criteria (80 cm for females and 90 cm for males) and even then satisfying the definition of MetS as per the NCEP-ATP-III criteria (at least 3 other component criteria).

The triglyceride level is most elevated in the 3 groups. It is notable that the triglyceride level is different between all the 3 groups and there is significantly elevated triglyceride level in Lean MetS compared to Obese MetS.

Comparison was done by one way ANOVA; Note: Post-hoc analysis by LSD test showed that the McAuley Index was significantly different between Lean MetS and Obese MetS.

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The triglyceride level is most elevated in the 3 groups. It is notable that the triglyceride level is different between all the 3 groups and there is significantly elevated triglyceride level in Lean MetS compared to Obese MetS.
MetS compared to Lean MetS, the trend is not seen with the other indices. In fact, all the indices of insulin resistance except the fasting insulin shows the trend of being statistically significantly different amongst groups, but are not significantly different between Obese MetS and Lean MetS.

**Discussion**

It is commonly stated that urbanization is one of the most important drivers of the worldwide rise in BMI because diet and lifestyle in cities lead to. However, results from recent surveys show that, contrary to the prevailing view, BMI is rising at the same rate or faster in rural areas compared to cities, particularly in low- and middle-income countries. These trends have resulted in a rural–urban convergence in BMI in most low- and middle-income countries.12

The generalized adiposity (as measured by BMI) and abdominal adiposity (as measured by waist circumference) are intimately associated with the development of MetS, which in turn is a harbinger of future development of diabetes and cardiovascular disease. The decreased insulin sensitivity associated with it is believed to be the driver of the diabetes and cardiovascular disease, and therefore should be subjected to measurement in apparently normal individuals to target them for future interventions for prevention of the diseases.

Insulin sensitivity and secretion can be measured best by the hyperinsulinemic-euglycemic clamp (HEC) and the insulin response to an intravenous glucose infusion. In nondiabetic subjects, these measures strongly predict the subsequent incidence of diabetes13,14 and are often considered the “gold standards” for assessment of insulin sensitivity and secretion. However, as these measures are labor intensive, they are difficult to obtain in the large numbers of persons typically required for epidemiologic investigations.

HEC is considered the ‘gold standard’ measure of peripheral insulin sensitivity, although it does not simulate the physiological state of continuously changing glucose and insulin levels or hepatic insulin extraction, nor the feedback mechanism between glucose and insulin.15 However, this specific quantification of insulin resistance, as assessed by measuring insulin mediated glucose disposal, is impractical at either a population or individual subject level and therefore had given rise to various surrogate measures and indices to estimate the prevalence of insulin resistance for use in population based studies. Plasma insulin concentrations in nondiabetic persons are significantly correlated with direct measures of insulin resistance,16,17 and measurements of plasma insulin concentration have been used to generate a number of indices to serve as surrogate estimates of insulin resistance.18-21

These various indices are similar in that they all contain a measure of plasma insulin concentration, but differ substantially in a number of ways; e.g., fasting versus post-glucose challenge insulin measurements, if post-glucose, what time-point(s) used, incorporation of additional measurements in the index, the nature of the relationship: insulin/glucose versus insulin x glucose, etc.

A meta-analysis comparing the various methods to measure insulin resistance in a fasting blood sample in an epidemiologic study has shown that QUICKI or modified QUICKI, which includes estimated free fatty acid at fasting state improves the correlation of insulin resistance measured by fasting insulin and glucose and their ratio. Moreover, estimating fasting triglycerides and including it in an equation (McAuley index) also improves the correlation with the insulin resistance.22,23

These surrogate measures of insulin resistance versus the gold standard HEC have been subjected to another meta-analysis.24 The results of the meta-analysis suggests that of the fasting surrogate measures, the pooled correlation coefficients of the QUICKI, revised QUICKI, HOMA-IR, computer generated HOMA of insulin sensitivity (HOMA-%S) and fasting insulin exhibited the strongest correlations with the HEC with a narrow 95% CIs.

In a cross-sectional study on Korean adults, McAuley index has been found to have the best predictive ability to assess insulin resistance in MetS.25

However, the surrogate measures have shown heterogeneous results depending on the population studied. Studies done in the Indian population showed a significantly improved correlation with the McAuley index compared to the other measures e.g. Fasting insulin, HOMA-IR or QUICKI.26 We therefore have included McAuley index as the important index for measuring insulin resistance in our study in addition to the other established ones e.g. HOMA-IR and QUICKI.

The logarithmic product of fasting levels of triglyceride and glucose (denoted TyG index) has been suggested to be a simple measure of insulin resistance.27 Both lipotoxicity and glucotoxicity play crucial roles in insulin resistance modulation, which are reflected in the TyG index.28 The TyG index is highly correlated with the HEC, the gold standard for determining insulin resistance (Pearson correlation coefficient = 0.68 between TyG index and HEC).29 Thus, due to its easy availability and costeffectiveness, the TyG index has been found to be a promising surrogate measure for insulin resistance in large-scale epidemiological studies and have been adopted in our study.

Flaws in the study: Fasting glucose shows only a very limited variation in a healthy population and is regulated by several factors besides insulin sensitivity, such as islet function and hepatic glucose release. It is therefore a poor index to distinguish between various degrees of insulin sensitivity among healthy subjects.24 It should be emphasized that fasting indices mainly measure hepatic insulin sensitivity and the HEC mainly measures muscle insulin sensitivity, while OGTT-based indices measure both types of insulin sensitivity.30,31 While cross-reactivity to proinsulin is an important source of error in a radioimmunoassay, it is as low as 5.3% in the newer, specific insulin assays.32 Moreover, insulin assays seem to exhibit most variability at low insulin levels, which could cause lower correlation coefficients in healthy individuals vs. type 2 diabetic patients.33

**Conclusion**

This study done in rural middle aged population showed presence of significant degree of insulin resistance as was measured by the indices which are the established surrogate measures
insulin resistance in asymptomatic normal individuals, especially the ones with features of MetS as is defined by NCEP and IDF. And subjects who do not satisfy the criteria of MetS by waist criteria of IDF (i.e. Lean MetS) also do have significant level of insulin resistance despite falling short of the MetS criteria by IDF methodology. Therefore we believe, the ethnicity specific waist criteria as was proposed by IDF needs to be re-evaluated and revised based on the level of measured parameter of insulin resistance in the population.

Acknowledgement

We gratefully acknowledge the fund received from The Department of Science and Technology, Govt. of West Bengal, India for this study.

References

Admission Serum Chloride Levels as Predictor of Stay Duration in Acute Decompensated Heart Failure

Abhishek Goyal1, Simran Kaur2, Bhupinder Singh1, Rohit Tandon3, Shibba Takkar Chhabra4, Naved Aslam4, Bishav Mohan4, Gurpreet Singh Wander5

Abstract

Objective: Recent studies have shown that lower serum chloride is associated with diuretic resistance and increased mortality in heart failure. Impact of lower admission chloride on duration of stay in acute decompensated heart failure (ADHF) has not been studied previously.

Methods: In this retrospective analysis, we studied the effect of admission serum chloride on the duration of hospital stay in patients admitted with ADHF. A total of 167 patients were studied. Serum chloride levels were divided into tertiles -<96 meq/L (tertile 1), 96–101 meq/L (tertile 2), and >101 meq/L (tertile 3) based on the distribution of serum chloride levels in our patients.

Results: The median lengths of hospital stay in tertiles 1, 2, and 3 were 8 (Interquartile range : 6 -11), 7 (Interquartile range : 5 -10.50), and 6 days (Interquartile range : 4.25 - 8), respectively (p = 0.011). Admission serum chloride levels were inversely associated with duration of stay (R² linear = 0.074, p = 0.001). On multiple linear regression analysis, serum chloride remained independent predictor of increased hospital stay (p=0.003) while association with serum sodium was not significant (p=0.07). 1 unit increase in chloride level was associated with 1.3% (p=0.003) decrease in hospital stay (95% CI: 2.2% to 0.5%).

Conclusion: This retrospective analysis suggests that admission serum chloride levels are independently and inversely associated with increased duration of stay. This is independent of admission sodium levels. Thus serum chloride, rather than sodium, is an important poor prognostic marker in heart failure patients.

Introduction

Heart failure (HF) is associated with multiple serum electrolyte abnormalities, including hyponatraemia, hypokalaemia, and hypochloraemia besides acid–base disturbances, the causes of which are multifactorial. Maladaptive activation of neurohormonal mechanisms, such as an increase in arginine vasopressin, results in free water absorption and thirst activation, causing dilutional hyponatraemia and hypochloraemia. The use of loop and thiazide diuretics also results in disproportionately higher solute loss than free water loss.

Most of the literature in HF till recently has primarily focused on hyponatraemia as the major predictor of short and long-term morbidity and mortality. Historically, sodium alone has been considered as the major contributor to volume hemostasis, and limited research attention has been given to chloride, a major extracellular anion that is abundantly present in intravascular and interstitial compartments and that counterbalances the positive charges of sodium. The role of chloride in volume hemostasis was appreciated when the concept of volume depletion and chloride responsive metabolic alkalosis became clear. Recent studies have shown that serum chloride levels provide stronger prognostic information for HF than serum sodium levels, and that patients with hypochloraemia have relatively high short and long-term mortality.

The initial treatment for acute HF is largely based on systemic decongestion with diuretics. Low serum chloride levels can cause decreased diuretic responsiveness owing to the upregulation of sodium and water absorption in the loop of Henle. Reduced intracellular chloride levels increase the number of sodium–potassium–chloride cotransporters (NKCC2) at the apical surface of the thick ascending limb (TAL) of the loop of Henle in the nephron. Low serum chloride levels also result in increased renin activity. The aforementioned diuretic resistance may affect the duration of hospitalisation because the initial recovery of HF patients is dependent on effective diuresis. The present study assessed the effect of admission serum chloride levels on the duration of hospital stay in HF patients and their correlation with serum sodium levels.

Methods

This retrospective study was conducted from 2005 to 2014 at a tertiary care hospital in North India. All patients older than 18 years and with a documented discharge diagnosis of acute decompensated HF (ADHF) due to dilated cardiomyopathy/ischaemic cardiomyopathy were included. Patients were excluded if they received chronic dialysis therapy, did not receive intravenous loop diuretics during their hospital stay, had sepsis, and exhibited any evidence of acute coronary syndrome or myocarditis (based on history, elevated troponin levels, and/or dynamic ECG changes).
Furthermore, patients with incomplete hospital records, pregnancy, or malignancy were excluded. The study was approved by the institutional ethics committee.

Hospital records from 2005 to 2014 were reviewed by two independent observers, which included a cardiologist, to identify patients with ADHF diagnosis. Clinical, demographic, biochemical, and echocardiographic parameters were recorded. Medication history was also noted.

Admission chloride and sodium levels were defined as those on the first day of admission. In case of multiple admissions, only the parameters on the first admission were included in the analysis. Hyponatraemia was defined as a serum sodium level of ≤135 meq/L. The serum chloride level was divided into tertiles: <96 meq/L (tertile 1), 96–101 meq/L (tertile 2), and >101 meq/L (tertile 3) based on the distribution of serum chloride levels in our patients. The use of beta blockers, mineralocorticoid antagonists and renin angiotensin system blockers (ACE inhibitors, and angiotensin receptor antagonists) was defined as initiation of the drug therapy during hospital stay or at discharge.

**Statistical analysis**

Continuous variables are expressed as median (interquartile range), and categorical variables are expressed as percentages. The Jonckheere-Terpstra and Cuzick methods were used to test the trend across tertiles of admission chloride levels for continuous and categorical variables, respectively. The duration of hospital stay showed a right skewed distribution; therefore, it was natural-log transformed to achieve normality. Pearson correlation coefficients were estimated to determine the correlations between continuous variables and the duration of hospital stay. For categorical variables, geometric means with 95% confidence intervals (CIs) were calculated. Multiple regression was applied to assess the independent effect of admission chloride levels, with adjustment for age, admission sodium levels, beta blocker use, and inotrope use in the model. A p value less than 0.05 was considered statistically significant. Missing values were excluded from the analysis. The normality of admission chloride levels was tested using Shapiro Wilks and visually checked using the box-and-whisker plot, and the normality test showed no violation of normality. All statistical analyses were conducted using Statistical Package for the Social Science (SPSS; version 21) and Stata (version 12).

**Results**

A total of 167 patients qualified for the analysis after stringent screening based on the inclusion and exclusion criteria. Baseline characteristics of study participants are shown in Tables 1a and 1b. The mean (± standard deviation) and median (interquartile range) ages of the study participants were 63.05 (±13.76) and 63 (55–73) years, respectively; 58.68% of the study participants were men. The median age was higher in the patients with low serum chloride levels. The median age was 69.50 years in tertile 1 compared with 62 and 60.50 years in tertiles 2 and 3, respectively (p = 0.001). Coronary artery disease accounted for approximately two-thirds of congestive HF cases (72.46%). No difference was observed in the aetiology of ADHF across the tertiles of serum chloride levels. The number of patients with dilated and ischaemic cardiomyopathy were not statistically different among the three tertiles (p < 0.05).

Serum chloride levels were normally distributed, and the mean serum chloride level was 97.96 ± 7.27 meq/L. Admission serum chloride levels were directly correlated with admission serum sodium levels (Figure 1a). A positive linear correlation was observed between serum chloride and

<table>
<thead>
<tr>
<th>Table 1b: Baseline characteristics according to admission serum chloride levels (continuous variables)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Overall mean ± SD</strong></td>
</tr>
<tr>
<td>Age (years)</td>
</tr>
<tr>
<td>Length of stay (Number of days)</td>
</tr>
<tr>
<td>Admission sodium levels (meq/L)</td>
</tr>
<tr>
<td>Potassium (mg%)</td>
</tr>
<tr>
<td>Urea (mg%)</td>
</tr>
<tr>
<td>Creatinine (mg%)</td>
</tr>
<tr>
<td>Hb (mg%)</td>
</tr>
<tr>
<td>EF (%)</td>
</tr>
</tbody>
</table>

*Ejection fraction*
serum sodium levels (R² linear = 0.482, p < 0.001). Thus, 48.2% of variation in serum chloride levels could be explained by admission serum sodium levels. The percentage of diabetes patients was 73.9% in tertile 1 compared with 68.1% and 42.3% in tertiles 2 and 3, respectively (p < 0.002, Table 1a). Moreover, low serum chloride levels were more common in diabetic patients (33%) with than in those without diabetes (18.8%).

The duration of hospital stay differed significantly among the three tertiles (Table 1b). The median lengths of hospital stay in tertiles 1, 2, and 3 were 8, 7, and 6 days, respectively (p = 0.011). Among various variables, low admission sodium levels, low admission chloride levels and inotrope use were correlated with an increased duration of hospital stay while beta-blocker use was associated with decreased stay (Tables 2a and 2b). However, only admission chloride levels and inotrope use were associated with prolonged stay in multiple linear regression analysis (Table 3). This finding revealed that the admission chloride level independently prolonged hospital stay. An inverse relation was observed between the serum chloride levels and duration of hospital stay [(R² linear = 0.074, p = 0.001) (Figure 1b)]. On multiple linear regression after adjusting the age, SBP, Beta blocker, Inotrope, and sodium at admission, Chloride at admission had significant negative relation with hospital stay. The results showed 1 unit increase in chloride level was associated with 1.3% (p = 0.003) decrease in hospital stay (95% CI: 2.2% to 0.5%) (Table 3). Inotrope use was also significantly positively associated with the duration of hospital stay.

Table 2a: Correlation between length of stay with various continuous parameter

<table>
<thead>
<tr>
<th>Variable</th>
<th>Correlation value</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>AGE</td>
<td>0.082</td>
<td>0.294</td>
</tr>
<tr>
<td>SBP</td>
<td>-0.108</td>
<td>0.164</td>
</tr>
<tr>
<td>DBP</td>
<td>-0.061</td>
<td>0.436</td>
</tr>
<tr>
<td>Sodium at admission</td>
<td>-0.156</td>
<td>0.044</td>
</tr>
<tr>
<td>Chloride at admission</td>
<td>-0.215</td>
<td>0.005</td>
</tr>
<tr>
<td>Potassium</td>
<td>-0.043</td>
<td>0.584</td>
</tr>
<tr>
<td>Urea</td>
<td>0.087</td>
<td>0.264</td>
</tr>
<tr>
<td>Creatinine</td>
<td>0.069</td>
<td>0.377</td>
</tr>
<tr>
<td>Hb</td>
<td>-0.079</td>
<td>0.308</td>
</tr>
<tr>
<td>EF</td>
<td>-0.056</td>
<td>0.474</td>
</tr>
</tbody>
</table>

SBP = systolic blood pressure, DBP = diastolic blood pressure, EF = Ejection fraction

Table 2b: Correlation of length of stay with various categorical variables

<table>
<thead>
<tr>
<th>Variable</th>
<th>Number</th>
<th>Geometric Mean (95% Confidence Interval)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CAD</td>
<td>Present 121</td>
<td>7.50[6.71-8.40]</td>
<td>0.159</td>
</tr>
<tr>
<td></td>
<td>Absent 46</td>
<td>6.80[5.79-7.96]</td>
<td></td>
</tr>
<tr>
<td>Diabetes</td>
<td>Present 103</td>
<td>7.24[6.45-8.15]</td>
<td>0.814</td>
</tr>
<tr>
<td></td>
<td>Absent 64</td>
<td>7.40[6.37-8.60]</td>
<td></td>
</tr>
<tr>
<td>HTN</td>
<td>Present 111</td>
<td>6.90[5.99-7.94]</td>
<td>0.223</td>
</tr>
<tr>
<td></td>
<td>Absent 56</td>
<td>7.91[6.69-9.34]</td>
<td></td>
</tr>
<tr>
<td>CKD</td>
<td>Present 22</td>
<td>7.31[6.012-8.87]</td>
<td>0.571</td>
</tr>
<tr>
<td></td>
<td>Absent 145</td>
<td>7.30[6.59-8.08]</td>
<td></td>
</tr>
<tr>
<td>Gender</td>
<td>Male 98</td>
<td>7.31[6.44-8.29]</td>
<td>0.592</td>
</tr>
<tr>
<td></td>
<td>Female 69</td>
<td>7.29[6.36-8.34]</td>
<td></td>
</tr>
<tr>
<td>COAD</td>
<td>Present 13</td>
<td>9.01[5.53-14.68]</td>
<td>0.248</td>
</tr>
<tr>
<td></td>
<td>Absent 154</td>
<td>7.18[5.54-7.87]</td>
<td></td>
</tr>
<tr>
<td>β-Blocker</td>
<td>Present 24</td>
<td>5.58[4.35-6.89]</td>
<td>0.024</td>
</tr>
<tr>
<td></td>
<td>Absent 138</td>
<td>7.72[6.97-8.54]</td>
<td></td>
</tr>
<tr>
<td>RAS</td>
<td>Present 124</td>
<td>7.17[6.45-7.97]</td>
<td>0.258</td>
</tr>
<tr>
<td></td>
<td>Absent 38</td>
<td>7.88[6.49-7.92]</td>
<td></td>
</tr>
<tr>
<td>Inotrope</td>
<td>Present 50</td>
<td>9.42[7.81-11.38]</td>
<td>0.0001</td>
</tr>
<tr>
<td></td>
<td>Absent 112</td>
<td>6.56[5.92-7.26]</td>
<td></td>
</tr>
</tbody>
</table>

CAD – coronary artery disease, HTN= Hypertension, CKD - Chronic kidney disease, COAD - Chronic obstructive airway disease, RAS - Renin angiotensin system
stay, and inotrope use increased the mean duration of hospital stay by 13.9% (95% CI: 4.9-22.9% p=0.003).

Discussion

The most important finding of the current study is the inverse relation between serum chloride levels and the duration of hospital stay; that is, low admission chloride levels are associated with a prolonged hospital stay in patients with ADHF, a prognostic effect that has not been documented previously. This effect is independent of the sodium levels at presentation.

Recent studies have investigated the effect of chloride levels on cardiovascular morbidity and mortality.14,15 In a recent study, admission serum chloride levels were independently and inversely associated with mortality in a multivariate model (hazard ratio per unit change: 0.93, p < 0.001); however, the admission sodium level was not associated with significantly higher mortality (p > 0.05).14

Low serum chloride is mainly the effect of dilutional hypochloraemia as a result of increased arginine vasopressin levels in HF patients. Moreover, chronic disturbances can be attributed to the effect of loop diuretics, particularly the escalating doses of such diuretics in HF patients. Diuretic use in ADHF is a major implicated factor for dyselectrolytaemia, because diuretics cause an increase in Na⁺ and Cl⁻ excretion (up to 25% of the filtered load) and volume contraction.6,7 This also increases aldosterone-mediated Na⁺ reabsorption in the distal nephron, causing higher chloride excretion. Loop diuretics are known to increase chloride excretion by almost 20 times, with a 10%–20% higher chloride loss than sodium and potassium excretion.6

Most importantly, although low serum chloride levels may be the passive effect of HF pathophysiology, they become pathogenic by promoting diuretic resistance. In a recent study, low chloride levels were associated with a poor diuretic response and the requirement of a higher total in-hospital furosemide dose.15 In the ‘chloride theory’, Kataoka proposed that the serum chloride level is the primary determinant of changes in the plasma volume and the renin–angiotensin–aldosterone system (RAAS) and an indirect determinant of changes in the antidiuretic hormone system.21

The chloride ion mediates the mechanism of action of diuretics, which are the primary treatment modality for ADHF. Chloride directly binds to the catalytic sites of serine-threonine kinases (with-no-lysine [K] (WNK)), the phosphorylation of which modulates sodium chloride homeostasis by regulating RAAS and the transporters that are targets of loop and thiazide diuretics, which in turn influence downstream sodium transport pathways.8,19,22 The direct regulatory role of sodium for WNK has not been described. The WNK3 subtype has been found to regulate the activation of NKCC2, which is the target of loop diuretics, in response to changes in intracellular chloride,20 and WNK4 mediates the regulation of Na–Cl cotransporter (NCC), which is the target of thiazide diuretics, in a chloride-dependent process.21 Chloride, not sodium, is the ion sensed by NKCC2 in the macula densa for tubuloglomerular feedback.6 The renin secretion rate from the macula densa is proportional to the chloride levels in the early distal tubule of the nephron. Thus, diuretic hyporesponsiveness occurs through various mechanisms, including increase in the number of NKCC2 cotransporters at the apical surface of the TAL due to reduced intracellular chloride levels, decrease in the quantity of the loop diuretic excreted in the urine (and thus the quantity of the loop diuretic reaching the tubular site of action), and higher total renin levels.15,22 This may partly explain the prolonged duration of hospitalisation in patients with lower serum chloride levels in our study, although we did not compare the total dose of diuretics used by patients in the different tertiles of serum chloride.

In this study, we also found that admission serum chloride levels were correlated with admission serum sodium levels, and although 48.2% of variation in serum chloride levels was explained by sodium levels, serum chloride remained an independent predictor of prolonged stay in multiple linear regression analysis, whereas serum sodium was not significant. Thus, compared with serum sodium levels, low serum chloride levels represent an abnormal electrolyte state with different prognostic implications, and in some cases, hypochloremia can occur without hyponatraemia. Testani et al23 also demonstrated a stronger relationship between serum chloride and the metrics of renal function and loop diuretic dose than did serum sodium, and hypochloremia in absence of hyponatremia portend an ominous prognosis. Gordin et al24 concluded that the chloride level was a more HF-specific marker of risk than the sodium

**Fig. 1b: Correlation between the length of stay and admission serum Chloride levels**
level and that the chloride level was independently and inversely associated with long-term mortality in AHF.

In the present study, we also found that low serum chloride levels are more common in diabetes patients than in those without diabetes. The reason for this remains unclear, but a study has proposed internal ion shift (the shift of chloride from the extracellular space to the intracellular space or of sodium and water to the extracellular fluid) and metabolic compensation for acidosis in diabetic ketoacidosis as possible mechanisms. That study also reported an inverse correlation between chloride and unmeasured anions; a high ketoad level results in low chloride levels. Chloride channels, activated by acidic pH of the extracellular fluid, and enhanced renal chloride excretion may also be possible mediators of acidosis-induced hypochloremia in diabetes patients.

Defects in chloride channels and their encoding genes, for example the loss-of-function DNA sequence variant in the CLCNKA chloride channel in the kidney and variants in HSPB7 and FRMD4B, have also been directly associated with the risk of advanced HF, which explains the cardio-renal association with the risk of advanced AHF.

Our study however had some limitations. First, the total dose of diuretics used by patients in the different tertiles of serum chloride level was not compared. Second, an objective assessment of the volume status was not conducted. Finally, because urinary electrolyte data were insufficient, they were not included in the analysis.

Conclusion

Serum chloride has an important role in the prognostication of HF in terms of the duration of hospital stay, which is independent of serum sodium levels. Serum chloride has an important role in regulatory pathways of heart failure and diuretic resistance. Further studies are needed to validate our findings and search for chloride sparing strategies which may improve outcomes in heart failure patients.

References

Blood-pressure Lowering Efficacy and Safety of Perindopril / Indapamide / Amlodipine Single-pill Combination in Hypertensive Patients: Phase III Trial in India

Hemant Thacker¹, Krishna Mala Konda Reddy², L Sreenivasa Murthy³, JPS Sawhney⁴, Gaurav Chaudhary⁵, Siddharth Shah⁶, Sofi Joseph⁷*, Manjusha Rajarshi⁸, Preeti Nikam⁹

Abstract

Background: Hypertension is the biggest contributor to global burden of disease and mortality. Increasing compliance with antihypertensive treatment and achieving a wide BP control in the population represents a major challenge for clinical practice. The benefits of single pill combination versus free-equivalent combination has been demonstrated in several meta-analyses and is now strongly supported by the latest 2018 ESC/ESH guidelines. The RAAS blocker with CCB and thiazide like diuretic is proposed as the optimal combination in patients inadequately controlled by two drugs.

Objective: To assess the blood pressure control rate, safety, tolerability and quality of life with triple-drug SPC in patients with grade II/III hypertension.

Methods: Hypertensive patients uncontrolled (BP ≥ 140/90 mmHg) on two-drug therapy were recruited in an open-label, phase III clinical trial conducted in outpatient setting in India with 6 months treatment period. No other antihypertensive medication except the study medication was received by the patients.

Results: Out of 218 evaluable patients the observed average blood pressure reduction achieved from baseline to end of study at 6 months was Systolic Blood Pressure (SBP) 28.5 mm Hg / Diastolic Blood Pressure (DBP) 13.8 mm Hg. The quality of life (QoL) questionnaire demonstrated improvement in QoL for all patients.

Conclusion: This study showed the clinical efficacy, safety and acceptability of the perindopril/indapamide/amlodipine SPC in patients with grade 2/3 hypertension inadequately controlled with two-drug therapy. The clinical effectiveness was observed in more than 96% patients. The benefit of single-pill combination (SPC) therapy in hypertension control was reconfirmed in this study.

Introduction

Hypertension is an important public health challenge worldwide¹ and the number of adults with hypertension in 2025 is predicted to increase by about 60% to a total of 1.56 billion (95%CI, 1.54-1.58 billion).

Studies from various parts of India have reported high prevalence of hypertension and one the most important risk factors for chronic disease burden in India. These studies have also reported that hypertension is increasing and there is low awareness and control. The Fourth National Family Health Survey evaluated hypertension in a large population based sample (n = 799,228) and reported hypertension in 13.8% men vs. 8.8% women (overall 11.3%) aged 15–49 and 15–54 respectively. More representative data (age > 18 years, n = 1,320,555) from the Fourth District Level Household Survey reported hypertension in 25.3% with greater prevalence in men (27.4%) than women (20.0%). This translates into 207 million persons (men 112 million, women 95 million) with hypertension in India.²

The goal of antihypertensive therapy is to reduce cardiovascular (CV) mortality and cardiovascular events (stroke, myocardial infarction, and heart failure) associated with blood pressure (BP) elevation without adversely affecting quality of life.³ The combination of ACE inhibitor, diuretic and calcium antagonist for the triple therapy is recommended by the ESH 2018 guideline, especially as a single Pill Combination (SPC) which offers better adherence to treatment. Based on the available clinical evidence today the algorithm of hypertension treatment pertains to age and ethnic background. The guidelines recommend tighter BP control in patients with cardiovascular risk factors such as patients with diabetes mellitus.⁴ This study examines the efficacy, in terms of BP control and acceptability of Perindopril + Indapamide + amloidipine SPC in moderate to severe hypertensive patients in India.

Materials and methods

Study Design

This study was an open-label, phase III clinical trial conducted in the outpatients setting across 5 centres in India. The clinical trial protocol was approved by the drug regulatory authorities of India and the Ethics committees...
of the participating institutes and was registered on the clinical trial portal (CTRI/2017/09/009786). The study medication consisted of a SPC containing Perindopril erbumine 4 mg + indapamide 1.25 mg + amlodipine 5 mg for the entire study duration. In patients who did not achieve the target control, the up titration with additional tablet of perindopril 4 mg was permitted on top of the study medication at the discretion of the investigator. The study treatment duration consisted of 6 months (180 days) with a total of 8 study visits by the patient post inclusion.

Selection of patients

Men and women adult patients in the age group of 18-65 years with history of confirmed diagnosis of grade II/III (moderate to severe) hypertension, presenting to the clinic with inadequate BP control were screened for inclusion. Uncontrolled patients with a baseline BP ≥140/90 mmHg despite receiving any two drug therapy comprising either ACEI, ARBs, CCBs and diuretics as individual tablets or in combination as a fixed dose combination therapy were included. Patients with uncontrolled diabetes (HbA1c% more than 7), history of myocardial infarction, cerebrovascular event within the previous 3 months, uncontrolled arrhythmias, history of heart failure class II/IV heart blocks, patients with known severe impaired renal function (serum creatinine levels > 5.3 mg/dl and/or serious liver disorders were excluded. Patients receiving beta blockers were excluded. The patients were included only when complied with the eligibility criteria.

This study followed the Indian GCP guidelines and ethical guidelines of biomedical research and schedule Y requirements as per the Indian regulations.

Evaluation criteria

The primary efficacy criterion was to assess the BP control rate in patients with grade II/III hypertension with the study medication (SPC) given once daily in the morning. The secondary criteria were assessment of safety, tolerability and quality of life criteria. The quality of life was evaluated by a self-administered WHOQOL BREF questionnaire.\(^5,6\)

Except the study medication (SPC), no other antihypertensive treatment was permitted during the study period.

In total, 8 visits were planned (Figure 1: Study Design), including baseline visit 1 at Day 0 until end of study visit 8 at Day 180 during which the study medication was dispensed and adherence to the treatment was monitored using the patient diaries to document daily medication intake. QoL questionnaire was used at baseline and at end of study. Heart rate and BP were measured at each visit as per JNC VII and Adverse Events (AEs) were recorded. The coded and labelled study medication during study visits was dispensed to each of the participants (daily dose of one tablet each day in the morning with breakfast).

Statistical analysis

Statistical analyses were performed using SPSS version 19. Descriptive statistics were used for baseline and demographic characteristics.

The primary endpoints evaluated were mean change in BP from baseline to end of the study with the study treatment and the number of patients achieving BP control (SBP ≤140 and DBP ≤90 mmHg) on an intention to treat basis as well as per protocol patients completing the study.

The WHOQOL BREF questionnaire responses at baseline and at end of study were computed and analysed for the mean scores.

Significance was defined as a p value of less than 0.05 (95% CI).

The patient satisfaction and investigator’s assessment of the study treatment was collected using standard questionnaire.

Results

Efficacy criteria

246 patients were screened, 241 (ITT) recruited and 218 (PP) patients completed the study as per the protocol.
2) already 60% of patients had achieved target BP of 140/90 mm Hg or lower and almost 90% were controlled after 2 months of treatment (day 60).

The sustaining effect on the BP reduction was maintained from month 3 (day 90) onwards until the end of the study in both the ITT and PP groups.

After 3 months of treatment, 204/218 patients from PP group (94%) achieved target BP demonstrating uniform efficacy of the study medication (Figure 2).

Patients with diabetes mellitus (n=49) also achieved the target BP at the end of study. (BP reduction below 130/85 mm Hg)

After the Up- titration performed in 19 patients at different visits all of them achieved the target BP control.

Safety and tolerability

In total, 41 patients reported at least one AE, mostly headache and fever in 4 and 5 patients respectively. The reported adverse events were mild to moderate and in majority not related to the study and/or study medication. Only 3 cases of pedal oedema and 1 case of dry cough were reported as probably related to study medication. The laboratory parameters, including serum electrolytes remained within the normal limits and no effect not related to the study and/or study medication. The laboratory parameters, including serum electrolytes remained within the normal limits and no effect was observed.

QoL analysis and satisfaction with treatment

Investigators expressed satisfaction regarding the efficacy of the study medication and the compliance offered due to same in 92% of the cases. 99% of the patients expressed satisfaction to the treatment. The QoL questionnaire demonstrated significant improvement following better control of BP. Patients expressed satisfaction to the health and its quality as GOOD in comparison to their responses at baseline QoL questionnaire.

Discussion

Hypertension is increasing over the world and multiple therapies are needed in order to control it. It is well known that more than 20% of hypertensive patients need to receive three different agents. Current national and international guidelines recommend the use of drugs belonging to four main treatment classes: RAAS modulators, calcium channel blockers, thiazide and/or thiazide-like diuretics or beta-blockers. According to current 2018 European and 2017 American guidelines on hypertension management, perindopril, indapamide and amlodipine fulfill the criteria for the choice of antihypertensive drugs.

The importance of evaluating and improving treatment adherence as major cause of poor BP control is underlined in all international guidelines. The benefit of SPCs in hypertension management and control is well documented and demonstrated through various studies. Guidelines for primary stroke prevention also consider adherence with antihypertensive therapy might reduce stroke risks by about one-third.

Greater use of single-pill combinations improves not only the hypertension control but also the cardiovascular outcomes in the first year of treatment.

Many patients with uncontrolled BP maintained on a two drug combination

Table 1: Patient demography

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Number of subjects (N)</th>
<th>Observations: Mean</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td></td>
<td>Male: 241 Female: 152</td>
</tr>
<tr>
<td>Mean age (completed years), SD</td>
<td>241</td>
<td>47.81(8.47)</td>
</tr>
<tr>
<td>Mean height (cm), SD</td>
<td>241</td>
<td>164.75(8.38)</td>
</tr>
<tr>
<td>Mean weight (kg), SD</td>
<td>241</td>
<td>69.09(8.50)</td>
</tr>
<tr>
<td>Mean BMI (kg/m²), SD</td>
<td>241</td>
<td>25.47(3.11)</td>
</tr>
<tr>
<td>HT duration (number of months), SD</td>
<td>239</td>
<td>39.91(29.14)</td>
</tr>
<tr>
<td>Associated diseases, n(%)</td>
<td>241</td>
<td>111 (46%)</td>
</tr>
<tr>
<td>Diabetes n(%)</td>
<td>241</td>
<td>50 (20.7%)</td>
</tr>
<tr>
<td>Dyslipidemia n(%)</td>
<td>241</td>
<td>34 (14%)</td>
</tr>
<tr>
<td>Hypothyroidism n(%)</td>
<td>241</td>
<td>11 (4.5%)</td>
</tr>
<tr>
<td>Others*</td>
<td>241</td>
<td>16 (6.63%)</td>
</tr>
</tbody>
</table>

*Hyperacidity, skin allergies, epilepsy, anaemia, joint pains and ailments related to Gastrointestinal tract.

Table 2: PP group: observed mean blood pressure reduction (mean ± SD)

<table>
<thead>
<tr>
<th>Study visit</th>
<th>SBP (mm Hg)</th>
<th>DBP (mm Hg)</th>
<th>HR (bpm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>V1: DAY 0</td>
<td>157.72(11.09)</td>
<td>95.16 (5.25)</td>
<td>81.70(7.22)</td>
</tr>
<tr>
<td>V8: DAY 180</td>
<td>129.25 (4.83)</td>
<td>81.36(5.22)</td>
<td>80.62(5.02)</td>
</tr>
</tbody>
</table>

P value <0.0001 (t-test) 95%CI

The patients recruited were of both sexes with the age group of 24-64 years with hypertension history of at least 3 or more years with inadequate control of hypertension on two-drug treatment (Table 1).

The 2 drug combination treatments consisted of various permutations and combinations between Calcium Channel Blockers (CCB), Angiotension-1 Receptor blockers (AT1RB), Angiotensin Converting Enzyme (ACE) inhibitors and/or diuretics (DU) as a single pill or free combination. From inclusion visit patients received only the triple drug study medication (SPC) for the treatment of hypertension.

Highly significant and gradual BP reduction was observed in all patients from the baseline to the end of study (p-value <0.0001; 95%CI: 26.19- 15.22) in both ITT (SBP/DBP -28.12/-13.21 mm Hg respectively) and PPS (-28.47 / -13.8 mm Hg DBP) groups and was comparable (Table 2). After 15 days treatment with study medication (visit
therapy achieved an adequate control of their BP with additional drug. The current evidence reemphasizes the need for moving from dual to triple therapy as a solution to clinical inertia in the treatment of hypertension.

Our phase III study with triple drug SPC of Perindopril erbumine 4 mg / indapamide 1.25 mg / amlodipine 5 mg aimed to address this clinical need. The study demonstrated highly significant BP reduction from baseline observed at the end of study (p value < 0.0001, 95% CI: 26.19-15.22) with good safety profile with the triple drug SPC.

After 1 month of treatment, target BP was achieved in more than 80% patients, almost 90% were controlled after 2 months of treatment and more than 96% achieved BP control at day 180 including the 49 patients with diabetes mellitus. The target BP achieved by Day 90, was maintained until the end of the study period.

The improved BP control improved quality of life for the patients, an important aspect towards health promotion; patient satisfaction improves compliance and clinical outcomes. In 2017 (World Hypertension day data), 50% of patients having “resistant” HT have been found to be completely or partially non-adherent to the prescribed therapy. SPC therapy confers advantages in terms of compliance, simplicity of treatment, improved efficacy and tolerability. The BP-lowering effect is remarkable when the combination drugs have synergistic and complementary action.

In the different studies/surveys, SPC treatment has been reported to lead to a 26% to 29% increase in compliance over their corresponding free drug components given separately.

In ACHIEVE cross-sectional survey performed in 8,006 patients, the need for the SPC in everyday clinical practice was confirmed by 742 general practitioners across 2 countries, who clearly expressed willingness to switch from free combinations to SPC in 66% patients for improved adherence (76%) and better blood pressure control (64%).

Using a similar SPC as in our study in India, several studies confirmed the efficacy of this strategy showing its effectiveness in the treatment of uncontrolled hypertension after 3 or 4-month therapy. Mazza et al have demonstrated that target BP values (mean 24-h ambulatory systolic/diastolic BP < 130/80 mmHg) were more frequently reached by patients receiving SPC than free-combination therapy (64.8% vs. 46.9%, p < 0.05). In the same way, high BP reduction was observed in 4,731 patients from 4-months PIANIST study (−28.3±13.5/-13.8±9.4 mmHg p<0.0001) and in 3 months PETRA study, in which the 24-h antihypertensive efficacy of similar SPC was confirmed by significant office BP decrease (by 24.8/11.4 mmHg), observed in all stages of hypertension (p<0.0001) and ABPM (by 21.0/7.5 mmHg), resulted in improvement of patient adherence. Similar reductions are observed in our study.

Finally, the study conducted in 796 hypertensive patients with similar SPC in Belarus resulted has demonstrated significant SBP and DBP reduction from 166.5±15.4/97.4±8.5 mm Hg to 130.3±9.2/80.3±4.5 mm Hg (p<0.001). Target levels of CSBP and CPBP were achieved in 86.7% and 90% of all patients, respectively.

The results from this triple drug SPC are encouraging and similar BP reduction and control rates are achieved across the various and diverse patient population from different countries. Moreover, the long-term experience with these 3 antihypertensive agents from this SPC is well established and robust clinical evidence is available from, large programs of randomized clinical trials performed with each component. The available clinical evidence and guidelines recommendations reinforce the clinical benefit on BP reduction as well as beneficial effect in terms of mortality and morbidity and on the protection of the hypertensive target organs such as the heart, kidney, brain and vessels. The benefits of triple drug therapy on BP-lowering effects and consequent reduction in stroke and ischemic heart disease is reported and demonstrated in SPRINT study. 5-year CV event rate was lower in the SPC group compared with free combinations (HR 0.74, 95% CI 0.70-0.77, p<0.0001) further corroborates the need for using this triple drug SPC in the management of hypertension and fostering long-term health benefits.

**Conclusion**

In this study, the triple drug SPC containing Perindopril, Indapamide and amlodipine, the well-established antihypertensive agents from 3 different classes (ACEI, DIU and CCB respectively), has demonstrated clinical effectiveness in more than 96% patients of grade 2-3 hypertension inadequately managed on two drug therapy. The synergistic and complementary mechanisms of action with improved treatment adherence and compliance demonstrates improved blood pressure reduction rates and QoL. Although our study comprised of 6-months treatment duration and was open-label, the fact of the established safety and efficacy of the individual BP-lowering agents cannot be ignored. They all have a well endorsed place in the treatment of hypertension and its combined use as SPC makes it a formidable choice for clinicians to achieve its goal of blood pressure management as supported by the EU guidelines.

**Acknowledgement**

Authors would like to thank Prof. C.Y. Nimkar for statistical analysis and their respective team members for assistance in the study conduct.

**Conflicts of interest**

The study was sponsored by Serdia Pharmaceuticals (India) Pvt. Ltd. Mumbai. Dr. P. Nikam, S. Joseph and Dr. M. Rajarshi are employees of Serdia Pharmaceuticals. All other authors have no conflicts of interest to declare. Editorial assistance and article processing were provided by Dr. M. Rajarshi.

**References**


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**Zinctonia®-50 Tablet Syrup**

*The Health Catalyst*

**Zu-Ć™500™**

*A Vista to Scavenge Effectively*

**Ivermectin Tablet 12mg**

Right Ć for Maximum benefits
Metabolic Diseases and Associated Complications in Patients with Psoriasis

Sarita Bajaj1, Shilpa Mandal2, KG Singh3, Rajpal Prajapati4

Abstract

Background: Psoriasis patients are at increased risk of developing metabolic diseases. Proinflammatory cytokines such as IFN-γ, IL-17, IL-23, and TNF-α, IGF that are increased in psoriasis play an important role in the development of diabetes mellitus (DM), hypertension, dyslipidemia, obesity, insulin resistance and their complications.

Aims: To study prevalence of insulin resistance (IR) using HOMA-IR index in psoriasis patients and its association with severity of psoriasis. To study prevalence of metabolic diseases, macro and microvascular complications of these diseases in psoriasis.

Materials and methods: A hospital based case control study was conducted involving 102 psoriasis patients and 102 age and sex matched controls. All patients were analysed for the presence of metabolic diseases and their complications.

Results: Mean age of cases was 38.41±16.37 years. Majority of cases (58.8%) as well as controls (55.9%) were males. Prevalence of hypertension, prediabetes, DM, raised TG, low HDL, MetS and IR was 46.1%, 28.4%, 27.5%, 42.2%, 31.4%, 31.4% and 48% respectively in cases as compared to 26.5%, 13.7%, 11.8%, 24.3%, 16.7%, 10.8% and 26.5% respectively in controls. However there was no significant difference in obesity (29.4% vs 21.6%, p=0.2024) and LDL among the cases and controls (14.7% vs 10.8%, p=0.4). Prevalence of all the metabolic disorders except LDL was significantly higher in cases as compared to that in controls. Prominent complications noted were retinopathy, neuropathy and CVD. With increased psoriasis severity insulin resistance increased.

Conclusion: There is a positive correlation of psoriasis with IR and it is associated with increased risk of metabolic diseases and their complications.

Introduction

Psoriasis is a relatively common and hyper-proliferative skin disease that affects 1.4% to 2.0% of the population.1 As a systemic, inflammatory autoimmune disease, psoriasis is also connected with an elevated risk for other serious, chronic and/or life-threatening conditions, including DM, hypertension, dyslipidemia, cardiovascular disease (CVD), cerebrovascular accident (CVA) etc. Exploring the correlations between psoriasis and other disease states is increasingly essential in elucidating the comprehensive pathophysiology of this “skin disease” and ultimately improving the long-term quality of life in these patients. The relationship of psoriasis with metabolic disorders is interdependent as both have a shared immunopathogenesis involving chronic low-level inflammation mediated by pro-inflammatory cytokines such as IFN-γ, IL-17, IL-23, and TNF-α.2-3 Additionally, some studies have implicated insulin-like growth factor 1 (IGF-1) as a shared mediator in the keratinocyte proliferation seen in psoriasis and the development of diabetes and dyslipidemia.3,4

Aims and Objectives

1. To study prevalence of insulin resistance using HOMA-IR index in patients of psoriasis.
2. To study prevalence of metabolic diseases in patients of psoriasis.
3. To study the correlation of metabolic diseases with psoriasis.
4. To study the prevalence of macro and microvascular complications of metabolic diseases in psoriasis.
5. To study role of insulin resistance as a link between psoriasis and metabolic diseases.
6. To study the association of insulin resistance with the severity of psoriasis.

Materials and Methods

This was a Case control study conducted at department of internal medicine in MLN Medical College, Prayagragj from January 2018-May 2019. Patients aged more than 18 years having definite clinical confirmation of psoriasis were the source of data and were compared with equal number of age and sex matched controls. Waist circumference, height, weight, blood pressure were measured. Fasting plasma glucose (FPG), postprandial glucose (PPG), HbA1C, fasting plasma insulin, fasting lipid profile, liver function tests, ura, creatinine were measured. Fundus examination, ECG, 2D-Echo were performed. Psoriasis area severity index (PASI) was calculated. HOMA-IR was calculated as follows:

\[
\text{HOMA-IR = FPG (mmol/L) } \times \text{ Fasting plasma insulin (µU/ml)/22.5}
\]

Exclusion criteria

1. Patients having any other skin lesion except psoriasis.
2. Psoriatic patients having received systemic treatment (cyclosporine and/
or systemic retinoids) for more than 1 month.

3. Pregnant patients.

Statistical methods: Statistical analysis was done with SPSS version 21.0 statistical software. Comparison of discrete variables were done by Chi square test and comparison of mean was done by Student ‘t’ test.

Results

Out of 204 patients 102 psoriasis patients and 102 apparently healthy controls were evaluated. Mean age of cases was 38.4±16.37 years. Majority of cases (58.8%) as well as controls (55.9%) were males. Mean HOMA-IR values were 2.03±1.05, 3.07±1.46 and 6.95±2.65 respectively among mild, moderate and severe grades of psoriasis. Prevalence of insulin resistance was 33.3%, 79.2% and 100% respectively (Figure 1). Statistically, there was a significant association between severity of psoriasis and HOMA-IR levels (p<0.001).

Prevalence of hypertension, prediabetes, DM, raised triglyceride(TG), decreased high density lipoprotein(HDL), metabolic syndrome(MetS) and insulin resistance(IR) was 46.1%, 28.4%, 27.5%, 42.2%, 31.4%, 31.4% and 48% respectively in cases as compared to 26.5%, 13.7%, 11.8%, 24.3%, 16.7%, 10.8% and 26.5% respectively in controls (Figure 2). However there was no significant difference in obesity(29.4% vs 21.6%, p=0.2024) and low density lipoprotein(LDL) among the cases and controls(14.7 %vs 10.8%, p= 0.4).

Prevalence of all the metabolic disorders except LDL was significantly higher in cases as compared to that in controls.

Retinopathy was seen in 11.8% of cases as compared to 3.9% of controls whereas microalbuminuria was detected in 11.8% of cases and 2.9% of controls. For both these microvascular complications, the difference between two groups was significant (p<0.05)

Abnormal ECG, Echo and CVA were detected in 20.6%, 39.8% and 0.9% respectively in cases as compared to 7.8%, 14.7% and 0% respectively in controls. Statistically, a significant difference between two groups was observed with respect to abnormal ECG and ECHO findings (p<0.05) (Table 1).

Discussion

In this case control study 102 patients with psoriasis of varying severity and equal number of apparently healthy individuals were assessed for the presence of IR and metabolic diseases.

A total of 72 (70.6%) had mild psoriasis (≤2% PASI) followed by 24 (23.6%) having moderate psoriasis (3-10% PASI) and remaining 6 (5.9%) had severe psoriasis (>10% PASI). Armstrong et al. found the same distribution regarding severity of psoriasis.

Recent studies show that psoriasis is associated with IR. The findings in this study demonstrates the increased prevalence of IR among two groups.
psoriatic patients as compared to the controls (48% vs 26.5%, p=0.001). Our results correlated with studies conducted by Bilir et al,6 Pereira et al,7 Boenhcke et al.8 The odds ratio in this study is 2.4.

Mean HOMA-IR values were 2.03±1.05, 3.07±1.46 and 6.95±2.65 respectively among mild, moderate and severe grades of psoriasis respectively. Prevalence of IR was 33.3%, 79.2% and 100% respectively. Statistically, there was a significant association between severity of psoriasis and HOMA-IR levels (p<0.001). Similar correlations were found in studies by Bilir et al who conducted the study among 48 psoriasis patients and 45 healthy controls and found PASI to be an independent risk factor for IR. Some other studies also found dose response relationship with MetS and psoriasis severity. However studies by Albaredaet et al9 and Milicic et al10 found no significant correlation with MetS and psoriasis severity.

This study also showed the association between psoriasis and comorbidities like hypertension, DM, dyslipidemia. The results revealed that hypertension (46.1% vs 26.5%, p=0.004), DM (27.5% vs 11.8%, p=0.005), increased TG (42.2% vs 24.3%, p=0.008), decreased HDL (31.4% vs 16.7%, p=0.014) are more common in psoriasis patients than controls.

Mean systolic blood pressure(SBP) and diastolic blood pressure(DBP) of cases of this study were 136.6±16.56 mmHg and 82.2±10.36 mmHg respectively as compared to 132.45±12.55 mmHg and 79.09±8.32 respectively for controls (Table 2). Statistically, both SBP and DBP values were significantly higher in cases as compared to that in controls (p<0.05). Studies by Madangobalane et al11 found no correlation between hypertension and psoriasis, in contrast to majority of case control studies.

Mean FPG and PPG levels were 109.17±33.90 and 162.42±57.05 mg/dl respectively in cases as compared to 96.51±16.34 and 137.12±21.34 mg/dl respectively in controls (Table 3). Mean HbA1C was 5.83 ±1.45% in cases as compared to 5.28 ±0.78 % in controls, p=0.001. Few similar studies12 also found increased prevalence of DM with psoriasis.

Studies have shown association of impaired fasting glucose (IFG), impaired glucose tolerance(IGT) and abnormal HbA1C (prediabetes) with psoriasis. This study revealed that a significant number of patients were prediabetic (28.4% vs 13.7%, p= 0.011). This correlated with other studies by Pereira et al,7 Nisa and Qazi13 and Ucak et al.14

Mean TG, total cholesterol (TC), LDL and HDL values were 162.86±72.77, 167.67±42.18, 83.29±33.05 and 51.81±14.28 mg/dl respectively in cases and 141.23±38.27, 160.35±32.51, 78.85±31.24 and 58.01±13.21 mg/dl respectively in controls. We however detected a significant difference in the levels of TG (17.9% increase in psoriasis) and HDL (14.7% decrease in psoriasis), but not in LDL (3.9% increase in psoriasis as compared to controls, which was not significant). Zindanci et al15 found 3 fold increase in MetS, they found statistically significant differences in the increased TG, decreased HDL, hypertension and dysglycemia which were 45.2%,43.5%,40.9%, 48.7% and 39.3%,32.9%,25.6%,35% among cases and controls respectively.

This study also showed an increase in TG levels independent of the effects of obesity. This is correlated by a study done by Sinead et al16 in UK.

MetS among cases in this study was 31.4% as compared to 10.8% (p value <0.001) among controls with hypertension being the most common metabolic derangement. Prominent complications noted were retinopathy, nephropathy and cardiovascular abnormalities. Sommer et al11 reported that DM, hypertension, dyslipidemia and coronary artery disease and MetS is increased by 2 folds in a study they conducted on 581 patients. Other studies showed an increased frequency of ischemic heart disease, DM, hypertension and dyslipidemia in patients with psoriasis as compared to controls.

Conclusions

There was a positive correlation of psoriasis with IR. IR was observed to be an independent risk factor for development of metabolic diseases among psoriasis patients. Individuals with psoriasis had a significantly increased incidence of hypertension, diabetes and prediabetes, increased TG and decreased HDL but not LDL. The major complications associated with psoriasis observed were retinopathy, nephropathy and cardiovascular abnormalities. Insulin resistance increased with the increasing severity of psoriasis. No significant difference was found in BMI and waist circumference among cases and controls.

References

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

**DOSAGE AND ADMINISTRATION:** The dosage of Glycomet GP should be individualized on the basis of effectiveness and tolerability while not exceeding the maximum recommended daily dose of glycoprotein and metformin 2000 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 several cases the tablet may remain intact during transit through the gastrointestinal tract and will be eliminated in the faeces as intact tablets. If tablets should be retained for a longer period, all drug components have already been released during GI transit. **CONTRAINdications:** Individuals hypersensitive to glimepiride, other sulfonylureas, metformin, other sulfonamides, or any of the excipients of Glycomet GP, pregnancy and lactation, diabetic ketoacidosis, diabetic coma, or coma, patients with renal failure or renal dysfunction, severe conditions with the potential to alter renal function (obstructive uropathy, severe infection, shock), severe intercurrent illness or severe hypoglycemia, elderly patients with decreased cardiovascular reserve, patients with severe renal impairment (creatinine clearance < 15 ml/min), patients with severe hepatic insufficiency, acute alcohol intoxication, chronic alcoholism, patients with severe hypothyroidism or significant electrolyte abnormalities, patients with a history of lactic acidosis, or conditions that may predispose to lactic acidosis (e.g., conditions that are associated with severe tissue hypoxia, severe sepsis, severe hepatic failure, severe infections, severe trauma, severe hypoxia, severe congestive heart failure, severe electrolyte abnormalities).** WARNINGS:** Glycomet GP contains sulfonamide-related substances that may cause allergic reactions. In case of adverse events, patient should be hospitalized immediately. **PREGNANCY:** In the initial weeks of treatment, the risk of hypoglycemia may be increased and may also be associated with the risk of hypoglycemia. **CONTRAINDICATIONS:** Hypoglycemia is a rare but serious complication of all antidiabetic drugs. For full prescribing information, please refer to: USV Limited (formerly USV Limited). Arvind Vithal Gandhi Chowk, B.S.D. Marg, Govandi, Mumbai, Maharashtra – 400088 INDIA | Updated on: 20th March 2019.

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*IMS MAT Dec 2018. # AIOCD MAT Jan 2020
Single-pill Combination of Empagliflozin and Linagliptin in Real World Indian Type 2 Diabetes Patient (GRID)

Rajiv Kovil¹, Banshi Saboo², Kiran Shah³, Dakshata Padhye⁴, Dipak Chudasama⁵, Viral Raj⁶, Nida Shaikh⁷

Abstract

Introduction: For the recently introduced single-pill combination of empagliflozin and linagliptin, real-world evidence has not been available. This observational study aims to assess real-world effectiveness of this combination, in the Indian outpatient setting of type-2 diabetes.

Methods: This was a prospective cohort study design, involving patients from 4 centres across western India. Patients with type-2 diabetes and uncontrolled HbA1c, were categorized into 4 groups, including: (1) Naïve to DPP-4i or SGLT-2i; (2) Receiving DPP-4i; (3) Receiving SGLT-2i; (4) Receiving SGLT-2i and DPP-4i as individual pills. Patients were initiated on the fixed-dose combination of empagliflozin + linagliptin, and followed-up over 12-week duration. Clinical parameters of changes in glycaemia, body-weight, and blood-pressure were observed.

Results: 251 patients were included in the analysis, with just over half of them being males (57%), or having pre-existing cardiovascular disease (54%). The group-wise patient distribution was approximately 47%, 18%, 15%, and 20% respectively. The study represented patients across broad range of duration of type-2 diabetes, use of background antidiabetic therapies, and comorbid cardiovascular risk. The use of combination demonstrated significant and clinically meaningful reductions in HbA1c, fasting and postprandial glycaemia levels across all the study groups. Reductions in body-weight and blood-pressure levels were also demonstrated. Interestingly, patients in group 4, who were switched from free drug combination to the fixed-dose combination, also demonstrated significant and meaningful improvements in HbA1c, fasting as well as postprandial glycaemia levels, suggestive of possible improvement in medication-adherence.

Conclusion: This real-world evidence complements the results observed in randomized controlled trials, for meaningful effectiveness with the use of empagliflozin-linagliptin fixed dose combination in the Indian outpatient setting. More evidence may facilitate further characterization of clinical value of this promising combination.

Introduction

The prevalence rates of diabetes and other metabolic diseases is steadily increasing in developing countries like India. Diabetes, obesity, and hypertension are no longer diseases of the affluent nations. The epidemiological transition occurring in the India, The rapid urbanization and economic development in India, has led to an epidemiological transition, and made it one of the epicentres of the diabetes epidemic. The increasing prevalence is not the only concern in India. According to the ICMR-INDIAB study (Phase 1), good glycemic control (HbA1c <7%) was observed only in 31.1% of urban and 30.8% of rural subjects. The study concluded that glycemic control among subjects with self-reported diabetes is poor in India, with less than a third of subjects exhibiting good glycemic control and a significant proportion having HbA1c levels>10%, even in urban areas.

The standard pharmacotherapy for management of type 2 diabetes mellitus (T2DM) involves initiation with monotherapy (usually metformin) unless there are contraindications or intolerance, followed by sequential addition of other single agents, when target glycaemic control is not achieved or maintained for 3 months. The two relatively recent classes of oral anti-diabetic medications, namely SGLT-2i (Sodium glucose co-transporter 2 inhibitors) and DPP-4i (Dipeptidyl peptidase-4 inhibitors) have been commonly used in diabetes management because of their individual benefits based upon appropriate patient selection. A common advantage of both these classes is the low risk of hypoglycaemia and no additional weight gain. However, each individual agent may not be able to lower the HbA1c by more than 1%. Recent guidelines recommend the initial use of a combination therapy when the HbA1c is 1.5% above the target. Early use of combination therapy leads to optimal glycemic control and better outcomes earlier compared to the staggered treatment approach. Fixed dose combinations offer the advantages of improved patient adherence, patient satisfaction and lower overall healthcare costs. When the need for fixed dose combinations has been established, drugs with complementary mechanisms of action

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should be employed for optimum glycaemic control.

A fixed dose combination of SGLT-2i and DPP-4i, such as Empagliflozin and Linagliptin offers good glycemic control, early achievement of goal HbA1c, and pleiotropic benefits such as weight loss, and blood pressure reduction. This combination has been in use in India since a year. There is evidence on this combination from various RCTs, however there is no real world evidence, especially from India. Real-World Evidence (RWE) can be helpful in bridging this knowledge gap. For any intervention, while the RCTs provide conclusive evidence of efficacy on a specific aspect of therapy, the RWE studies provide suggestive evidence of effectiveness for several aspects of therapy, involving broader patient groups. The present study aims to generate real-world data from the use of this combination in clinical practice across India.

Methods

This was an observational study planned across four centres in India. A total of 251 patients were initiated on the fixed dose combination of Empagliflozin and Linagliptin and followed up for 12 weeks. The study was initiated in August 2018 and the last patient to complete follow-up was in January 2019. Patients initiated on the FDC were categorized into four groups-

1. Patients naïve to DPP-4i or SGLT-2i use
2. Patients previously using DPP-4i
3. Previous users of SGLT-2i
4. Patients already using SGLT-2i and DPP-4i individually being switched over to the FDC

HbA1c, Fasting and Post-prandial blood sugar levels, weight and BP were recorded and compared at the end of 12 weeks. Use of antidiabetic medications at baseline was also noted. Duration of diabetes mellitus and prevalence of other comorbidities was also accounted for.

Primary endpoint

Change in HbA1c levels from baseline at the end of 12 weeks in the total population.

Secondary endpoints

- Change in HbA1c levels at the end of 12 weeks in each of the four subgroups
  - Change in fasting and post-prandial blood sugar levels at the end of 12 weeks.
  - Change in body weight at the end of 12 weeks.
  - Change in systolic and diastolic blood pressure at the end of 12 weeks.

Statistical Analysis Plan

Categorical variables are expressed as Number of patients and percentage of patients. Continuous variables are expressed as Mean, Median and Standard Deviation and compared across the groups using Mann-Whitney U test. Over time comparison is done using Wilcoxon Signed Ranks Test.

The statistical software SPSS version 20 has been used for analysis. An alpha level of 5% has been taken, i.e. if any p value is less than 0.05 it has been considered as statistically significant.

Results

Of the 251 patients in the study, 143 were males (57%) and 108 were females (43%). The mean age of patients was 56.78+ 10.80 years. The median duration of type 2 diabetes mellitus is 6.16 years. At baseline, 136 patients (54.2%) patients had a pre-existing cardiovascular disease. Of the total patient-population, 118 patients were naïve to both SGLT-2i and DPP-4i at baseline. 46 patients were naïve to SGLT-2i and 38 of them were naïve to DPP-4i. 49 patients were receiving SGLT-2i and DPP-4i as individual drugs and were interchanged with the fixed-dose combination.

Overall population

At the end of 12 weeks, the mean change in HbA1c in the overall population was -1.11% (Mean Baseline HbA1c=8.86%). The mean change in fasting blood sugar levels was -32.8mg/dl (Mean Baseline= 176.2mg/dl). The mean change in post-prandial blood sugar levels was -60mg/dl (Mean Baseline PPG= 245.4mg/dl). The mean weight change at the end of 12 weeks was -1.8 kg (Mean baseline weight= 81.8 kg). The mean change in systolic blood pressure was -5.3 mm Hg (Mean baseline SBP=133 mm Hg). The mean change in diastolic blood pressure was -2.4 mm Hg (Mean baseline DBP=81.2 mm Hg). Each of these changes were statistically significant with a p value of <0.001.

Group 1: Naïve to both (SGLT-2i and DPP-4i)

In the subgroup of patients naïve to both SGLT-2i and DPP-4i, at the end of 12 weeks, the mean change in HbA1c was -1.2% (Mean Baseline HbA1c=8.81%). The mean change in fasting blood sugar levels was -35 mg/dl (Mean Baseline= 177.8mg/dl). The mean change in post-prandial blood sugar levels was -45mg/dl (Mean Baseline PPG= 214.5mg/dl). The mean weight change at the end of 12 weeks was -1.6kg (Mean baseline weight= 76.5kg). The mean change in systolic blood pressure was -4mm Hg (Mean baseline SBP=133.1 mm Hg). The mean change in diastolic blood pressure was -1.6 mm Hg (Mean baseline DBP=81.2 mm Hg). Each of these changes were statistically significant with a p value of <0.001.

Group 2: Naïve to SGLT-2i

In the subgroup of patients naïve to SGLT-2i and, at the end of 12 weeks, the mean change in HbA1c was -1.16% (Mean Baseline HbA1c=8.59%). The mean change in fasting blood sugar levels was -34 mg/dl (Mean Baseline= 169.9 mg/dl). The mean change in post-prandial blood sugar levels was -62 mg/dl (Mean Baseline PPG= 245.4mg/dl). The mean weight change at the end of 12 weeks was -1.8 kg (Mean baseline weight= 81.8 kg). The mean change in systolic blood pressure was -5.3 mm Hg (Mean baseline SBP=133 mm Hg). The mean change in diastolic blood pressure was -2.4 mm Hg (Mean baseline DBP=81.2 mm Hg). Each of these changes were statistically significant with a p value of <0.001.

Group 3: Naïve to DPP-4i

In the subgroup of patients naïve to DPP-4i and, at the end of 12 weeks, the mean change in HbA1c was -1.3% (Mean Baseline HbA1c=9.71%). The mean change in fasting blood sugar levels was -29.6 mg/dl (Mean Baseline= 189.9 mg/dl). The mean change in post-prandial blood sugar levels was -45mg/dl (Mean Baseline PPG= 248.2mg/dl). The mean weight change at the end of 12 weeks was -1.6kg (Mean baseline weight= 87.2 kg). The mean change in systolic blood pressure was -5.3 mm Hg (Mean baseline SBP=137.8 mm Hg). The mean change in diastolic blood pressure was -2 mm Hg (Mean baseline
DBP=83.2 mm Hg). Each of these changes were statistically significant with a p value of <0.001.

Group 4: Interchange to FDC

In the subgroup of patients already on SGLT-2i and DPP-4i, interchanged to the fixed drug combination, at the end of 12 weeks, the mean change in HbA1c was -0.6% (Mean Baseline HbA1c=8.37%). The mean change in fasting blood sugar levels was -20 mg/dl (Mean Baseline= 159.9 mg/dl). The mean change in post-prandial blood sugar levels was -37 mg/dl (Mean Baseline PPG= 214.9 mg/dl). Each of these changes were statistically significant with a p value of <0.001. The mean weight change at the end of 12 weeks was -1 kg (Mean baseline weight= 77.4 kg). The mean change in systolic blood pressure was -1.2 mm Hg (Mean baseline SBP=125.6 mm Hg). The mean change in diastolic blood pressure was -0.6 mm Hg (Mean baseline DBP=78.86 mm Hg).

Discussion

Diabetes is a progressive metabolic disorder. Metformin, combined with lifestyle modifications, is considered as the first pharmacological option. In most cases, monotherapy fails to reach or maintain target glycated haemoglobin (HbA1c) with time. Thus, combination therapy is recommended soon or later in T2D. Various pharmacological approaches may be added to metformin as dual therapies or combined together as triple therapies, among which dipeptidyl peptidase inhibitors (DPP-4i) and/or sodium-glucose cotransporter type 2 inhibitors (SGLT2i) play an important role (Scheen 2016).

This study evaluated the effectiveness of the fixed dose combination of empagliflozin and Linagliptin in the real-world setting. The efficacy of the combination was similar to that observed in clinical trials. The patient baseline characteristics are highly representative of day-to-day clinical practice. The median diabetes duration was 6.16 years with a mean age of 56.78 years. The patients were either naïve to both the drug classes, or were receiving a DPP-4i and were started on the combination; rather than adding another SGLT-2i or they were receiving an SGLT-2i and were put on the combination instead of adding a DPP-4i separately. The results in each of these groups are comparable in terms of HbA1c lowering, reduction in fasting and post-prandial blood glucose, weight, systolic, and diastolic blood pressure. The findings in each of the subgroups and the overall population are statistically significant at the end of 12 weeks as compared to baseline. The findings represent a real-world setting where it may be practical to replace a failing regimen with a fixed-dose combination instead of adding another agent and increasing the pill burden which may reduce adherence.

There was another subgroup where patients were already receiving an SGLT-2i and a DPP-4i as individual agents and were replaced with a fixed dose combination of empagliflozin and Linagliptin. In this subgroup as well, an HbA1c reduction of 0.6% was observed which was statistically significant. Replacement of two individual agents with a fixed dose combination is known to improve medication adherence and this improvement in HbA1c may be attributed to it. Each of the other parameters except the blood glucose levels had a marginal change.

Over 45% patients in this study did not have a pre-existing cardiovascular disease, and thus the therapy was not limited to patients with established cardiovascular disease. The therapy was started in patients with early T2D, right after metformin, as second-line; in others as third line or beyond, in certain patients with insulin, as well as used as replacement therapy. Thus, the findings of this study may be generalized to a broader population with evidence of its effectiveness across all subgroups.

This is the first real-world study with the fixed-dose combination in India across multiple centres in a broad range of patients. It included patients with early as well as long-standing T2D; and patients with or without cardiovascular disease. The efficacy of the combination is well-studied in RCTs; however its effectiveness in the real-world setting compliments to the existing evidence and reassures the clinician.

This study primarily provides insights on the efficacy parameters and pleiotropic benefits in terms of weight and blood pressure reduction with the combination. Further analysis on the incidence of adverse events, particularly possible reduction in genitourinary infections may provide further insights on the use of this combination.

Conclusion

Treatment of T2D most often requires the combination of several glucose-lowering agents to tackle the various pathophysiological defects of the disease and maximize the chance of reaching individual HbA1c targets. The combination of Linagliptin (a DPP-4i) and Empagliflozin (a SGLT2i) is attractive because their complementary modes of action contribute to improve blood glucose control in patients with T2D without deteriorating the safety/tolerance profile of each compound (on the contrary, a reduction in some adverse events may be expected). Findings from the real-world complement the results from trials albeit in a broader population. Large real-world studies may add further value to the pool of evidence with this relatively new combination.

References

COVID-19 Care in India: Evolving Paradigms from Public Health to Critical Care

Shashank R Joshi

Abstract
COVID-19 pandemic in India has rapidly grown though we have a low case fatality rate, high recovery rate and large population is asymptomatic or presymptomatic. Public health measures to close the tap across the country need hyper vigilance and follow simple dictum of aggressive testing, tracing and isolation. The covid cases need an early diagnosis with treat and care model. Most can be managed with home isolation under telemedicine supervision with oxygen saturation screening by a simple six minute walk test. Hospitalised cases have emerging evidence in different therapies from antivirals, steroids, immunologic to heparins but high flow oxygen, prone position and supportive care remains the cornerstone in critical care with nursing and nutrition. Vaccine research is ongoing but currently only social vaccine can mitigate the pandemic. Covid appropriate behaviour of Masking, sanitisation and physical distancing with immune modulating behaviour like adequate sleep, digital detox for two hour and clean well ventilated environment is the key with breathing exercises including yoga and positive mental health and avoidance of crowds the only vaccine to live with COVID-19 today.

As COVID-19 pandemic enters in its tenth month even today the corona virus (SARS COV2)is predictably unpredictable both in its virology and immunological response. India has rapidly peaked in the last few months at more than five million cases though the disease has been asymptomatic or mild in most cases. Most Indians have strong immunity but our vulnerable populations namely the elderly or the ones with co morbidies like diabetes or hypertension or obesity one still need vigilance and possibly reverse isolation of this cohort to save their lives. Indians have when compared globally a lower case fatality rate and better recovery rate. Independent of all the advances in medical treatment of COVID 19 which include access to latest antivirals,steroids or immunologics, plasma, nasal Oxygen in prone position as well as advance critical care facilities for the most needy we still need to close the tap at the base of the pandemic which is break the chain of transmission. “In order to break the chain of transmission and close the COVID 19 tap the only way to close it is to have an alert well behaved citizen with a hyper vigilant public health system in each city, town and village of one of the most densely populated countries on planet earth.” In order to close the COVID-19 tap we need to test aggressively and early at the first suspicion or symptom to limit further exposure and transmission by isolation. The test has to preferably RT PCR (which can still be negative in 30 percent cases) is still the gold standard but the rapid antigen test is quicker to detect and diagnose Covid in few hours.Unfortunately a negative antigen test must merit RT PCR test or a close follow up with isolation till we prove that suspected case does not progress into COVID-19. The cycle threshold value of RT PCR (CT value: number of cycles to detect the virus) has been set by IMCR to 40 though now we know the infectivity cut off could well be below 24 and lower values indicate higher viral load (usually picked up by antigen test). However caution is needed to use this CT value for treatment as a well validated as tool (currently in research mode). Every human must self-protect and protect all their near and dear ones they are in contact with when they suspect. Self-protection and COVID appropriate behaviour is the key so please isolate and contact your physician immediately even via telehealth is the key to disease limitation. The biggest challenge is asymptomatic carriers which are often our children and younger generation which must ensure that they do their SMS all the time, especially the sanitisation, masking and social distancing. Avoiding crowded clusters and poorly ventilated spaces the key. The eating places one tends to unmask and eat and in public places poses a risk which everyone needs to be careful with. Toilets especially in public and office spaces are another focal point of transmission. So citizens need to take care of themselves as we unlock gradually India. But to close the tap mere testing and Covid appropriate behaviour is not enough. We need a hyper vigilant public health system which traces each and every contact of the positive case and isolates them. Only way to truly contain the virus is to to aggressive tracking and tracing every single contact and ensuring they are supervised and testing. Often this may be mandate door to door surveillance. Unfortunately this step needs people’s voluntary cooperation and participation and unless we have a popular movement we will again fail to contain the pandemic and close the tap.

The next step to close the COVID-19 tap is Isolation Isolation is the next key step where home or institutional are the options. Most can home isolate and self-protect if they are below 55 years and do not have comorbidities but
with constant teleconnect with your physician. All asymptomatic Covid 19 cases that home isolate must be very careful for 14 days as the second week often they can suddenly deteriorate due to happy hypoxia. Every home isolated case should have a separate room with a toilet, 24 x 7 connectivity with a medical or health care provider and a simple pulse oxygen monitor and thermometer. If twice a day under medical clearance a six minute walk test is done and the oxygen saturation does not drop below 3 percent or below 94 percent. However if the person gets breathless or symptomatic or the oxygen saturation drops then you need to rush to an oxygen health care facility or hospital. Home care for covid has evolving protocols. Most cases can have atypical symptoms beyond dry cough, dysnoea and fever like anosmia, change or lack of taste (often bitter taste is preserved), myalgia, fatigue, diarrhoea, chills, rashes etc. Usually cases with smell or taste recover well. A simple hand grip test to test strength can also be used. Its imperative to identify the progressors to moderate to severe covid and if any interventions can limit it. At home usually most important is clean, well ventilated environment with positive mental health and good high protein diet apart from vitamin D, vitamin C, zinc apart from many herbs (Turmeric, Tulsi etc) with mouth-throat gargling and steam inhalation. Evidence base on this is compelling only in a few like vitamin D, vitamin C or zinc while rest is emerging or anecdotal which is the constant narrative in this pandemic. Nutrition and dietary habits especially proteins and food diversity is the key and occasionally oral nutritional supplements can also help. Key to Covid management is the lungs and respiratory exercises including yogic kriyas, pranayama including steam inhalation have role but need evidence base generation. Prone positioning often difficult in obese hypoxic individuals is a key in success of supportive care. Adjuvant therapies of low dose aspirin, novel oral anticoagulants, statins or fibrates have role but many other treatment options like montelukast or inhaled steroids like ciclesonide etc need evidence base generation. Most repurposed virus directed therapies have low level of evidence but need better validation especially from hydroxychloroquine, azithromycin, doxycycline, ivermectin, nitonoxide but can’t be ruled out or shunned out till we prove or disprove their efficacy and safety with good quality trails. Currently most of them are in research mode. These repurposed drugs also had some antivirals like lopinavir, ritonavir, oseltamivir which now have now been eased out from covid care. Favipiravir a Japanese oral antifufl medication possibly may improve if used early the viral clearance in a week or more but awaits larger data generation and clinical trails. Favipiravir is best used in the first 72 hours of the illness in mild disease but it remains to be seen if it can alter outcomes or impacts mortality. Steroid should be avoided in home isolated cases unless impending hypoxic situation is predicted and case is awaiting hospitalisation.

Often aggressive co-morbidity care helps especially monitor blood glucose and blood pressure and keep them to goal can be the key to save lives. ICP ICP have formulated recommendations for comorbidities like Heart disease, hypertension, obesity and diabetes. Home monitoring should usually include some basic tests like complete blood count (which include neutrophil to lymphocyte ratio) as well as C reactive protein (CRP) with ferritin and lactate dehydrogenase are sufficient. IL 6 levels are often misleading if not collected, transported or done correctly though if done properly may have a role. D dimer is another key marker which is often useful to unmask coagulopathy. Role of HRCT or sonography is often restricted to hospitalised cases and in suspect negative cases in the community. Simple X-ray chest with artificial intelligence based algorithms and tools can often have a high yield and are undergoing testing. The most sensitive test to unmask happy hypoxia is the six minute walk test to diagnose occult hypoxia and triage the patient for oxygen support to a health care facility. 

Managing COVID-19 cases which are moderate, severe and critical care is the most challenging part today during to emerging pandemic, with varying degrees of evidence base, often expert opinion and loco regional practises. This is the space which has only shown three strong evidence based treatment options clearly one being supportive care with prone position helps, two oxygen especially high flow nasal oxygen and finally dexamethasone in oxygenated especially mechanically ventilated cases. In moderate to severe cases there is a role if used early possibly to improve recovery time of remdesivir for five days only though the evidence on its final verdict may still change in the future. Plasma therapy which is more than a century old can effectively neutralise the virus has unfortunately not impacted in the evidence base space still but more data may emerge if used early. Plasma therapy trails hold promise. The role of Low molecular weigh heparins and heparins in covid coagulopathy is clearly compelling and life saving but await validation in a randomised controlled study.
securing higher amounts of IFNγ, TNFa, IL-2, and IL-17 compared with non-COVID controls. This cytokine profile suggests that the aberrant T cell responses are skewed towards the Th1 and Th17 phenotypes. This subset would not be sensitive to steroids, but may be sensitive to anti-CD6 blockade or other immune-based interventions. Common targets for inhibition include IL6, IL1 family (IL1 β, IL18), TNF α, IFN μ and JAK pathways apart from anti CD6 blockade. The anti cytokine therapies have also got mixed results or are still emerging. Single cytokine IL6 blockers like Tocilizumab has no data to support mortality impact in a single RCT but may enhance recovery. IL6 blockers like Tocilizumab has no data to support mortality impact in a single RCT but may enhance recovery. The anti cytokine pathways early in the immune cascade impact the CD6 pathway and activated ALCAM pathways in CD6 pathway and activated leukocyte cell adhesion molecule - ALCAM pathways early in the immune cascade may have a clear scientific role in the pathophysiology of the storm. Currently it has a small pivotal phase two data with an emergency use label and a study from Cuba. Itolizumab needs better validation in the future and may be the monoclonal biologic to watch for. Many other covid specific antibodies are under investigation. As immune systems in covid cooveract creating a thrombin inflammatory cascade many targeted therapies are being experimented to block some key enzymes. White blood cells release NETS-“neutrophil extracellular traps” to esnare and kill pathogenic microbes. Many drugs which target NETS like Fostamatinib, etc. are undergoing trials. Bruton tyrosine kinase - BTK inhibitors like Acalabrutinib and others are also undergoing research.

Understanding the thromboinflammatory nature as well as immunology of the cytokine / bradykinin covid storm will be the key to device life saving strategies to mitigate the storm. It’s imperative to build pragmatic adaptive real world trails to document evidence base on areas like recovery time, mortality as well as viral clearance time. Mechanical ventilator and ECMO are still the final critical stops and better supportive and critical care nursing can improve outcomes. The role of early enteral nutrition as well as parenteral nutrition to improve length of stay, ventilator time and mortality also need careful scrutiny and may have role in outcomes.

Post covid recovery is often impacted by fatigue, pulmonary fibrosis, neurological as well as cardiac issues including post covid inappropriate sinus tachycardia and many other complications. Mental health needs post covid care as many suffer from post traumatic stress disorder. Vaccines in covid care in India has 3 candidates in trails. The DNA based yzudus cadila vaccine with DBT, the IMCR -Biotech Biotech adenovector vaccine and the Oxford-Astra-Serum institute vaccine are in different stages of the trails but possibly be ready for use hopefully by early 2021. Vaccines need strong pharmacovigilance and support and when fast tracked need safety issues to be closely supervised. Pauses for safety should not lead to fear or panic but should reassure that best practices are being followed.

This pandemic has clearly identified our senior citizens and people living with comorbidities and chronic illness which need maximum care and attention. However we should never lose focus on the youth or children as well as they can also get the disease occasionally or they are potential spreaders or super spreaders. COVID-19 tap can only be closed by dual participation of both our population and public health system working as one team for India. The key is aggressive testing, tracing with tracking and isolation apart from prompt treatment and care for those who need it. Equally important is to avoid crowded spaces, poorly ventilated environments and ensure we Mask with strict distancing and hygiene. Remember your health is in your own hands it’s time to protect our own self and protect other with the new mantra “Covid appropriate behaviour” of masking with hygiene and distance and avoiding crowds or poorly ventilated spaces.

References

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Continuing Burden of Rheumatic Heart Disease in India

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Abstract
Rheumatic heart disease (RHD) disables millions in Asia and Africa. Epidemiological data and clinical studies in India have reported a significant decline in its prevalence in last century. Global Burden of Disease (GBD) study estimated that RHD in India led to 395/100000 disability adjusted life years (DALYs) and 9.2/100000 deaths in 1990. This declined to 780/100000 and 7.9/100000, respectively, in 2017. The Million Death Study evaluated serial trends in cardiovascular deaths and it contributed to one-third of global RHD burden. RHD in India led to 3.44 million DALYs and 80,470 deaths which has increased to 3.73 million DALYs and 108,460 deaths in 2017. India Disease Burden Initiative has reported high RHD burden in many less developed states of the country, e.g., Bihar, Odisha, Assam, Chhattisgarh, Uttar Pradesh, etc. Echocardiographic epidemiology studies have reported high burden of subclinical RHD. Significant proportions of patients in hospital-based echocardiographic clinics have RHD and it contributes to 25-45% of cardiac surgeries in government hospitals. The continuing burden of RHD needs proper public health and clinical response.

Introduction
Rheumatic heart disease (RHD) is included in the neglected diseases of tropics and is an endemic cardiovascular disease (CVD) among the poorest billion of the globe. A spectacular success has been achieved in control of RHD globally—especially in temperate countries of Western Europe and North America—but this condition continues to be prevalent in tropical countries of Asia and Africa. A front-page review in the New York Times has placed RHD at the center of global health agenda.

Decline in RHD in developed countries has been due to socioeconomic progress leading to better environmental and personal sanitation, less crowded housing and economic prosperity. For example, in USA the incidence per 100,000 population was 100 at the start of 20th century, declined to 45 to 65 between 1955 and 1960 and currently is less than 10 cases/100,000. Better management of streptococcal sore throat infections and widespread use of penicillin have also contributed to the eradication. However, recent data from World Health Organization (WHO), Global Burden of Disease (GBD) study, World Heart Federation and others have highlighted persistent burden of this condition in South Asia, Middle East, Eastern Europe, Africa and indigenous communities of Australasia. In this qualitative narrative we debate the assumption that RHD is declining in India, highlight regional variation in RHD in the country and document the continuing burden of streptococcal throat infections and RHD in India. We posit that RHD poses a continuing burden on health systems and health care professionals in the country.

Declining RHD Burden

Global Burden of Diseases Study
GBD Study estimated that there has been a decline in RHD in terms of disease burden measured as disability adjusted life years (DALYs)/100,000 as well as mortality rates/100,000 globally as well as in high-burden countries. The data are shown in Table 1. Globally, in 1990 RHD was responsible for 12.4 million DALY’s and 336,000 deaths. This declined in 2005 to 10.3 million DALY’s and 292,000 deaths, and in 2017 to 9.4 million DALY’s and 285,000 deaths. Substantial inter-country variation exists in incidence of rheumatic fever and prevalence of chronic RHD globally. Table 1 shows that the highest population burden in term of DALYS, DALYS/100,000, death and death rates is in countries of South Asia, Africa and Central Asia. In many of these countries there has been a decline in RHD burden (mortality and DALY rates) but not in absolute numbers.

In India, clinical observations and anecdotal evidence suggest that acute rheumatic fever as well as RHD are declining. Estimates of RHD burden and mortality in India are available at GBD Study website. Interrupted time-series estimates from the year 1990 to 2017 are shown in Table 2. There is significant decline in RHD/per 100,000 population DALYs and deaths. However, in terms of absolute numbers, disease burden (DALY) as well as mortality are increasing (Figure 2).

Multiple limitations of GBD study have been reported earlier, including limited data from most of the countries and limitation of geospatial multiple regression. Outcome-data from India are based on computer modeling and may not reflect the true situation. The Million Death Study evaluated serial trends in cardiovascular deaths from the years 2003 to 2015 using nationally representative data from Registrar General of India and Sample...
It was reported during this period, overall CVD mortality rates increased in India. Mortality from ischemic heart disease increased while from cerebrovascular disease declined. No data regarding trends in RHD mortality in India were available in this study.

### School-Based Clinical Surveys

There have been a number of population based and school based epidemiological studies to determine the prevalence of RHD in India. These studies have been reviewed earlier. Community based surveys were performed in Delhi, Agra and Chandigarh in 1960’s and included men and women 5-30 years of age. The prevalence of rheumatic fever and RHD was in Delhi 5.1/1000, Agra 7.2/1000 and Chandigarh 2.1/1000. A clinic-based opportunistic survey in rural populations of Haryana in 1990’s reported the prevalence of 0.1/1000.

Multiple school based surveys for determining prevalence of RHD among children 5-15 years have been performed at various sites in India from 1950’s to 1980’s. All these surveys relied on clinical examination for determining prevalence of rheumatic fever and RHD. These studies are listed below (Table 3) and reported prevalence rate of 1-11/1000 with only a few locations reporting higher prevalence, e.g., Shimal 39.6/1000. Recent surveys using clinical criteria for diagnosis of RHD also have reported variable prevalence rates across the country. Methodological issues are important in school based surveys. Multiple biases in these studies include selection bias, reporting and evaluation bias, and, therefore, these surveys may not truly reflect the burden of RHD among Indian children. Moreover, clinical evaluation tends to over-diagnose RHD as many children suffer from innocent systolic murmurs due to a variety of non-cardiovascular causes.

Studies that used initial clinical suspicion followed by echocardiographic evaluation for...
Table 3: Prevalence of clinical rheumatic heart disease in school based surveys in India

<table>
<thead>
<tr>
<th>First author (Year reported)</th>
<th>Site</th>
<th>Sample size</th>
<th>Age-range</th>
<th>Prevalence / 1000</th>
</tr>
</thead>
<tbody>
<tr>
<td>Athavale (1958)</td>
<td>Bombay</td>
<td>1004</td>
<td>3-19</td>
<td>2.0</td>
</tr>
<tr>
<td>Rao (1961)</td>
<td>Vellore</td>
<td>1281</td>
<td>5-16</td>
<td>7.0</td>
</tr>
<tr>
<td>Padmavati (1962)</td>
<td>Delhi</td>
<td>1317</td>
<td>5-14</td>
<td>1.5</td>
</tr>
<tr>
<td>Devichand (1963)</td>
<td>Shimla</td>
<td>1315</td>
<td>1-16</td>
<td>39.6</td>
</tr>
<tr>
<td>Zaathe (1973)</td>
<td>Aligarh</td>
<td>9155</td>
<td>3-15</td>
<td>3.9</td>
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<tr>
<td>Malhotra (1973)</td>
<td>Calcutta</td>
<td>10874</td>
<td>7-18</td>
<td>4.6</td>
</tr>
<tr>
<td>ICMR (1977)</td>
<td>Delhi</td>
<td>34198</td>
<td>5-16</td>
<td>11.0</td>
</tr>
<tr>
<td>Sharma (1978)</td>
<td>Amrisril</td>
<td>500</td>
<td>12-19</td>
<td>1.0</td>
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<tr>
<td>ICMR (1980)</td>
<td>Alleppy</td>
<td>28359</td>
<td>5-16</td>
<td>5.1</td>
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<td>Koshi (1981)</td>
<td>Vellore</td>
<td>3890</td>
<td>4-16</td>
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<tr>
<td>ICMR (1982)</td>
<td>Agra</td>
<td>29922</td>
<td>5-16</td>
<td>5.1</td>
</tr>
<tr>
<td>Patel (1986)</td>
<td>Anand</td>
<td>11346</td>
<td>5-15</td>
<td>2.0</td>
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<tr>
<td>Avasthi (1987)</td>
<td>Ludhiana</td>
<td>6005</td>
<td>6-16</td>
<td>1.3</td>
</tr>
<tr>
<td>Kumar (1992)</td>
<td>Churu</td>
<td>10168</td>
<td>5-15</td>
<td>3.3</td>
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<tr>
<td>Gupta (1992)*</td>
<td>Jammu</td>
<td>10263</td>
<td>6-16</td>
<td>1.4</td>
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<td>Grover (1993)*</td>
<td>Ambala</td>
<td>31200</td>
<td>5-15</td>
<td>1.1</td>
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<tr>
<td>Vashishta (1993)*</td>
<td>Agra</td>
<td>8449</td>
<td>5-15</td>
<td>1.4</td>
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<tr>
<td>ICMR (1994)</td>
<td>Ballabhgarh</td>
<td>22729</td>
<td>5-15</td>
<td>1.0</td>
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<tr>
<td>Padmavati (1995)</td>
<td>Delhi</td>
<td>40000</td>
<td>5-10</td>
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<tr>
<td>Agarwal (1995)</td>
<td>Aligarh</td>
<td>3760</td>
<td>5-15</td>
<td>1.4</td>
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<tr>
<td>Thakur (1996)</td>
<td>Shimla</td>
<td>15080</td>
<td>5-16</td>
<td>3.0</td>
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<tr>
<td>Jose (2003)*</td>
<td>Vellore</td>
<td>229829</td>
<td>6-18</td>
<td>0.7</td>
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<tr>
<td>Kaul (2006)*</td>
<td>Srinagar</td>
<td>4125</td>
<td>5-15</td>
<td>5.1</td>
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<tr>
<td>Periwal (2006)*</td>
<td>Bikaner</td>
<td>3292</td>
<td>4-18</td>
<td>0.5</td>
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<tr>
<td>Misra (2007)*</td>
<td>Gorakhpur</td>
<td>118212</td>
<td>4-18</td>
<td>0.6</td>
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<tr>
<td>Soman (2010)*</td>
<td>Kochi</td>
<td>25033</td>
<td>5-16</td>
<td>0.1</td>
</tr>
<tr>
<td>Negi (2013)</td>
<td>Shimla</td>
<td>15145</td>
<td>5-15</td>
<td>0.6</td>
</tr>
<tr>
<td>Rama Kumari (2013)*</td>
<td>Andhra</td>
<td>4213</td>
<td>5-16</td>
<td>8.3</td>
</tr>
</tbody>
</table>

*These studies first identified clinically suspected cases and then confirmed RHD using echocardiography.

Table 4: State level rheumatic heart disease burden (DALY, DALY rates) and mortality (deaths, death rates) in India: Indian Disease Burden Initiative 2016

<table>
<thead>
<tr>
<th>State (alphabetical)</th>
<th>DALY (thousands)</th>
<th>DALY rate/100,000</th>
<th>Deaths (n)</th>
<th>Death rate / 100,000</th>
</tr>
</thead>
<tbody>
<tr>
<td>Andhra Pradesh</td>
<td>152.3</td>
<td>291.8</td>
<td>4304</td>
<td>8.3</td>
</tr>
<tr>
<td>Arunachal Pradesh</td>
<td>2.2</td>
<td>150.4</td>
<td>60</td>
<td>4.0</td>
</tr>
<tr>
<td>Assam</td>
<td>124.2</td>
<td>354.8</td>
<td>3398</td>
<td>9.7</td>
</tr>
<tr>
<td>Bihar</td>
<td>422.2</td>
<td>384.9</td>
<td>12240</td>
<td>11.2</td>
</tr>
<tr>
<td>Chhattisgarh</td>
<td>97.1</td>
<td>351.0</td>
<td>2812</td>
<td>10.2</td>
</tr>
<tr>
<td>Delhi</td>
<td>49.7</td>
<td>240.9</td>
<td>1325</td>
<td>6.6</td>
</tr>
<tr>
<td>Goa</td>
<td>1.5</td>
<td>99.0</td>
<td>46</td>
<td>3.0</td>
</tr>
<tr>
<td>Gujarat</td>
<td>170.6</td>
<td>254.1</td>
<td>4895</td>
<td>7.2</td>
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<tr>
<td>Haryana</td>
<td>70.4</td>
<td>246.0</td>
<td>2017</td>
<td>7.0</td>
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<tr>
<td>Himachal Pradesh</td>
<td>13.1</td>
<td>178.9</td>
<td>411</td>
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<tr>
<td>Jammu and Kashmir</td>
<td>29.3</td>
<td>237.6</td>
<td>816</td>
<td>6.6</td>
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<tr>
<td>Jharkhand</td>
<td>101.1</td>
<td>295.7</td>
<td>2870</td>
<td>8.4</td>
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<tr>
<td>Karnataka</td>
<td>195.4</td>
<td>295.0</td>
<td>5544</td>
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<tr>
<td>Kerala</td>
<td>59.8</td>
<td>161.1</td>
<td>1991</td>
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<tr>
<td>Madhya Pradesh</td>
<td>53.3</td>
<td>319.8</td>
<td>7368</td>
<td>9.3</td>
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<td>Maharashtra</td>
<td>271.1</td>
<td>221.8</td>
<td>8095</td>
<td>6.6</td>
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<td>Manipur</td>
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<td>Meghalaya</td>
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<td>Nagaland</td>
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<td>187.6</td>
<td>123</td>
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<tr>
<td>Odisha</td>
<td>173.8</td>
<td>379.9</td>
<td>5316</td>
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<tr>
<td>Punjab</td>
<td>71.0</td>
<td>236.9</td>
<td>2111</td>
<td>7.0</td>
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<tr>
<td>Rajasthan</td>
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<td>261.3</td>
<td>5653</td>
<td>7.5</td>
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<tr>
<td>Sikkim</td>
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<td>158.3</td>
<td>30</td>
<td>4.3</td>
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<tr>
<td>Tamilnadu</td>
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<td>229.5</td>
<td>5384</td>
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</tr>
<tr>
<td>Telangana</td>
<td>90.5</td>
<td>242.9</td>
<td>2712</td>
<td>7.3</td>
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<tr>
<td>Tripura</td>
<td>14.9</td>
<td>309.6</td>
<td>434</td>
<td>7.3</td>
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<td>Uttarakhand</td>
<td>28.4</td>
<td>265.6</td>
<td>868</td>
<td>8.1</td>
</tr>
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<td>Uttar Pradesh</td>
<td>677.5</td>
<td>312.9</td>
<td>19782</td>
<td>9.1</td>
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<tr>
<td>West Bengal</td>
<td>297.6</td>
<td>290.2</td>
<td>8382</td>
<td>8.2</td>
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</tbody>
</table>

GBD 2017 has estimated that more than one-third of global RHD DALY’s and deaths occur in India as shown in Table 1. India State Level Disease Burden Initiative has reported that although RHD related burden continues to be high, especially in less developed states of the country, its disability and death rates are declining.

**Global Burden of Disease Study**

State specific RHD burden estimates are available at GBD website as part of the India State Level Disease Burden Initiative. There are large variations in RHD burden as estimated by number of DALYs and deaths as well as rates/100,000 across the country (Table 4). Highest absolute burden is in the largest states of the country (Uttar Pradesh, Bihar, West Bengal, etc.). Numbers of DALYs per 100,000 vary from less than 100 in Goa to more than 300 in less developed states such as Assam, Bihar, Chhattisgarh, Madhya Pradesh and Odisha. These data, therefore, indicate persisting RHD burden in empowered action group of states in the country. However, to confirm state-level GBD estimates there is a need for state-based surveys and surveillance systems to exactly assess burden of RHD.

**Echocardiographic Surveys and Subclinical RHD**

An expert group at World Heart Federation has developed more comprehensive echocardiographic criteria for diagnosis of RHD. The criteria have been developed on basis of the best available evidence. Three categories are defined on basis of assessment by two-dimensional, continuous-wave and color-Doppler echocardiography- (a) definite, (b) borderline, and (c) normal. To reflect various disease patterns, four subcategories of definite RHD and three subcategories of borderline RHD have been developed.

Some studies have been performed in India using earlier and recent echocardiographic criteria (Table 5). High prevalence of RHD was reported when usual criteria were used. However, following implementation of World Heart Federation criteria, studies have reported a lower prevalence rate of 5.6-7.7/1000. We performed...
a school-based epidemiological using echocardiography and recent World Heart Federation criteria for diagnosis of RHD. Preliminary data from 1508 children shows a greater prevalence (35.2/1000) compared to contemporary studies (Table 5). Thus echocardiographic studies, show that prevalence of RHD, especially subclinical RHD, among school children varies at different locations. Table 5 shows that the prevalence is significantly greater in Bikaner (Rajasthan) as compared to other locations. This could be an artifact due to either selection bias or methodological issues. Regional variation in RHD has also been reported in the 4-site eRHEUMATIC study in India. In this multisite study of school children 5-15 years of age, the highest prevalence rate/1000 was in Goa (11.4) followed by south Gujarat (9.2), Haryana (7.2) and Manipur (5.4). This variation is similar to that reported in GBD study.

High prevalence of RHD and subclinical carditis among school children using echocardiography has been reported from other countries also. A review reported high prevalence of echocardiographic RHD in Nicaragua (48/1000), Tonga (33.4/1000), Cambodia (21.5/1000) and Mozambique (30.4/1000) which is similar to the recent Indian studies. More studies using echocardiographic methods are needed in India to exactly map the burden of RHD in the country. Such studies should include not only the school going children but also out-of-school children and young adults.

Streptococcal Throat Infections

Streptococcal upper respiratory tract infection is an important global health problem. Role of Group A Streptococcus in pathogenesis of acute rheumatic fever is unequivocal although the molecular pathways are not yet well defined. Evidence supports the view that acute rheumatic fever is result of an autoimmune response to pharyngeal infection with Group A Streptococci in genetically predisposed individuals.

Epidemiological studies have reported regional differences in the prevalence of streptococcal throat infections in India with prevalence varying from 10-15%. A prospective study among slum dwelling school children in Chandigarh in mid-1990’s reported a high incidence of sore throat (7.05 episodes/year) as well as Group A streptococcal sore throat infection (0.95 episodes/year) especially in children living in crowded conditions and exposed to indoor air pollution. An eight-year prospective surveillance study in rural Punjab reported prevalence of rheumatic fever/RHD of 0.8-1.3/1000, rheumatic fever was more common than RHD. The prevalence of Group A streptococcus in selected children was 2% (13/656) in children with sore throat and 0.5% (14/2920) among those not having sore throat. Recent epidemiological studies continue to report significant burden of Group A streptococcal infections in various regions of the country.

Burden on Health Systems

The burden of RHD on health systems can be at multiple levels. The social and economic burden of RHD on individuals, families and regional and national health systems are massive and has been highlighted. Economic burden is also significant but formal assessment of this burden on Indian healthcare system is not available.

Economic burden

Watkins et al estimated economic burden of RHD in low and middle-income countries as part of the Disease Control Priorities-3 Project. The authors conducted a modeling study using data from 107 countries to estimate the economic impact of excess mortality from RHD. The analysis used data from the Global Burden of Disease 2010 study, WHO life tables, UN population estimates and the World Bank macroeconomic indicators such as gross domestic product (GDP) per capita and used them in full-income calculations. The RHD mortality pattern in Costa Rica in 2010 was used to define...
excess mortality. The authors estimated that cost of the approximately 222,000 excess RHD deaths in 2010 was US$ 2·2 trillion (discounted) or US$ 5·4 trillion (undiscounted). Most of the economic burden of RHD was in countries with large populations in South and Central Asia. These estimates are 10–100 times higher than those obtained using other economic methods, such as multiples of GDP per capita per DALY. The authors reported that RHD continues to exert massive economic effects globally, mainly because of premature death in children and working-age adults.

**Primary care**

The exact burden of RHD in primary care in India is unknown. In 1980’s a study in a primary care clinic in Rajasthan evaluated 1362 successive cases with chronic diseases and reported RHD in 110 (8.1%) patients overall and in more than a third of cardiac patients (110/306, 35.9%).

In a surveillance program for pediatric heart diseases in Himachal, Thakur et al. examined 15,080 school children 5-15 years of age. RHD was diagnosed in 45 cases (288/100,000) suggesting a high burden of this condition. Kumar et al determined prevalence of RHD in primary care clinics at a single district in Punjab with a population of 1.1 million. A high prevalence 74/100,000 population (n=813) of RHD was reported. Although lower than the studies among school children, this rate suggests a continuing burden of RHD in primary care.

**Hospital based data**

Hospital-based data from India from 1940s to 1960’s reported that RHD patients comprised 20-40% of all hospital admissions for cardiovascular diseases. Statistics from Employees State Insurance Corporation from multiple hospitals in the country reported a prevalence of RHD varying from 0.4% in Delhi to 18.5% in Orissa, the all India average being 10.6%.

In Vellore, South India, over a thirty year period (1960-89) it was observed that RHD patients as proportion of cardiac admissions remained at about 40%. More recent data have reported a continuing high prevalence of RHD as proportion of cardiovascular disease admissions in Orissa.

**Echocardiographic data**

In absence of recent hospital data regarding RHD admissions to hospitals, we can estimate burden on health systems by study of hospital-based echocardiographic data. We obtained data on RHD patients as proportion of total echocardiograms at representative government and non-government hospitals in Rajasthan from years 2015-2017 (Figure 3). In government hospitals 8-10% of patients undergoing echocardiography have RHD, compared to less than 5% in non-government hospitals. Thus, RHD still poses a significant burden on echocardiographic centres across the country.

**Surgical data**

Non-surgical and surgical interventions are mainstay of treatment for chronic valvular RHD. Balloon mitral valvuloplasty (BMV) has emerged as a treatment of choice for mitral stenosis. At a government tertiary care hospital in Delhi during year 2017, of 8618 cardiac interventions 345 (4.0%) were BMV. In contrast, burden of RHD valve surgeries remains high, especially in the government hospitals. It has been reported that in these hospitals 20-50% of cardiac surgeries are for RHD. This is in contrast to non-government or corporate private hospitals where less than 5-10% of cardiac surgeries are due to RHD.

In India, about 150,000 cardiac surgical procedures are performed annually. The number of RHD surgeries in India is unknown but estimates suggest this to be about 30% of the total data, n= 45,000, implying a huge burden on patients and health systems. Himachal Pradesh RHD Registry (n=2005) reported that only 9.7% of patients with RHD underwent surgery. Clearly the actual burden of RHD surgery on health system shall be much greater if all the eligible patients undergo surgery.

**Conclusion: The Way Forward**

Rheumatic fever and RHD are conditions of poverty and are largely preventable. Decline in RHD in most temperate countries has been achieved by addressing social determinants of health such as poverty, illiteracy, overcrowded housing and sanitation. Relevant to RHD prevention are ending poverty in all its forms, ensuring healthy lives and promoting well being for all at all ages, achieving universal health coverage, ensuring inclusive and equitable quality education, making cities and homes inclusive, safe, resilient and sustainable.

World Heart Federation has enumerated five key targets for control of RHD. These include: (a) development of comprehensive registry based control programs, (b) providing global access to benzathine penicillin, (c) identification of RHD champions to deliver messages for prevention, (d) better training of healthcare professionals for RHD management, and (e) support for vaccine development. Subsequently, the Cairo Accord on RHD has outlined multiple approaches for its control. These include enhancing existing databases for better understanding the epidemiology and natural course of RHD, provision of high quality benzathine penicillin to endemic areas for treatment of suspected streptococcal throat infections, accelerating development of regional centers of excellence, enhancing efforts to produce an effective vaccine, study of genetic
profile of rheumatogenic streptococcal strains and susceptible individuals, development of biomarkers for early diagnosis and follow-up, evaluation of newer anti-inflammatory and immunomodulatory drugs, optimal therapy for prophylaxis against thromboembolism and management of heart failure, dedicated training programs for valve repair procedures and efforts to develop easily implantable tissue engineered valves.

In India we need to health programs focused on social determinants of health including health-in-all-policies approach for RHD prevention and control. This approach should focus on inter-ministerial approaches at central and state levels to reduce poverty, provide quality education, promote hygiene, curb indoor and outdoor environmental pollution, improve maternal and fetal nutrition and provide universal health coverage. Government should act as “champions” to realize the global goal of elimination of RHD. The Indian Universal Health Care (UHC) program must include prevention and control of RHD as important priority at primary care. Only then the continuous burden of RHD in India can be controlled.

References

10. Government should act as “champions” to realize the global goal of elimination of RHD. The Indian Universal Health Care (UHC) program must include prevention and control of RHD as important priority at primary care. Only then the continuous burden of RHD in India can be controlled.
Takayasu Arteritis Masquerading as Resistant Hypertension and Tuberculosis

Dilip Kumar R¹, Adhiti K²

Abstract

We here report a case of Takayasu arteritis who came to us with uncontrolled hypertension, arm claudication and a history of Pott’s spine (treated). She was treated with steroids which led to significant improvement in the patient’s clinical profile.

Introduction

Takayasu arteritis is an uncommon disease affecting approximately 2.6 cases per million population. The disease is relatively common in Asians, especially women. The exact prevalence of the disease in India is not known. Takayasu arteritis is a disease of large and medium sized arteries with maximum predilection towards the branches of the aortic arch. Most of the patients with takayasu arteritis are known to have active tuberculosis or history of tuberculosis and whether there is etiological association with tuberculosis or not is yet to be elucidated.

We here report an interesting case of Takayasu arteritis who presented with right arm claudication due to involvement of right subclavian artery and uncontrolled resistant hypertension due to involvement of abdominal aorta at the origin of renal artery. She also had a history of Tuberculosis in the form of Pott’s spine. She was treated with Prednisolone and also with antihypertensives which led to significant improvement in her clinical profile.

Case Report

A 28 year old lady presented to us with complaints of severe right arm pain which was steadily increasing in severity since last 2 days. She had history of Pott’s spine 2 years ago for which she was treated with ATT (category 1) for 9 months. She was diagnosed hypertensive an year ago for which she was currently on treatment with a Calcium channel blocker, beta blocker and a thiazide diuretic. Other than that she had a recent history of tubo-ovarian mass which was operated based on clinical suspicion of Tuberculosis. She also had a history of loss of weight (>5% from baseline) with history of nodular rashes in the lower limbs for the past 4 months.

Upon further examination she had unequal pulses between both arms and as well as between the arms and legs. She also had blood pressure difference between the two arms and as well as between arms and legs which turned out to be the clinching point for the diagnosis. Her blood pressure was charted as follows:

<table>
<thead>
<tr>
<th></th>
<th>Right upper limb</th>
<th>Left upper limb</th>
<th>Right lower limb</th>
<th>Left lower limb</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood Pressure</td>
<td>60/30 mm Hg</td>
<td>214/142 mm Hg</td>
<td>176/132 mm Hg</td>
<td>168/134 mm Hg</td>
</tr>
</tbody>
</table>

with complaints of severe right arm pain which was steadily increasing in severity since last 2 days. She had history of Pott’s spine 2 years ago for which she was treated with ATT (category 1) for 9 months. She was diagnosed hypertensive an year ago for which she was currently on treatment with a Calcium channel blocker, beta blocker and a thiazide diuretic. Other than that she had a recent history of tubo-ovarian mass which was operated based on clinical suspicion of Tuberculosis. She also had a history of loss of weight (>5% from baseline) with history of nodular rashes in the lower limbs for the past 4 months.

Fig. 1: Healed skin lesions in the lower limb and a partially healed nodular lesion in the dorsum of left foot

Aldosterone and renin levels were elevated suggesting that the hypertension was due to renal artery hypoperfusion (Secondary to involvement of abdominal aorta).

Echocardiogram was done which revealed concentric LVH with an EF of 68%. No significant valvular or other structural heart diseases were identified.

Chest X-ray showed no signs of tuberculosis or parenchymal lung disease.

This patient met almost all the ACR criteria for Takayasu Arteritis, hence standard immunosuppressive therapy was started. She was started on Prednisolone 60 mg once daily. She was also started on Aspirin 75 mg once daily.
as an adjunct. Her blood pressure was controlled with Nifedipine 10 mg thrice daily and Telmisartan 40 mg twice daily along with hydrochlorothiazide 12.5 mg twice daily. The patient had complete resolution of symptoms within a month of starting treatment and her inflammatory markers normalized. She is currently on steroid and no relapses have been encountered as of now.

**Discussion**

Takayasu arteritis is a stenotic inflammatory disease of the large vessels that predominantly affects the branches of the aorta. It is significantly more common in women with geographical preponderance to Asia. Patients typically present before the age of 40 but can occur in pediatric ages also. Approximate incidence in the world is 2.6 cases per million population. There is no concrete data regarding the incidence and prevalence of disease in India.

Though the exact pathogenesis of the arteritis is still unknown, tuberculosis, streptococcal infections, rheumatoid arthritis and other collagen vascular diseases have been debated as its etiology in the past. Recently more emphasis has been given on an immunopathological cause.

Subclavian artery is the most common artery involved in Takayasu arteritis which is then followed by Common carotid, abdominal aorta, renal arteries, Aortic arch and vertebral arteries in the descending order. The disease can also uncommonly involve celiac, superior mesenteric, pulmonary and coronary arteries.

Typical symptoms include arm claudication and systemic symptoms like fatigue, malaise, low grade fever, weight loss and myalgia. Systemic symptoms may precede the actual disease by months and termed as pre-pulseless phase. Rashes can occur as a part of vasculitic syndrome. Patients may also syncope, TIA’s (Common carotid, vertebral artery involvement), Abdominal pain/nausea (abdominal aorta involvement), Hypertension (renal artery involvement) or Aortic regurgitation and heart failure (aortic arch involvement). Examination may reveal absent pulses on the involved vessels particularly in the subclavian artery with other findings mentioned before. They usually also have unequal blood pressures between the arms and between the arms and legs as well.

**Takayasu arteritis is very often associated with Tuberculosis** (usually before the disease onset) and this association is not clearly delineated eventhough there are insufficient evidences for mycobacterial antigens as a possible etiology for the origin of the disease. Despite many advancements the etiology yet is to be elucidated and it is unclear.

The mainstay for diagnosis is vascular imaging with the demonstration of arterial thickening with or without stenosis – especially of the characteristic arteries that are mentioned above. Biopsy is rarely essential and hence rarely performed.

The mainstay of treatment is immuno-suppression, with steroids forming an integral part of the treatment. Methotrexate is recommended as a steroid sparing agent for refractory disease, with aspirin as an adjunctive therapy.

Complications are mainly due to arterial occlusion and related damage including limb ischemia, hypertension, renal damage and cardiac failure.

**ACR criteria for the diagnosis of Takayasu arteritis (3 or more of the 6 criteria is diagnostic)**

1. Age at disease onset ≤ 40 years.
2. Claudication of extremities.
3. Decreased brachial artery pulse.
4. Blood pressure difference > 10 mm Hg.
5. Bruit over subclavian arteries or aorta.
6. Arteriogram abnormality

**Angiographic classification of Takayasu Arteritis**

Type I: Branches from the aortic arch
Type IIa: Ascending aorta, aortic arch, and its branches
Type IIb: Ascending aorta, aortic arch and its branches, thoracic descending aorta.
Type III: Thoracic descending aorta, abdominal aorta, and/or renal arteries.
Type IV: Abdominal aorta and/or renal arteries.
Type V: Combined features of Type IIb and IV.

**References**

6. Takayasu’s arteritis: role of Mycobacterium tuberculosis and its 65 kDa heat shock – Agarwal A, Ghag M, Sinha N. Department of Immunology, Sanjay Gandhi Postgraduate Institute of Medical Sciences, Raebareli Road, Lucknow 226 014, India.
Erik Adolph Von Willebrand (1870-1949) was born, in Vaasa, a seaport city located in the Gulf of Bothnia, western Finland. He studied medicine at the University of Helsinki. During his summer breaks, he worked as a physician at a spa in Maarianhamina, the capital of Åland Island. Here he first learned about Alandic hemorrhagic disease.

Von Willebrand received his medical degree from the University of Helsinki in 1896. He was awarded a doctorate from the same institution for his doctoral thesis, “Blood changes after venesection,” which detailed his investigation on how blood changes after significant loss.

From 1897 to 1900, von Willebrand worked as an intern and assistant physician at the Deaconess Institute of Helsinki. After finishing his lectureship in anatomy and physiology between 1901 and 1903 Von Willebrand became a lecturer in internal medicine at the University of Helsinki. In 1908. During this time, he focused on blood changes during muscular exercise, metabolism and obesity, as well as carbon dioxide and water exchange through human skin. He became physician-in-chief of the Deaconess Institute from 1922 to 1931, and worked at the university until his retirement (1935).

Von Willebrand wrote many articles on obesity, diabetes mellitus and also described technique for evaluating ketone in urine (1912). He was a pioneer in insulin use and treatment of diabetic coma.

Von Willebrand remains most famous, however, for his description of a familial bleeding disorder he encountered among the inhabitants of Åland Islands. In 1925, he examined a 5-year-old girl with a history of bleeding, brought to Helsinki for treatment. Little girl was the ninth of 12 children. Four of her siblings bled to death at an early age. Both of her parents came from families with bleeding disorders. To learn more, he traveled to the Åland Islands in order to study the disease in depth. He mapped the family pedigree and found that 23 of the 66 family members had bleeding problems. Willebrand concluded that this was previously unknown type of hemophilia. Initially, he called the disease “hereditary pseudo-hemophilia” because of the prolonged bleeding time. As he studied the disease more, he came to believe that platelets were involved, so he renamed it “constitutional thrombopathy.” Willebrand published his findings in 1926.

His work is coined in the eponym ‘Von Willebrand’s disease’ and ‘Von Willebrand factor’. Von Willebrand’s disease is the most common inherited bleeding disorder. It is an Autosomal dominant disorder which results from several abnormalities in the production of a large adhesive protein-Von Willebrand factor (vWF). There are several types but type-1 is most common, which results from decreased release of vWF from the endothelial cells. Factor VIII levels may also be low.

Von Willebrand was keenly interested in nature and birds in particular. He established an aviary reserve on an island. Willebrand died on Dec. 12 1949, in Perna, Finland.
API-ISG Consensus Guidelines for Management of Gastro-oesophageal Reflux Disease

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Abstract

Gastro-oesophageal reflux disease (GERD) is a common problem in the community. The Indian Society of Gastroenterology and Association of Physicians of India have developed this evidence-based practice guideline for management of GERD in adults. A modified Delphi process was used to develop this consensus containing 43 statements, which were generated by electronic voting iteration as well as face-to-face meeting, and review of the supporting literature primarily from India. These statements include 4 on epidemiology, 9 on clinical presentation, 11 on investigations, 18 on treatment (including medical, endoscopic, and surgical modalities), and one on complications of GERD. The statement was regarded as accepted when the proportion of those who voted either to accept completely or with minor reservation was 80% or higher. The prevalence of GERD in large population-based studies in India is approximately 10% and is probably increasing due to lifestyle changes and increase in obesity. The diagnosis of GERD in the community should be mainly based on presence of classical symptoms like heartburn and sour regurgitation, and empiric treatment with a proton pump inhibitor (PPI) or H2 receptor antagonist should be given. All PPIs in equipotent doses are similar in their efficacy in the management of symptoms. Patients in whom symptoms do not respond adequately to PPI are regarded as having PPI-refractory GERD. Invasive investigations should be limited to patients with alarm symptoms and those with refractory GERD.

Introduction

The prevalence of gastro-oesophageal reflux disease (GERD) is around 8-12%. There is heterogeneity in the practice and availability of technology throughout our country with unavailability of standardised guidelines for GERD. These guidelines are made through a collaborative effort of The Indian Society of Gastroenterology (ISG) and Association of Physicians of India (API). A set of consensus statements relevant for the diagnosis and management of GERD in India have been complied.

Methods

A modified Delphi process was adopted to develop consensus statements for the diagnosis and management of GERD in India. Seven areas were identified, namely, epidemiology, clinical presentation, diagnosis and investigations, medical treatment, surgical and endoscopic management and complications.

An initial list of statements was generated and circulated to the Task Force members. The first vote was conducted by Survey-Monkey, without explanation or justification for the statements. Feedback regarding the statements was collated and modifications made where appropriate. Literature on GERD, both Indian and international, was then collated and copies were circulated to all the members online via Dropbox. The literature included all accessible Indian and International (original papers and abstracts) articles and guidelines on GERD. The members voted again on the statements by email after reviewing the literature. The results of the second vote were collated. Finally, the Task Force members met in Delhi and discussed the 48 statements developed based on feedback from the two rounds of votes. All relevant available literature was reviewed, with emphasis on Indian data, whenever available.

The third vote followed these presentations, and was captured using electronic vote pads. The options given for each statement were (A) accept completely, (B) accept with some reservation, (C) accept with major reservation, (D) reject with reservation, and (E) reject completely. Consensus on a statement was considered achieved when 80% or more of the voting members chose to “accept completely” or “accept with some reservation” the statement. A statement was considered refuted when 80% or more of the voting members indicated “reject completely” or “reject with some reservation.” When no consensus was reached on a particular statement, it was modified.
1. Gastroesophageal reflux disease is defined as reflux of gastric content into the esophagus, resulting in significant symptoms and/or complications. 

Voting percentage: A 91.6, D 8.3

Level of evidence: II-1

Grade of recommendation: III

2. GERD is common in India, in both urban and rural population.

Voting percentage: A 92.3, B 7.6

Level of evidence: II-2

Grade of recommendation: B

3. The risk factors for GERD include obesity, smoking, increase in intra-abdominal pressure and certain dietary factors.

Voting percentage: A 92.3, B 7.6

Level of evidence: II-2

Grade of recommendation: B

Multiple dietary and lifestyle factors have been implicated as risk factors for GERD. The associations with most of these factors except for obesity have been weak or inconsistent. Obesity has a detrimental effect on the barrier function of gastroesophageal junction and also results in increased intra-abdominal pressure. There is a direct association of waist circumference and application of abdominal belt with increased intra-gastric pressure. This in turn results in more frequent gastroesophageal reflux. Both the community-based studies from South India showed a higher risk of GERD with BMI > 25. Meta-analysis of global data has shown an OR of 2.16 (2.05-2.28) for GERD in obese individuals.

Smoking and consumption of tobacco has been linked with GERD. The results from the recent meta-analysis of 30 studies show an OR of 1.26 (1.04-1.52) with smoking. As smoking is not protective and considering other health hazards associated with it, it may be prudent to advice against tobacco consumption or smoking. Existing data from India and from meta-analysis of global data does not support alcohol as a risk factor for GERD.

Dietary factors are often considered as a trigger for reflux symptoms but data supporting this is weak. As there are many items in the diet, studying the effect of individual factors is challenging. Some of the studies from India that meat consumption was a risk factor for GERD in obese individuals.

4. There is an inverse association between Helicobacter pylori infection and GERD.
H pylori and GERD.

have investigated the association of otitis media) pulmonary fibrosis, and recurrent (pharyngitis, sinusitis, idiopathic and those with proposed associations reflux-dental erosion syndromes) reflux-laryngitis, reflux-asthma, and established associations (reflux-cough, further classified into those with esophageal syndromes were further classified into symptomatic syndromes or syndromes with esophageal injury. The extra-esophageal syndromes were further classified into those with established associations (reflux-cough, reflux-laryngitis, reflux-asthma, and reflux-dental erosion syndromes) and those with proposed associations (pharyngitis, sinusitis, idiopathic pulmonary fibrosis, and recurrent otitis media) of the occurrence of extraesophageal symptoms can be explained by two plausible mechanisms -1) reflux theory and 2) reflex theory.

There is a paucity of prevalence studies from Asia on extraesophageal symptoms of GERD. A systematic review from population based studies from Asia showed GERD was prevalent in 11-65% patients with extraesophageal symptoms (asthma, dental erosions, ENT symptoms and chronic laryngitis). A multicentre study (12 centres) by ISG task force showed presence of nocturnal cough (15.5% vs 2.9%, p=0.001) and hoarseness of voice (6.1 % vs 0.9%,p=0.0001) was higher in patients with GERD than with no GERD symptoms.

Thus, GERD may present with both esophageal and extraesophageal symptoms. However, extraesophageal symptoms rarely occur in isolation without typical symptoms of GERD.

6. The cardinal symptoms of GERD are heartburn and sour regurgitation.

Voting percentage: A 92.3, B 7.6

Level of evidence: II-1

Grade of recommendation: A

Heartburn is defined as a burning sensation in the retrosternal area, and sour regurgitation is defined as the perception of flow of refluxed gastric content into the mouth or hypopharynx. Heartburn and regurgitations are the typical and predominant symptoms of GERD. A clinical diagnosis of GERD can be made on the basis of history alone with sensitivity and specificity of 67% and 70%, respectively. 23,24

7. Approximately 30-50% of patients with GERD have additional symptoms of functional dyspepsia.

Voting percentage: A 100, B

Level of evidence: II-2

Grade of recommendation: A

Functional dyspepsia is a functional GI disorder defined by the presence of one or more of these dyspeptic symptoms- post prandial fullness, early satiety, epigastric pain and epigastric burning. 21

The overlap between GERD and functional dyspepsia can be explained by the similar pathogenic mechanism - dysmotility or visceral hypersensitivity. 25 Heartburn, regurgitation, and chest pain are typical GERD symptoms originating from reflux-related sensory stimulation of the esophageal mucosa, while belching, epigastric pain, and epigastric burning appear to be dyspeptic symptoms that might arise from the distal esophagus. A systematic review showed that dyspeptic symptoms were present in more than one third of subjects with GERD. 25

The ISG Task Force study reported that abdominal pain was present in 34.3%, difficulty in passing stool in 21.7%, and mucus in stool in 9% of patients with GERD, which was higher than in the no-GERD group (8%, 6.7% and 3.5%, respectively). Shah et al found that the prevalence of heartburn (34.6% vs 2.8%) and regurgitation (17.9% vs 1.5%) was higher in subjects with dyspepsia as compared to those with no dyspepsia. 26

Thus, overlap between functional GI disorder and GERD is common and early identification is mandatory for future treatment implication.

8. The alarm symptoms in patients with GERD include dysphagia, odynophagia, GI bleeding, weight loss, anaemia and new onset symptoms in age > 55 years.

Voting percentage: A 100

Level of evidence: II-2

Grade of recommendation: A

Alarm features in GERD are dysphagia, odynophagia, GI bleeding, iron deficiency anaemia, progressive weight loss, and new onset of atypical symptoms at age 45-55 years. Erosive reflux esophagitis may cause upper GI bleeding, odynophagia and dysphagia. In ISG task force multicenter study, 4.1% with GERD had previous hematemia. 1 In a patient with dysphagia motility disorder, rings, peptic stricture and malignancy should be ruled out. As result of widespread use of PPI, GERD complications have drastically reduced. GERD is an independent risk factor for esophageal malignancy. UGI endoscopy is advocated subjects with heartburn associated with alarm symptoms, and in elderly patients with new onset of GERD symptoms.

9. The extra-esophageal symptoms of GERD include chronic cough, asthma, chronic laryngitis, and globus symptoms.

Voting percentage: A 100

Level of evidence: II-2

Grade of recommendation: A

Extraesophageal symptoms are not uncommon in GERD patients. Four syndromes (reflux cough, reflex laryngitis, reflux asthma, and reflux dental erosions) have been found to be associated with GERD. 8 Temporal association between cough and reflux was established with 24-hour ambulatory acoustic cough monitoring with simultaneous impedance /pH monitoring technique. 27 A population based Chinese study reported that
extra-esophageal symptoms including snoring (28% vs 12%), laryngitis (23.7% vs 11.8%), globus sensation (23.7% vs 5%), asthma (6.5% vs 2.2%), bronchitis (15.4% vs 8.9%) and chronic cough (21.4% vs 11%) was higher in patients with symptomatic GERD than in those with no GERD symptoms. Reflux laryngitis may lead to hoarseness, dysphonia, burning throat, excessive throat clearing, chronic cough, globus sensation, laryngospasm, postnasal drip and dysphagia. However, it is important to note that most patients with extra esophageal symptoms also have symptomatic GERD.

10. Patients with difficult to treat non-seasonal asthma and chronic cough should be evaluated for GERD

Voting percentage: A 100
Level of evidence: II-2
Grade of recommendation: B

Almost one third of asthmatic patients have GERD. GER may not only worsen during an episode of airways obstruction, but also may serve as a trigger for an asthmatic attack by causing bronchospasm. Patients with reflux-associated asthma may manifest with typical symptoms of GER, but approximately 25 to 30% have clinically silent reflux. Studies from India have shown that GERD was prevalent in 50-70% asthmatics, and that addition of PPI improved pulmonary function test in patients with difficult to treat asthma and GERD.

There appears to be a temporal relationship between chronic cough and reflux in 30-48% of patients. In the ISG task force study, 15.5% GERD subjects had nocturnal cough compared to with 2.9% no GERD subjects. A survey of 500 physicians from India reported that 10.4% of their patients with chronic cough had cough related to GERD. About 80% of the physicians treated these empirically with PPI. However response of chronic cough to PPI is not consistent. In 9 studies comparing PPI to placebo, prolonged PPI therapy (2–3 months) did not have significant improvement over placebo in resolution of cough (odds ratio 0.46; 95% CI 0.19–1.15). Nevertheless, PPI trial is recommended in chronic cough patients with typical symptoms of GERD.

11. Non-cardiac chest pain (NCCP) is defined as recurrent episodes of angina-like retrosternal chest pain in the absence of cardiac abnormalities. Gastroesophageal reflux disease (GERD), esophageal motility disorders and functional chest pain (visceral or central hypersensitivity) are the main underlying mechanisms for NCCP. GERD is seen in 25-60% of patients with NCCP; 10-70% of patients have erosive esophagitis, and abnormal acid exposure is seen in 50-60% patients.

Jain et al showed that 49% of patients with NCCP had erosive esophagitis, and 85% responded to 2 weeks of PPI therapy. The chest pain in patients with abnormal oesophageal acid exposure and/or reflux oesophagitis tends to respond to PPI treatment, whereas patients without objective evidence of GERD have little or no response. It is advocated to do endoscopy and ambulatory pH monitoring in patients with NCCP who fail to respond to trial with PPI therapy.

12. Symptoms of GERD can lead to sleep disturbance.

Voting percentage: A 100
Level of evidence: II-1
Grade of recommendation: A

Nocturnal symptoms in GERD are common and associated with sleep disturbance. Mechanisms responsible for night time reflux include delayed gastric emptying, reduced esophageal peristalsis, decrease in swallowing and salivary secretion, delayed esophageal clearance during sleep, and heightened sensory perception. In nationwide telephone survey of 1000 adults with GERD, 79% reported night-time heartburn, 75% had sleep disturbances and 71% using over-the-counter medications. In systematic review of 59 studies, nocturnal symptoms was prevalent in 54% ± 22% of subjects. In a study from Kerala, 10.2% of subjects had nocturnal symptoms of GERD. Thus, nocturnal symptoms are common, and adversely affects the quality of life in subjects with GERD.

13. GERD may adversely affect quality of life.

Voting percentage: A 100
Level of evidence: II-2
Grade of recommendation: B

Disease severity and non-disease factor (anxiety, depression) both are strongly correlated with impaired health related quality of life (QoL). To assess QoL in GERD various survey/instruments have been used. Few of them are generic (SF-36, Euro QoL) and some are disease specific (GERQ,GORD-HRQoL, HBQoL). In a systematic review of 19 studies, patients with severe GERD scored lower for physical and mental health, as well as psychological and general well-being. Absenteeism from work was also higher among patients with severe GERD. A systematic review of 19 studies showed patients with persistent symptoms despite of PPI scored 8–16% lower for physical health and 2–12% lower for mental health compared to those who responded. Nocturnal GERD have a significant negative impact on sleep and well-being. In another study, higher severity of symptoms, sleep abnormalities and work loss were more common among GERD patients with nocturnal symptoms. There are no data from India on QoL in GERD patients.

Investigations

14. The clinical diagnosis of GERD is based on symptoms (heartburn and/or sour regurgitation) and investigations are necessary in only a few patients.

Voting percentage: A 100
Level of evidence: II-1
Grade of recommendation: A

The cardinal symptoms of GERD are heartburn and sour regurgitation. The use of a symptom based questionnaire has a sensitivity and specificity of 62% and 67%, respectively. In a meta-analysis the accuracy for a symptom based diagnosis by a primary care physician was comparable to that made by a specialist. Investigations to diagnose GERD, such as endoscopy, 24-h impedance pH-metry, are required only when initial treatment fails, or prior to surgery.

15. Positive response to PPI challenge may be used for confirmation of GERD in the community

Voting percentage: A 92.3, B 7.6
Level of evidence: I
Grade of recommendation: A

A “PPI challenge” is a test where a PPI is given to patients with a
The presumptive diagnosis of GERD to assess the response to treatment. A rapid symptomatic improvement is considered “positive response” and commonly used to validate the diagnosis of GERD. \(^{49}\) Empirical therapy with PPI is considered useful and simple diagnostic tool to identify patients with GERD. A meta-analysis of 8 studies showed pooled sensitivity and specificity for PPI test was 80% and 74%, respectively. \(^{49}\) The optimal duration, dose and selection of the PPI varies across studies with most using standard (single) dose for 7 to 14 days. It is an inexpensive and easy to administer test. Its limitation is a poor specificity and hence a negative PPI challenge does not rule out GERD. The PPI challenge must be used only in patients without any warning signs.

16. Patients with GERD and alarm symptoms should be referred for a prompt upper gastrointestinal endoscopy.

Voting percentage: A 100
Level of evidence: II-2
Grade of recommendation: A

The alarm symptoms in patients with GERD include dysphagia, odynophagia, GI bleeding, weight loss, anaemia and new onset symptom in age > 55 years. These alarm symptoms are present in upto 10% of the patients with GERD. \(^{46}\) In a prospective study, endoscopy in patients with GERD and alarm symptoms influenced the overall management in 40% of the patients, mainly by dilating esophageal strictures, finding Barrett’s esophagus, or detecting severe esophagitis. \(^{31}\) In a meta-analysis, the sensitivity of individual alarm symptoms for detection of GI malignancy was between 9 to 41%, but the pooled sensitivity, specificity, positive and negative predictive values for “any alarm symptom” were 75%, 79%, 5.9% and 99.4% respectively. \(^{46}\) The majority of endoscopies in patients with alarm symptoms are normal or show minor disease, \(^{25}\) leading to a low sensitivity.

17. Patients with GERD, especially those with long standing symptoms should be considered for upper gastrointestinal endoscopy.

Voting percentage: A 92.3, B 7.6
Level of evidence: III
Grade of recommendation: C
Upper GI endoscopy should be done to determine whether the patient has endoscopic reflux disease, the grade of GERD, and the presence of hiatus hernia and its type and size, complications such as peptic stricture and Barrett’s esophagus, and for histologic presence of dysplasia. Patients with long standing GERD may have a higher prevalence of complications. Although there is no literature to support this practice, the core committee felt that an endoscopy will help in optimizing the management of these patients.

18. Patients with GERD undergoing endoscopy should be evaluated for grade of esophagitis, hiatus hernia and Barrett’s esophagus.

Voting percentage: A 100
Level of evidence: II-1
Grade of recommendation: A

Esophagitis is the presence of mucosal breaks on endoscopy. The severity of esophagitis is graded by the Los Angeles (LA) classification system on endoscopy. The grading is from A to D and represents mild to severe erosions. \(^{34}\) Esophagitis is seen at endoscopy in only 8.8% of Indian patients of GERD. \(^{45}\) The grade of esophagitis has important bearing on treatment, patient response, complications and prognosis. Patients with higher grade of esophagitis may have more severe symptoms, \(^{44}\) respond better to PPI as compared to H2RA, \(^{56}\) require longer duration of treatment with PPI, \(^{25}\) and have higher prevalence of esophageal motility disorders. \(^{55}\)

The displacement of a part of the stomach through the esophageal hiatus of the diaphragm is known as hiatal hernia. Hiatus hernia alters the integrity of the gastroesophageal junction and predisposes to reflux. In a study from India, the presence of a hiatus hernia was associated with GERD (odds ratio 6.93 [95% confidence interval, 2.58-18.5]). \(^{59}\) Hiatus hernia is more often present in severe esophagitis (70%) as compared to mild esophagitis (22%). \(^{40}\) A hiatus hernia also predisposes to formation of an ‘acid pocket’, which serves as a reservoir for acid reflux. \(^{61}\)

Barrett’s esophagus is the condition in which an abnormal columnar epithelium replaces the stratified squamous epithelium that normally lines the distal esophagus. \(^{52}\) There are no data on prevalence of Barrett’s esophagus in patients with GERD in India. A tertiary hospital based study has reported a frequency 16%. \(^{63}\) The abnormal columnar epithelium is predisposed to malignancy, with an annual risk of progression to cancer of 0.12% for non dysplastic Barrett’s and upto 13.4% for confirmed high grade dysplasia. \(^{64,65}\)

19. A proportion of patients with GERD, especially those who respond poorly to proton-pump inhibitors (PPI) or have dysphagia, should be evaluated for eosinophilic esophagitis.

Voting percentage: A 92.3, B 7.6
Level of evidence: II-3
Grade of recommendation: B

Eosinophilic esophagitis represents a chronic antigen mediated esophageal disease characterized clinically by symptoms related to esophageal dysfunction and histologically by eosinophil predominant inflammation. \(^{66}\) Symptoms of eosinophilic esophagitis can mimic those of GERD; additional symptoms of dysphagia and food bolus impaction are more often present in eosinophilic esophagitis. \(^{67}\) There are no data on population based prevalence of eosinophilic esophagitis in India. In a hospital based study from northern India, of 185 consecutive patients with GERD, 3.2% had eosinophilic esophagitis. On multivariate analysis, a history of allergy [OR 11.6 (95% CI 1.5-90.1, p=0.01)], and non-response to PPI [OR 0.04 (95% CI 0.004-0.48, p=0.01)] were predictors of eosinophilic esophagitis. \(^{68}\) Therefore, it is important to consider this entity in refractory gastroesophageal reflux symptoms.

20. Symptoms of GERD do not necessarily correlate with endoscopic severity of GERD.

Voting percentage: A 100
Level of evidence: II-2
Grade of recommendation: A

GERD-symptom based score of patients with non-erosive, mild erosive and severe erosive esophagitis are similar. \(^{69}\) Elderly patients, and those with Barrett’s esophagus complain of less symptoms despite severe degree of endoscopic esophagitis. \(^{70}\) In contrast, patients with non-erosive GERD complain of significant heartburn, as esophageal hypersensitivity is a major determinant of symptoms. \(^{70}\) For this reason, in the Rome IV criteria, a new subgroup of patients with
reflux hypersensitivity and functional heartburn have been recognized.\(^{29}\)

21. A) Barium esophagogram has limited role in diagnosis of patients with GERD

Voting percentage: A 100
Level of evidence: II-2
Grade of recommendation: A

21. B) Radionuclide Scintigraphy has limited role in diagnosis of patients with GERD

Voting percentage: A 100
Level of evidence: II-2
Grade of recommendation: B

Barium swallow can detect spontaneous gastroesophageal reflux or it can be provoked by manoeuvres. It may also detect esophageal strictures and hiatus hernia. However, barium swallow has a low sensitivity (67%) and specificity (47%) to identify GERD.\(^{72}\)
Hence, barium studies are not of value in diagnosis of GERD.\(^{29}\)

In radionuclide scintigraphy, a radiolabeled colloid is administered orally and followed by a gamma camera to detect reflux episodes. It is commonly used for children due to its non-invasive nature and a relatively low radiation dose. In various studies, the diagnostic accuracy of radionuclide scintigraphy for GERD were very low.\(^{74,75}\)
The testing in scintigraphy lasts for only few hours compared to 24 hour recording with a pH probe. The joint North American and European guidelines for paediatric GERD also recommend against the use of scintigraphy for the diagnosis of GERD.\(^{76}\)

22. Patients not responding with PPI should be referred for further evaluation including UGI endoscopy and 24-hr pH monitoring.

Voting percentage: A 100
Level of evidence: II-2
Grade of recommendation: A

The causes of PPI failure include non-compliance to treatment, ongoing acidic reflux, weak acidic or alkaline reflux, reflux hypersensitivity and functional heartburn.

The role of endoscopy in patients not responding with PPI is to demonstrate erosive esophagitis, rule out alternative diagnosis like eosinophilic esophagitis and to diagnose complications like peptic stricture or Barrett’s esophagus.

Ambulatory reflux monitoring involves insertion of a pH probe 5 cm above the lower esophageal sphincter and recording the pH exposure data for 24 hours continuously. A fall in pH to <4 from a baseline pH of 7 is considered as an acid reflux.\(^{77}\)
Reflux monitoring demonstrates evidence of excessive esophageal acid exposure time (AET) and an abnormal number of reflux events; adding impedance allows measurement of nonacid reflux events, and association between symptoms and reflux events. Symptom index (SI) and symptom association probability (SAP) are useful to differentiate reflux hypersensitivity from functional heartburn. An AET of <4% is definitively normal (physiological) and >6% can be considered definitively abnormal.\(^{77}\)
A total of >80 reflux episodes per 24 hours is considered as definitively abnormal, while a number <40 is physiological.\(^{77}\)

Thus, a combination of endoscopy and 24-hr pH with impedance testing can help to confirm GERD, provide alternative diagnosis and further characterize patients and help in the optimal management of these patients.

23. While a 24-h impedance pH monitoring is the gold standard for diagnosis of GERD currently, this test is required only a few select subjects.

Voting percentage: A 100
Level of evidence: II-2
Grade of recommendation: A

The 24-h impedance pH monitoring is the current gold standard for detection of reflux episodes as impedance can detect anterograde and retrograde bolus (gas, liquid and mixed) flow along with chemical characterization of the refluxate.\(^{77}\)

The sensitivity and specificity of 24-hour pH study is 77-100% and 85-100%, respectively for discrimination of esophagitis from normal controls.\(^{77}\)
Amongst six diagnostic tests to detect GERD (omeprazole challenge, endoscopy, esophageal histology, barium swallow, scintigraphy, 24-hour pH monitoring),\(^{21}\) pH monitoring has the highest diagnostic accuracy (82.2%).

The current indications for 24-hour pH monitoring include the following:\(^{27}\)

a) Refractory GERD: to determine if there is ongoing acid reflux, symptomatic non acidic reflux or no reflux; b) Atypical symptoms; and c) Prior to anti-reflux surgery.

24. Patients with extra esophageal symptoms should undergo tests for proving the diagnosis of GERD, if they do not respond to PPI.

Voting percentage: A 83.3, B 16.7
Level of evidence: II-1
Grade of recommendation: B

The extra esophageal symptoms of GERD include reflux induced cough, asthma, laryngitis and dental erosions.\(^8\)

Studies from India have reported a prevalence of GERD in about 50% of the patients of asthma,\(^{31}\) and a higher prevalence of 70% in patients with difficult to treat asthma.\(^{32}\) It is important to remember that almost 25% of patients with asthma and GERD diagnosed by 24-hour pH monitoring, do not have any symptoms of reflux.\(^{32}\)
In a physician survey from India, 10% of patients with chronic cough were attributed to GERD clinically and 80% of these were treated empirically with PPI.\(^{34}\)
Dental erosions were found to be present in 88% of GERD patients as compared to 32% in controls in a study from South India.\(^{79}\) There are no Indian studies for prevalence of laryngitis in patients with GERD, but one from Malaysia showed a GERD prevalence of 65% among patients of chronic laryngitis.\(^{79}\)

International guidelines recommend PPI trial to treat extraesophageal symptoms in patients who also have typical symptoms of GERD, and 24-hour pH monitoring in patients who do not have typical symptoms of GERD.\(^{28}\)
However, considering the cost and lack of widespread availability of 24-hour pH monitoring in India, the consensus of the group was to give short-term PPI to patients with extraesophageal symptoms, and investigate only if there is no improvement.

**GERD treatment**

25. Triggers for reflux symptoms should be identified in individual patients and if present should be avoided.

Voting percentage: A 100
Level of evidence: II-2
Grade of recommendation: C

Dietary modification for GERD is based upon evidence and presumptions that certain food items and habits may trigger reflux by altering the anti-reflux mechanisms. However, the evidence regarding food items is weak, inconsistent and controversial,
and hence, a general recommendation on avoidance of food items cannot be made.

Similarly, the relationship between caffeine, tobacco, alcohol and GERD remains heterogeneous and unclear.30,80-83

There is weak evidence regarding the association of food items like chocolate, citrus fruits, carbonated beverages, spicy foods, fatty foods, mint etc. with GERD symptoms. However, there are no studies which have evaluated the effect of their cessation on symptom response.48

26. Weight reduction is recommended for obese/overweight patients with GERD

Voting percentage: A 81.8, B 18.1
Level of evidence: I
Grade of recommendation: B

Elevation of the head end of bed (HOB) should decrease the reflux of acidic gastric contents in the esophagus. As compared to patients who sleep flat, those with elevated HOB have fewer and shorter reflux episodes and lesser reflux symptoms.72,93 There is also reduced esophageal acid exposure and acid clearance time in nocturnal refluxers, and improvement in heartburn and sleep.74

28. Patients of GERD should be advised not to lie down within 2 hours after a meal.

Voting percentage: A 81.8, B 18.1
Level of evidence: II-3
Grade of recommendation: C

Early meal (6 hours before bed-time) is associated with less supine reflux as compared to a late meal (2 hours before bed-time).95 Such an association is not found in healthy.96

29. Patients who have infrequent symptoms of GER may be treated with antacids and/or H2 receptor antagonists

Voting percentage: A 100
Level of evidence: I
Grade of recommendation: A

Histamine H2 receptor blockers (H2RAs) reduce acid secretion by competitively antagonizing the H2-receptors on the parietal cells. Antacids (basic aluminium, calcium, or magnesium compounds), act by neutralizing acid in the stomach; raft forming agents such as alginate create a physical barrier against reflux, and sucralfate (aluminium hydroxyd and sucrose sulphate) coats the denuded mucosa in the esophagus/proximal stomach. In a meta-analysis, that evaluated the role of over the counter (OTC) medications such as H2RAs (10 trials, 6382 patients), antacids (4 trials, 1155 patients) and alginate/antacid combination (4 trials, 284 patients) in patients with GERD, all OTC medications were more effective than placebo in providing symptom relief.97

30. The initial standard of care of GERD is use of proton pump inhibitors for 4 weeks in standard doses.

Voting percentage: A 100
Level of evidence: I
Grade of recommendation: A

Proton pump inhibitors (PPIs) irreversibly inhibit the activated H+K+ ATPase proton pump in the gastric parietal cells, and this effect lasts until the generation of new pumps. PPIs should be administered daily for sustained acid suppression.98

PPIs should be administered 30 – 60 minutes before a meal for optimal effects. In a Cochrane review on short term treatment of un-investigated heartburn and NERD, both PPIs and H2RAs were more effective than placebo for heartburn remission, both in the empirical treatment group ([PPIs-OR: 0.37 (2 trials, 95% CI 0.32 to 0.44)]) and NERD group ([PPIs-OR: 0.71 (10 trials, 95% CI 0.65 to 0.76)].99 PPIs were also more effective than H2RAs for heartburn remission. Overall heartburn remission rates with PPIs varies from 37 – 61% in patients with NERD (placebo response: 12.6%) or un-investigated heart burn (placebo response: 25.1%) and 56 – 77% (placebo response: 7.5%) in patients with esophagitis, while healing of esophagitis occurs in 72 – 83% patients with erosive reflux disease (ERD) (placebo response: 28.3%).

The standard dose of all PPIs have been mentioned in Table 2. Patients with typical symptoms of GERD, in the absence of alarm signs such as dysphagia, odynophagia, gastrointestinal bleed, anorexia, and weight loss can be treated empirically with PPIs, and PPI trial can be considered before any diagnostic test. Further testing is indicated in patients not responding to 4 weeks of PPI therapy. In a meta-analysis of 59 RCTs (26,885 patients), symptom relief on PPIs in different groups of patients was lower in patients with uninvestigated heartburn than that in patients with ERD or confirmed NERD. Further, the response rates at 8 weeks were similar to those at 4 weeks, indicating that PPI use beyond 4 weeks does not increase the response rates.100 There is also no difference between low dose and high dose PPI therapy,100 or between once vs. twice daily PPI in terms of symptom resolution at week 4.102

31. If there is partial or no response to once daily PPI, increasing the dose of the same PPI to twice daily may be considered.

Voting percentage: A 91.6, B 8.3
Level of evidence: I
Grade of recommendation: A

Ten to 40 percent patients with GERD have partial or no response to a standard dose of PPI.\textsuperscript{103} Given the complex pathophysiology of GERD, this group of patients is heterogeneous, comprising of patients with heart burn of other aetiologies, oesophageal dysmotility disorders, functional heartburn or functional chest pain. One third of these patients have abnormal pH test. Patients who have persistent symptoms usually have longer duration of symptoms, associated hiatus hernia, obesity, and suboptimal use of PPI. Only up to 60% patients are adherent to treatment, and less than half the patients take PPI at appropriate time.\textsuperscript{[104]} In patients with NERD or ERD, in the absence of alarm symptoms, doubling the dose of PPI or switching to another PPI may be tried. This approach leads to an overall incremental benefit of about 20%.\textsuperscript{105,106}

32. Patient not responding to 8 weeks of PPI in optimal dose is defined as refractory GERD.

   Voting percentage: A 100
   Level of evidence: III
   Grade of recommendation: C

In patients with NERD or ERD, in the absence of alarm feature, partial or no response at 4 weeks on standard dose PPI can be overcome by doubling the dose of PPI or switching to another PPI, with an overall incremental benefit of 20%. Continuing optimal PPI therapy beyond 8 weeks will not increase the response rates, and such patients should be investigated further.

33. Patients with recurrent symptoms of GERD and refractory GERD should be referred for further evaluation.

   Voting percentage: A 100
   Level of evidence: III
   Grade of recommendation: C

Most patients with proven GERD develop recurrence of symptoms when PPI therapy is discontinued.\textsuperscript{107} If a patient relapses after an initial response to PPI, he should be referred for further diagnostic evaluation including an upper GI endoscopy to differentiate between ERD and NERD. This is because relapse rates are higher in patients with ERD as compared to patients with NERD. Patients with ERD may require long term PPI for symptom control and healing, while patients with NERD should be evaluated further with 24 pH-metry to prove (or disprove) GERD as their cause of symptoms. Patients in whom GERD has been excluded, other causes for symptoms including non-acid reflux, eosinophilic esophagitis,\textsuperscript{108} esophageal dysmotility disorders, functional heartburn, and functional chest pain should be considered.\textsuperscript{108}

34. A) Presence of erosive esophagitis even after 8 weeks of PPI may be treated with further 4-8 weeks of PPI and long term maintenance for prevention of relapse.

   Voting percentage: A 75, B 16.6, C 8.3
   Level of evidence: I
   Grade of recommendation: A

A meta-analysis of 43 studies (7635 patients) evaluated the speed of healing and symptomatic relief in patients with moderate to severe erosive esophagitis.\textsuperscript{109} Overall healing proportion with PPIs at 8 weeks was 83.6% (95% CI: 79% - 88%). Extending PPI beyond 8 weeks showed increment in healing from 86% to 91%. Therefore, extending the PPI therapy beyond 8 weeks (for 4 – 8 weeks), may have an additional incremental benefit in terms of healing.

   For maintenance therapy in patients with ERD proportion of patients in remission at one year is higher (>80%) with PPI (with or without cisapride) as compared to H2RA (49-66%) or prokinetics (54%).\textsuperscript{110-112} H2RAs were also superior to placebo, and could be considered in PPI intolerant patients.

B) In a patient with refractory GERD, further evaluation for alternate diagnosis and functional heartburn should be done if endoscopy is normal.

   Voting percentage: A 91.6, B 8.3
   Level of evidence: III
   Grade of recommendation: C

Patients with GERD symptoms, who have absence of erosions on endoscopy are labelled as having NERD; they should be further evaluated with pH-metry to rule out acid / non acid reflux as the cause of their symptoms. In patients with negative endoscopy and pH-metry, other causes of heartburn include non-acid reflux, heart burn of other etiologies like eosinophilic esophagitis, esophageal dysmotility disorders, and functional heartburn.\textsuperscript{108}

35. Patients with non-cardiac chest pain, maybe given double daily PPI for 4 weeks, after a cardiac cause has been ruled out.

   Voting percentage: A 91.6, B 8.3
   Level of evidence: I
   Grade of recommendation: A

GERD is the most common cause of non-cardiac chest pain. This has led to PPI trial being used as diagnostic test for patients with reflux chest pain syndrome. The overall sensitivity and specificity of a PPI test is 80% and 74% respectively,\textsuperscript{116} indicating that such an approach can be used both for diagnostic and therapeutic purposes. The response to PPI is better than with placebo,\textsuperscript{113} but depends on the presence or absence of typical GERD symptoms; the therapeutic gain over placebo is 56 – 85% in GERD positive as compared to only 0 – 17% in GERD negative patients.\textsuperscript{39}

36. The dose of PPI should be optimized or adding H2RA at night should be considered in patients having nocturnal reflux symptoms despite use of PPI.

   Voting percentage: A 72.7, B 27.2
   Level of evidence: II-3
   Grade of recommendation: C

Optimizing the PPI therapy is the first strategy in patients who experience nocturnal reflux symptoms. Although single dose morning PPI achieves good day time pH and symptom control, nocturnal pH control remains inadequate in some patients. This can be improved with evening dose of PPI.\textsuperscript{114} However, even on twice-daily PPI dose, patients with GERD may experience symptoms at night, which may be due to nocturnal acid breakthrough (NAB), defined as gastric pH below 4 for more than one continuous hour at night time in subjects on PPIs.\textsuperscript{115} Addition of bedtime H2RA to double dose PPI in patients with GERD decreases gastric acidity.\textsuperscript{116} However, there are concerns about tachyphylaxis associated with H2RA. Although PPI + H2RA combination reduced NAB, the effect waned over one week, highlighting the tolerance associated with continued H2RA therapy.\textsuperscript{117}

37. A) Prokinetics have no proven role in routine management of GERD

   Voting percentage: A 100
   Level of evidence: I
   Grade of recommendation: A

B) Patient with GERD having
functional dyspepsia overlap, volume reflux and evidence of delayed gastric emptying may benefit from addition of prokinetics.

Voting percentage: A 100
Level of evidence: II-2
Grade of recommendation: C

Although prokinetics may alleviate the pathophysiology of GERD by increasing gastric and esophageal emptying, the evidence behind their clinical efficacy as add on therapy over PPI is lacking. In a RCT of 66 patients from North India, addition of mosapride to PPI was not effective in symptom control in patients with NERD, or healing in patients with ERD.\(^{118}\) In a recent meta-analysis of 12 RCTs (2403 patients), combination therapy did not have better efficacy than PPI alone for symptom control or endoscopic response, and the combination therapy was associated with worse adverse effects.\(^{119}\) A subset of patients with GERD who have delayed gastric emptying may benefit from addition of prokinetics.\(^{120}\) Given the adverse effect of many prokinetics on cardiac and neurologic function, these drugs should be used judiciously.\(^{121}\)

Baclofen, a GABA-B agonist can relieve GER by decreasing the transient LES relaxations. In a meta-analysis of 9 studies (283 patients), baclofen resulted in a short-term decrease in the number and average length of reflux episodes.\(^{122}\)

38. For recurrence of symptoms after initial treatment in patients with uninvestigated GERD, NERD or mild erosive reflux disease, the lowest effective dose of PPI or H2RA should be advised.

Voting percentage: A 81.8, B 18.1
Level of evidence: I
Grade of recommendation: A

After withdrawal of PPI, almost 50% patients with uninvestigated GERD remain asymptomatic over one year of follow-up.\(^{123}\) In patients with NERD, on demand therapy, but not intermittent therapy, with H2RAs or PPI provided symptom control in a proportion of patients.\(^{124,125}\) This approach is not useful in erosive GERD.\(^{125}\) For patients who improve on double dose PPI, stepping down to single dose for maintenance treatment can be successful in 80% patients.\(^{126}\) Overall, up to 50% patients with mild GERD/NERD will remain asymptomatic off any therapy, indicating that a definite proportion of such patients can be off therapy, and recurrences can be managed with low doses of PPI or H2RA.

39. All available PPIs in equipotent doses have similar efficacy for symptom control.

Voting percentage: A 90.9, B 9.1
Level of evidence: I
Grade of recommendation: A

In a meta-analysis of 10 studies on 15,316 patients with erosive esophagitis, at 8 weeks there was significant but clinically modest benefit of esomeprazole over other PPIs in terms of healing (5% relative increase) and symptom control (8% relative increase).\(^{127}\) Recent network meta-analysis and systematic review showed that in equipotent doses all PPIs had similar efficacy for symptom relief in patients with NERD.\(^{128,129}\)

40. A) Long-term unnecessary use of PPI should be avoided.

Voting percentage: A 100
Level of evidence: II-2
Grade of recommendation: A

Long term use of PPI has been associated with a multitude of adverse events including increased incidence of Clostridium difficile-associated diarrhea, bacterial gastroenteritis, community acquired pneumonia, osteoporosis and increased risk of bone fractures, kidney disease, dementia, and micronutrient absorption (calcium, magnesium and B12 deficiency).\(^{130-132}\) One prospective study showed showed no difference in adverse events between pantoprazole vs. placebo, except for enteric infections.\(^{133}\) After complete symptomatic relief with PPIs, an effort should be made to stop PPI, so as to avoid some long-term risks associated with these drugs.

B) The routine use of fixed dose combination therapy of PPI and prokinetics should be avoided.

Voting percentage: A 81.8, B 18.1
Level of evidence: III
Grade of recommendation: C

Given the side effects of prokinetics and lack of evidence on their efficacy in patients with GERD, fixed dose combination of PPI and sustained release high dose prokinetic does not offer any additional advantage of PPI, in the routine management of GERD. Moreover, it increases the cost of therapy, and hence fixed dose combination of PPI and prokinetic should be avoided.\(^{134}\)

41. Patients who require long term medical management and proven GERD should be evaluated for surgery

Voting percentage: A 90.9, B 9.1
Level of evidence: I
Grade of recommendation: A

PPI are the treatment of choice for GERD patients. However, in the long-term management of GERD anti-reflux surgery may be considered as an alternative treatment. Anti-reflux surgery is indicated in patients with proven GERD who have failed medical management, those with volume reflux, large hiatal hernia, and complications (peptic stricture and Barrett’s esophagus) and occasionally for extra-esophageal manifestations.\(^{135}\)

Anti-reflux surgeries are either in the form of fundoplication (complete or partial) which can be done by open or laparoscopic technique. The Nissen fundoplication is a complete 360° wrap, and has been replaced by partial wraps -- Dor (anterior-180°) and Toupet (posterior-270°), due to associated dysphagia and bloating with complete wrap. On long term follow up, the remission rate is higher in the medication group (esomeprazole) than the surgical group (92% vs 85%, p=0.048).\(^{136}\) Regurgitation is significantly less in surgery group (2% vs 13%,p<0.001). Laparoscopic surgery is effective and associated with shorter hospital stay, better control of reflux symptoms and reduced risk of complications compared to open surgery.\(^{137}\)

42. Endoscopic anti-reflux procedures are evolving therapeutic modalities for a select group of patients.

Voting percentage: A 81.8, B-18.1
Level of evidence: II-2
Grade of recommendation: B

Though PPIs are the mainstay for GERD treatment, about one third of patients have suboptimal response. The management options in such cases include anti-reflux surgery or endoscopic ant-reflux treatments. Compared to anti-reflux surgery, endoscopic anti-reflux therapies are minimally invasive and can be used in PPI-refractory GERD.
These endoscopic therapies include radiofrequency application (Stretta), endoscopic plication modalities (Esophyx, MUSE and GERDx) and mucosal resection techniques (anti-reflux mucosectomy). Various technique have variable response and treatment response ranges from 16%-82%. Durability of response is seen in less than 50% in long term. A systematic review of 28 studies on Stretta showed the subjective and objective improvements in health related quality of life (HRQL), heartburn score, esophageal acid exposure, and erosive esophagitis. A RCT on Stretta by Kalpala et al showed 80% had improvement in QoL compared to 40% in the control group.

Endotherapy is not feasible in all patients (large hiatus hernia and obese), however can be considered in a selected group of patients with mild esophagitis, small hiatal hernia (<2 cm), endoscopic Hill’s grade II-III, and absence of Barrett’s esophagus. Similar to anti-reflux surgery, objective evidence of GERD should be documented and motility disorder should be ruled out in patients with GERD undergoing endotherapy.

43. The complications of GERD include peptic stricture, Barrett’s esophagus and GI bleeding.

Voting percentage: A 100
Level of evidence: II-1
Grade of recommendation: A

Widespread use of PPI has reduced GERD complications dramatically. Peptic esophageal stricture is infrequently seen, and occurs in elderly patients with long history of reflux disease. It usually occurs at the squamo-columnar junction and measure 1–4 cm in length. Predictive factors for stricture formation are lower esophageal sphincter tone of (<8 mmHg), hiatus hernia, impaired esophageal motility, and duodenogastric reflux. Patients with peptic stricture usually present with dysphagia. Barium esophagram may be used to define location, length and character of stricture. Once the malignancy is ruled out, patient can be posted for sequential esophageal dilatation followed by long term PPI therapy.

GI bleeding in GERD is predominantly seen in patients with erosive esophagitis; the prevalence is as high as 8.2%. Factors associated with bleeding are severe esophagitis, low performance status and anticoagulant therapy. Treatment with PPI is the standard treatment option.

Barret’s esophagus (BE) is a premalignant condition in which the normal stratified squamous epithelium of the distal esophagus is replaced by columnar mucosa with intestinal specialized metaplasia. BE should be diagnosed when normal light pink color of esophagus is replaced by salmon pink color of gastric mucosa extending ≥1 cm above the gastroesophageal junction. The Prague C and M classification system is commonly used for characterization BE on endoscopy. In Prague classification C stands for circumferential extension of metaplasia and M for maximal length of metaplasia (length between the most proximal point of columnar epithelium and the gastroesophageal junction). The risk factors for BE in the Asia-Pacific region are ethnicity, older age and male gender, long duration of reflux symptoms, abdominal obesity and smoking. Prevalence of BE in India ranges from 2.6% - 9% of patients with GERD.

Conclusion

The prevalence of GERD in large population-based studies is approximately 10% and is probably increasing due to lifestyle changes and increase in obesity. H. pylori infection has a negative association with GERD. Diagnosis of GERD should be mainly based on symptoms in the community, and empiric treatment with PPI/H2RA should be given. All PPIs in equipotent doses are similar in their efficacy in the management of symptoms. Patients with symptoms not adequately responding to PPI trial are regarded as having PPI-refractory GERD. Invasive investigations should be limited to patients with alarm symptoms and those with refractory GERD. The management algorithm is provided in Figure 1.
References


Pneumomediastinum as a Presenting Feature of COVID-19—an Observation

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Sir

There is a major health emergency in the world due to the pandemic by the novel Coronavirus COVID-19 with more than a million people infected in India as well.

Many features of the infection have been described on CT scans worldwide, both parenchymal and extraparenchymal. The presentations on CT depend on the evolution in time of the pathology.

The most common and early seen presentation is the parenchymal ground glass opacifications. The occurrence of spontaneous pneumomediastinum is a rare presentation. We aim to highlight an event of a COVID-19 pneumonia presenting as a Spontaneous Pneumomediastinum (SPM) and discuss the possible mechanism and prognosis of this association.

A 67-year-old gentleman, known hypertensive and a recently diagnosed Diabetic, presented to the Emergency Department of a tertiary care hospital, with complaints of acute onset chest tightness and breathlessness of 1 day duration, which had worsened over the last few hours. At presentation he had tachycardia (HR 110 beats/min), tachypnoea (RR – 26/min), blood pressure was 140/90 mmHg, and temperature was normal, with an Oxygen saturation of 90% on room air. He was immediately started on oxygen with Non Rebreather mask, following which saturation improved to 94%. Random blood glucose was 285 mg/dl and a complete blood count showed significant leucocytosis (Total leucocyte count 21,900 cells per ul), with neutrophilia (93%) and lymphopenia (3%). There was evidence of acute kidney injury (urea – 74.8 mg/dl, Creatinine – 2.4 mg/dl) and inflammatory markers were markedly elevated, with C Reactive Protein –263.4 mg/L and ferritin – 1559 ng/mL. D-dimer and NT-pro BNP were done, which were elevated as well (5043 ng/mL and 10400 pg/mL respectively). High Resolution Computerised Tomography (HRCT) thorax was done which showed diffuse ground glass opacities with interlobular septal thickening. Note of pneumomediastinum and pneumopericardium was also made(fig 1 and 2). Due to the ongoing pandemic and the patients symptom profile, a COVID-19 RT PCR was sent which was positive.

Patient deteriorated rapidly in the Emergency following which he was intubated and put into mechanical ventilation. He succumbed within 6 hours of arrival to the Hospital.

Spontaneous Pneumomediastinum is a rare condition described by Hamman in 1939 and is defined as the presence of interstitial air in the mediastinum known to occur spontaneously. It is not associated with any surgical intervention, trauma or organ injury, mechanical ventilation, or any intrathoracic infection.

The presence of extra-alveolar air in the mediastinum is recognized as Pneumomediastinum. Free air from ruptured alveoli leaks, dissecting through the bronchovascular sheaths on towards the mediastinum part.

Macklin in 1944 described the pathophysiology as presence of a pressure gradient between the alveoli and the lung interstitium which results in alveolar rupture causing pneumomediastinum. The resultant gush of air accumulates in the interstitium and circulates through the venous sheaths to the mediastinal area. There can be two ways that can create this pressure gradient. The presence of high intra-alveolar pressure or low pressure in peri-alveolar interstitial space can be seen in an intentional Valsalva maneuver or similar conditions that precipitate the maneuver like sneezing, violent coughing, defecation, fetus delivery. The second proposed mechanism results from any extreme respiratory effort, rapid decrease in atmospheric pressure, diabetic ketosis or marijuana smoking. Pneumomediastinum was found to be a known complication of severe acute respiratory syndrome by Coronavirus outbreaks in the early 2000s. In case of infections like COVID-19, the virus can infect both type I and II pneumocytes resulting in breakdown of the alveolar membrane integrity. Viral infections can also result in increasing of alveolar pressure due to violent coughing and eventually causing alveolar damage.

The development of pneumomediastinum in a COVID-19 Pneumonia is considered a bad prognostic indicator of worsening disease indicating severe damage to the alveolar membrane.

It is considered a self-limiting disease and is managed conservatively. However, it can potentially lead to severe respiratory and circulatory collapse.

We postulate that diffuse alveolar damage due to Covid-19 infection may have resulted in alveolar rupture and cause interstitial emphysema. The resultant air may have dissected along the bronchovascular sheaths into the mediastinum to present as
pneumomediastinum, which may further lead to pneumothorax and subcutaneous emphysema which can prove fatal.

The presence of Pneumomediastinum early in the course of illness indicates severe destruction of the alveolar membrane and should alert the physician of a possible catastrophic fatal event and hence needs closed monitoring.

**COVID-19 Pandemic - Internal Medicine’s Days of Glory!**

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Sir,

In the race of popularity between super-speciality subjects and Internal Medicine, the latter has been an also-ran over the last two decades. The students are no sooner done with the exhausting medicine practical that almost all of them sit for the super-speciality exams, only to come back with sweets for their professors they are soon going to beat with an extra degree.

Medicine is a humble department in any hospital, but for the odd ‘Dengue’ season when the nephrologists or cardiologists don’t want to risk touching the complex fever. The patient of thyroid disorder definitely seeks an opinion or second opinion of the Endocrinologists – ‘He’ may have studied at least something extra in the additional three years of training’. The patient with headache will be at peace only after an MRI advice by the neurologist – ‘Sure there’s nothing there but perhaps he wants to see something?’

Medicine is left with ‘gas’ or ‘generalised body-aches’ which will happily be referred to the gastroenterologists or rheumatologists, if only the ‘doctor-shoppers’ had not become the bread and butter of a physicians’ OPD.

What pride did the physician have all these years? Is it a case of denial or that the ‘grapes are sour’? Or is it unconditional love for Mr. Harrison. Or the power of knowing it all. Or the joy of being the most popular doctor in a party. The proud physician will always respond to the call of ‘Is there a doctor in the room / plane / train?’

Wikipedia describes Internal Medicine as – “Internal medicine or general internal medicine (in Commonwealth nations) is the medical specialty dealing with the prevention, diagnosis, and treatment of internal diseases. Physicians specializing in Internal Medicine are called internists, or physicians (without a modifier) in Commonwealth nations. Internists are skilled in the management of patients who have undifferentiated or multi-system disease processes. Internists care for hospitalized and ambulatory patients and may play a major role in teaching and research.”

A physician is proudly everything this and more. The impeccable diagnostic acumen, to separate one from many; the talent of eliciting clinical signs with hammers and stethoscopes; the admiring gaze of medical students who first learn the beauty of clinical subjects from him; the tremendous potential for research in diseases A-Z. A physician is always a winner in his own eyes.

But for the rest of the medical fraternity just the existence of a ‘looming’ super-speciality, the peer pressure, the yearning for an extra edge, degree or fellowship, leaves Internal Medicine as a stepping stone to more attractive horizons.

Covid-19 in its wake has brought changes one too many. And amidst the gloom there is some cheer for the faculty of Internal Medicine. The physician is the front-line warrior here. When entire countries to continents had its super-specialists in lockdown, the real ‘super-hero’ proudly donned his PPE and let the Covid patient breathe on him. The claps were for him. The lamps were lit in his gratitude. It is the physician on every prime-time news or the covers of leading national magazines talking about drugs, vaccine research, latest guidelines, or taking calls of the hapless common man. He is imparting training to other specialities, sharing his skill-set, and travelling in teams to peripheries to help start Covid services.

The medicine residents are passionate and proud amidst the fear and uncertainty. Following a survey to learn how Covid-19 is affecting students and trainees, Gallagher and Schleyer concluded that while they feel anxious and vulnerable, there is a desire and commitment to serve the sick. They volunteer to fill extra shifts, and are eager to do more.

The pandemic may or may not end one day, the spotlight on the physician will surely last longer. A physician is always a student of medicine, and he is now happily learning the most challenging lesson of his life.

‘To be read as gender-neutral.

**References**


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BISOLONG
(Bisoprolol 2.5 / 5 mg Tablets)

BISOPROLOL IMPROVES SURVIVAL...PROLONGS LIFE

Bisoprolol is included in 2019 WHO* Essential Medicine list

Presenting The Most Appropriate Antibiotic Power in RTI

Zostum-O
Cefditoren Pivoxil 200mg Tablets

For Outright Success

☑ Preferred Option in Cephalosporins in 12 countries

USA, Japan, Italy, Spain, Mexico, Russia, Thailand, Portugal, Egypt, China, Turkey, Indonesia.

☑ 7 International Clinical Trials in 1910 RTI Patients

• 94.4% bacterial eradication in RTI
• 100% success rate as switch over therapy

☑ Robust Indian Data in AECOPD

77.36% Clinical Success & Decreased exacerbations from > 1.5 /2 to avg. 1.3

☑ USFDA approved

Zuventus Healthcare Ltd.