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Dr. E. Moses Road, Opp. Shakti Mill
Compound, Mahalaxmi (West),
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Hypertension and Diabetes: “Predict, Prevent and Protect”

M Chenniappan

India in 2022 is undergoing a transformation in all fields. The health sector is not an exception. The noncommunicable diseases (NCD) have overtaken the communicable disease long back as the major contributor to mortality and morbidity of the Indian population. The ischemic heart disease (IHD) continues to be the number one killer among the NCDS. The major risk factors for IHD are diabetes mellitus (DM), hypertension, and lipids. Despite major advances in the management of these diseases medically, the prevalence, incidence, complications, and mortality due to these diseases are increasing due to various factors including lifestyle changes. At this point, it is about important to know and understand, the complete information about the two gatekeepers to NCD (DM and hypertension) in India. In India, which is a country of “unity among diversity” the disease pattern may also vary region by region, thereby altering the approach to management and prevention of these diseases. In this context, the article by Raghuram et al. titled “The deadly duo of hypertension and diabetes in India: further affirmation from a new epidemiological study” is very relevant. The four main reasons for developing hypertension in type II DM are:

1. Insulin resistance (IR),
2. Diabetic nephropathy,
3. Volume expansion,
4. Macro and microvessel changes.

The other reasons are leptin, advanced glycation end products, and downregulation of peroxisome proliferators active receptor and insulin growth factor receptor. Hence, the IR behaves like a common soil for developing both hypertension and DM. In some, DM comes first, and subsequently, hypertension emerges; in others hypertension precedes DM. The crucial practical implication is that IR is a prediabetic and prehypertensive situation. Although we have many investigations to diagnose IR, the combination of mid-segment obesity and a triglycerides/high-density lipoprotein ratio of >3.5 will serve as a simple surrogate pointer to suspect IR. In type I DM onset of microalbuminuria accelerates the onset of hypertension. Hypertension prevalence is 1.5–3 times more in DM when compared to the general population. At the same time, one should realize that hypertensive patients have a 2.5-time greater risk of developing DM within 5 years than normotensives. Hypertension in a diabetic usually has the absence of nocturnal dipping which predisposes to many cardiovascular complications. In type 1 DM, an increase in night-time systolic blood pressure (BP) precedes the development of microalbuminuria. So nondipping and nocturnal hypertension in a diabetic may be the early predictors of diabetic nephropathy. So, ambulatory blood pressure monitoring helps to identify the patients at risk of cardiovascular disease (CVD) as well as kidney disease in DM. The therapeutic intervention with angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers is warranted in these patients. Moreover, when hypertension and diabetes coexist, the mortality due to CVD increases by four times when compared to those who do not have both of these diseases. When we diagnose hypertension in DM or DM in hypertension, it is too late for preventing future complications. So, it is prudent to identify those who are in prediabetic and prehypertensive (high normal BP) status and employ appropriate methods to prevent both these diseases. In this context, the article by Raghuram et al. assumes significance.

The important information in this study is the different prevalence of hypertension in DM across various regions of India as well as the crucial statistics regarding the relationship between prediabetes and prehypertension, now renamed as high normal BP (120–139/85–89). When compared to established hypertension which is the highest in the Northeast (58.3%) and lowest in Jammu and Kashmir, the high normal BP is highest in Jammu and Kashmir (67.5%) and lowest in the Northeast (51.8%). This reverse statistic is interesting in the sense that, in addition to taking care of established hypertension in the Northeast, we have to prevent the development of hypertension in more than 50% of the Jammu and Kashmir population by employing lifestyle measures. This study also highlights that in newly diagnosed DM, hypertension was pre-existing in 10–18% of patients (highest in Northeast), and new hypertension was detected in 24–42% of new diabetics (maximum in Northeast). The prevalence of high normal BP is between 50 and 70% (highest in Jammu and Kashmir). Another interesting fact is that regarding prediabetes and people at high risk of developing DM. The presence of hypertension in prediabetes is the highest in the North and Northeast and lowest in the West. About 57% of patients had both prediabetes and high normal BP. In this situation, we aim to prevent both DM and hypertension. High normal BP is more than 50% irrespective of DM, pre-DM, or high risk for DM. Here is the window of opportunity to prevent hypertension in all these subjects, across India.

The Screening India’s Twin Epidemic (SITE) study conducted in 2012 reported about 45% of patients had DM and hypertension. In DM, hypertension prevalence was about 60%. In 20% of known DM patients, new hypertension was diagnosed and new DM was identified in 7% of known hypertensives. In the present study, new hypertension was diagnosed in >30% of known DM patients in North and Northeast indicating the increasing trend of new hypertension in DM. In Chennai Urban Rural Epidemiology Study (CURES-52), it was shown that the average HbA1c in known hypertension was 6.7, establishing the fact that hypertension predisposes to DM. In an interesting article about the relationship between hypertension and DM, Sun et al. reported through bidirectional Mendelian randomization analysis that type II DM to systolic hypertension may be causal but hypertension to DM is unlikely to be causal and may be genetically determined.

In diabetes, hypertension should not be allowed to develop by employing appropriate measures. In hypertension, DM should be prevented. Although we keep concentrating on the diagnosis and management of hypertension in DM and vice versa, individuals with...
IR (pre-DM and high normal BP) should be identified before the development of DM and hypertension, and appropriate measures like lifestyle modification should be applied to prevent these “deadly duo.” For this approach, we need epidemiological information about DM, pre-DM, and patients who are at high risk of developing DM and their relationship to high normal BP, known hypertension, and newly detected hypertension across India to plan various preventive and management strategies according to the regional characteristics. The study by Raguram et al. and future bigger epidemiological studies may be able to give a great insight into this area. So, what we need is to “predict, prevent and protect” Indians from these two “ghostly ghosts.”

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<td>YES</td>
<td>NO</td>
<td>NO</td>
</tr>
<tr>
<td>Synergistic effect</td>
<td>YES</td>
<td>YES</td>
<td>NO</td>
</tr>
<tr>
<td>Published efficacy data in Indian patients</td>
<td>92.5%</td>
<td>85.6%</td>
<td>No data</td>
</tr>
<tr>
<td>Published safety data in Indian patients*</td>
<td>9.6%</td>
<td>23.2%</td>
<td>No data</td>
</tr>
</tbody>
</table>

**References**
1. Walekar A, Chodankar D, Naqvi M, Trivedi C. Assessment of Bioequivalence of Fexofenadine and Montelukast Fixed Dose Combination Tablet Versus Separate Formulations of the Individual Components at the Same Dose Levels. Indian journal of pharmaceutical sciences, 2016, 78(5), 656-56
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The Deadly Duo of Hypertension and Diabetes in India: Further Affirmation from a New Epidemiological Study

Kashinath G Metri1, Nagaratna Raghuram2*, C Venkata S Ram3, Amit Singh4, Suchitra S Patil5, Sriloy Mohanty6, Sreedhar Palukuru7, Nagendra HR8

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ABSTRACT

Introduction: Hypertension is highly prevalent in patients with type II diabetes mellitus. India has some of the highest rates of diabetes and hypertension worldwide, but there is a lack of local data on the coexistence of these two risk factors. This study determined the prevalence of hypertension in patients with, or at high risk of, type II diabetes mellitus across India.

Methods: Data came from a nationwide trial evaluating the effects of yoga-based lifestyle modification for the prevention/management of type II diabetes. Participants were recruited based on randomized house-to-house screening in urban and rural areas from 65 districts of 29 states/union territories. Eligible individuals were aged 20–80 years and had diabetes or were at high risk of diabetes (IDRS ≥ 60). Anthropometric and demographic data were obtained, and resting blood pressure and blood glucose levels were recorded.

Results: This analysis included data from 14,135 individuals. Of these, 25% had self-reported diabetes, 19% were diagnosed with diabetes during the trial, and 26.8% were at high risk for type II diabetes. In these three patient groups, hypertension prevalence rates were 58%, 41.0%, and 35.8%, respectively. The prevalence of hypertension was highest in the North East region and lowest in the North West.

Conclusion: The high prevalence of hypertension in patients with, or at risk of diabetes, highlights the urgent need for policies to manage this population, who are at high risk of cardiovascular disease and death.

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INTRODUCTION

There is a growing worldwide epidemic of noncommunicable diseases (NCDs), and two of the most common of these are cardiovascular disease (for which hypertension is a significant risk factor) and diabetes mellitus.1 In India, NCDs contribute to 62% of all deaths and 48% of total national mortality occurs prematurely.2 This makes hypertension and diabetes a significant public health issue.

Individually, both hypertension and diabetes mellitus are associated with increased risk of cardiovascular disease.3,4 Risk is even greater when these two conditions are present simultaneously, and the coexistence of hypertension and diabetes makes a substantial and important contribution to the development and progression of micro and macrovascular complications, and the development of cardiovascular disease.5–8 Hypertension is the main contributor to morbidity and mortality in patients with diabetes, and substantially increases both the direct and indirect costs of diabetes.5 Data from the Framingham Heart Study showed that the coexistence of hypertension and diabetes increased rates of all-cause mortality and cardiovascular events compared to patients with diabetes and normal blood pressure (BP).9 Furthermore, both diabetes and hypertension are significant contributors to the development of dementia and Alzheimer’s disease.10–12

India has some of the highest rates of diabetes and hypertension worldwide. To facilitate the informed development of strategies to manage these conditions, it is important to know the local prevalence of hypertension in diabetes. Therefore, this study determined the prevalence of hypertension in patients with, or at high risk of having, type II diabetes mellitus.

METHODS

Study Design

The current study used data from the Niyanta Madhumeha Bharata Abhiyana study, a nationwide trial evaluating the effects of yoga-based lifestyle modification for the prevention and management of type II diabetes.13 The trial was conducted in 29 of the 35 Indian states and union territories. The Niyanta Madhumeha Bharata Abhiyana study was approved by the Institutional Ethical Committee of the Indian Yoga Association. The trial was registered in the Central Trial Registry of India. All patients provided written informed consent prior to enrolment in the study.

Study Population

Individuals (males and females) aged 20–70 years who had self-reported diabetes (confirmed based on prescription and/or medication use), newly diagnosed diabetes (glycosylated hemoglobin (HbA1c) > 6.5%), prediabetes (HbA1c 5.3–6.49%), or an Indian Diabetes Risk Score (IDRS) ≥60 indicating high diabetes risk were eligible for the parent study.

Sampling Units

To account for cultural heterogeneity, the country was stratified into seven regions (zones) that included contiguous states/union territories: North West; North East; North; West; Central; East; and South. Ten percent of the total number of districts in the country were sampled. The statistician then randomly shortlisted two districts in the state (double the number of districts needed), then one of the two shortlisted districts was chosen by the local zonal co-coordinator based on suitability of the local conditions. Next, a list of all urban and rural clusters in the selected district (as per the 2011 Census) was prepared; four villages were randomly selected from each selected district. Similarly, from the list of urban clusters, one town/city then one ward in that town/city and finally two census enumeration blocks (CEBs) from each

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ward were selected. All households within the selected rural or urban clusters (village or CEB, respectively) were surveyed and a unique number was assigned to each household.

**Assessments**

Height, weight, body mass index (BMI), and waist circumference were determined using standard techniques. Socioeconomic status (low, middle, and high) was determined using the Kuppuswamy scale, taking into account education, occupation, and income.

Blood pressure was measured by using the same electronic measuring device (Omron HEM-7120) at all locations. Blood pressure was measured in the right brachial artery after 5 minutes of rest with the subject seated, with feet resting on the floor and the arm supported at heart level. Two measurements at an interval of 10 minutes were recorded and the average of the two was used for analysis.

Hypertension was defined based on the JNC-VII criteria, with BP categories as follows: normal BP, ≤120/80 mmHg; prehypertension, 120–139/80–89 mm Hg; stage I hypertension, 140–159/90–99 mm Hg; and stage II hypertension, ≥160/100 mm Hg. Individuals with a confirmed diagnosis of hypertension (based on medical records and/or prescriptions), with or without good BP control, and those with hypertension diagnosed during the study were included in this analysis.

Diabetes risk was determined using the IDRS, a screening tool to identify patients at high risk of developing diabetes that has a sensitivity of 72.5% and specificity of 60.1% in the Indian community. It takes into account age, family history, physical activity, and waist circumference, and scores ranging from 0 to 100, with a score of ≥60 indicating high diabetes risk. Glycosylated hemoglobin was determined by high-pressure liquid chromatography using the Variant II Turbo machine (Bio-Rad, Hercules, California) certified by the National Glycohemoglobin Standardization Program. All samples were processed in an accredited central laboratory (SRL, India). Prediabetes was defined as HbA1c 5.7–6.49% and no diabetes was defined as HbA1c <5.7%.

**Data Collection and Analysis**

An android app developed for the purpose was used for data collection. Uploaded data from assessment forms and laboratory data were checked for matching of codes. Cases with incorrect entries, extreme values, and missing data were excluded. Clean data were analyzed using SPSS (Ver21.0) and R (Ver3.5.1) software. Zone-wise weighted prevalence was calculated after determining the response and nonresponse rates. Cross tabs and frequencies were calculated using response rate as "weights." Logistic regression was implemented to determine the association between diabetes status and the presence of hypertension. Reference was set to sequential contrast for all variables.

**RESULTS**

**Study Population**

A total of 17,875 individuals had hypertension prevalence data available (63.2% urban and 36.8% rural). Of these, 3,560 were excluded due to extreme values and/or incomplete data, leaving 14,315 who were included in the current analysis (61.2% urban and 38.8% rural). Patient demographical and clinical data at baseline are summarized in Table 1, both in the overall study population and in subgroups based on diabetes status.

**Prevalence of Hypertension and Prehypertension**

The weighted prevalence of hypertension in patients with known or newly-diagnosed type II diabetes mellitus was 45.8% (Table 2). Hypertension prevalence was highest in the North East zone (58.3%) and lowest in the North West zone (36.5%) (Table 2).

Prehypertension was also common in patients with diabetes (overall weighted prevalence 59.7%) and in those with prediabetes (overall weighted prevalence 57.3%) (Table 2). Regional prevalence of prehypertension was the opposite of that for hypertension, being highest in the North West (67.5%) and lowest in the North East (51.8%) (Table 2).

Logistic regression showed a strong predictive association between the presence of diabetes (known and newly diagnosed) and both hypertension and prehypertension (Table 3). There was also a significant association between prediabetes and hypertension (but not prehypertension). In addition, increasing age and male sex were significantly associated with the presence of both hypertension and prehypertension (Table 3). No significant associations between area of residence (urban or rural) or socioeconomic status and hypertension were identified (Table 3).

**DISCUSSION**

This cross-sectional multicenter study found a high prevalence of hypertension in patients with, or at high risk of, type II diabetes mellitus in the Indian population, with regional variation in rates. The overall prevalence of...
The Deadly Duo of Hypertension and Diabetes in India

The prevalence of hypertension in patients with diabetes in this study (58.1%) is much higher than that in the general population, as reported in systematic reviews of local and regional hypertension epidemiology in India (25–30% in urban adults and 10–20% in rural adults).17–19, confirming type II diabetes as an important risk factor for hypertension. While there is a reasonable body of data regarding the general prevalence of hypertension in India (which appears to be increasing),20 to the best of our knowledge, none have investigated hypertension prevalence specifically in patients with, or at risk of, type II diabetes mellitus. The high rate of hypertension in Indian patients with or at risk of type II diabetes is consistent with findings in other populations. For example, the hypertension prevalence rate in patients with known diabetes in the current study (58.1%) was nearly identical to that reported in a recent cross-sectional study conducted in Ethiopia (59.5%),22 and is similar to the high rates documented in other parts of Africa and Israel.23–26 The occurrence of hypertension in at least 50% of patients with diabetes mellitus has also been reported in Japan,27 Europe,28 and the US.29

Hypertension and diabetes share many risk factors, including pathological changes such as increased inflammation, dysregulated autonomic function, and perturbations of the renin–angiotensin system.30 Other contributors to the high prevalence of hypertension in patients with diabetes could include urbanization, a high salt diet, and stress. In addition, possible roles for single nucleotide polymorphisms related to HbA1c and increased muscle sympathetic nerve activity (as revealed by microneurographic recordings) have been identified.31,32 Effective management of risk factors is central to the effective prevention and management of NCDs, and for limiting the substantial socioeconomic burden imposed by these conditions.33,34 This requires the cooperation of scientists, the medical community, and policymakers to facilitate the development and implementation of prevention and control strategies for hypertension in patients with type II diabetes mellitus. We strongly recommend periodic screening of both BP and blood glucose to allow both hypertension and diabetes to be

<table>
<thead>
<tr>
<th>Diabetes categories</th>
<th>HTN/Pre-HTN</th>
<th>Overall India</th>
<th>Central</th>
<th>East</th>
<th>Jammu and Kashmir</th>
<th>North</th>
<th>North East</th>
<th>South</th>
<th>South East</th>
<th>West</th>
</tr>
</thead>
<tbody>
<tr>
<td>Known + new diabetes</td>
<td>45.8%</td>
<td>50.2%</td>
<td>44.6%</td>
<td>36.5%</td>
<td>50.4%</td>
<td>58.3%</td>
<td>43.0%</td>
<td>50.2%</td>
<td></td>
<td></td>
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<tr>
<td>n = 6,461</td>
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<tr>
<td>Known T2DM</td>
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<td>n = 3,626</td>
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<td>(A1c &gt; 6.5)</td>
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</tr>
<tr>
<td>Prediabetes*</td>
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<td></td>
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<tr>
<td>(A1c 5.7–6.49%)</td>
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<td></td>
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<tr>
<td>Nondiabetes**</td>
<td></td>
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<td></td>
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<tr>
<td>(A1c &lt; 5.7%) with only high IDRS (&gt;60)</td>
<td></td>
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<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Values are number of patients (%); *Prediabetes was defined as HbA1c of 5.7–6.49%. **No diabetes was defined as HbA1c of <5.7%; HTN, Hypertension; T2DM, Type II diabetes mellitus

<table>
<thead>
<tr>
<th>Predictors</th>
<th>Odds ratio (95% CI) for total hypertension</th>
<th>Odds ratio (95% CI) for prehypertension</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>1.042 (1.039–1.045)*</td>
<td>1.032 (1.027–1.036)*</td>
</tr>
<tr>
<td>Sex (male vs female)</td>
<td>1.074 (1.099–1.154)*</td>
<td>1.437 (1.303–1.585)*</td>
</tr>
<tr>
<td>Area (urban vs rural)</td>
<td>1.035 (0.961–1.114)</td>
<td>1.011 (0.916–1.115)</td>
</tr>
<tr>
<td>Total diabetes (yes vs no)</td>
<td>1.688 (1.568–1.818)*</td>
<td>1.365 (1.220–1.528)*</td>
</tr>
<tr>
<td>Self-reported diabetes (yes vs no)</td>
<td>1.963 (1.808–2.132)*</td>
<td>1.245 (1.084–1.430)*</td>
</tr>
<tr>
<td>Newly diagnosed diabetes (yes vs no)</td>
<td>1.355 (1.218–1.516)*</td>
<td>1.456 (1.243–1.706)*</td>
</tr>
<tr>
<td>Prediabetes (yes vs no)</td>
<td>1.244 (1.124–1.377)*</td>
<td>1.080 (0.953–1.225)</td>
</tr>
<tr>
<td>Socioeconomic status (vs low)</td>
<td>Middle</td>
<td>0.966 (0.871–1.071)</td>
</tr>
<tr>
<td></td>
<td>Upper</td>
<td>1.000 (0.895–1.116)</td>
</tr>
</tbody>
</table>

*p < 0.001; CI, Confidence interval
The Deadly Duo of Hypertension and Diabetes in India

detected, and to facilitate early intervention with the goal of preventing complications. In addition, education and supervised implementation of a healthy lifestyle including physical activity, a healthy diet, and stress management should be implemented in patients with type II diabetes and hypertension. Complementary therapies such as yoga have also been shown to make a contribution to the prevention and management of type II diabetes and hypertension. 55–37

A key strength of this study is that it is the first to report the prevalence of hypertension in patients with type II diabetes in India. In addition, data were collected in a consistent manner from all populous states in the country. However, several limitations also need to be taken into account when interpreting these findings. Hypertension prevalence data were obtained from a randomized controlled translational trial that had dual objectives and was not specifically designed as a survey for estimating the prevalence of hypertension. In addition, the nonresponse rate of more than 50% may limit the generalizability of the data and conclusions, although data were collected using a four-level (states grouped into zones, districts, and rural villages or CEUs of a ward in a town) cluster randomization procedure supervised by a monitoring team (central research team, zonal coordinator, and senior research fellows). Furthermore, the proportion of rural and urban patients was not equal, and any discrepancies in contributing factors in these different population regions could have influenced our findings.

In summary, this study showed that the prevalence of hypertension in Indian patients with type II diabetes patients is very high. Therefore, early screening and effective prevention and management of hypertension should be included in the care of patients with type II diabetes.

References


Clearing the Myths around non-nutritive/noncaloric Sweeteners: An Efficacy and Safety Evaluation

Mangesh Tiwaskar1, Viswanathan Mohan2*

Received: 27 November 2021; Accepted: 10 March 2022

ABSTRACT

Non-nutritive sweeteners (NNSs) are used to substitute sugar in the diet and are approved by the regulatory bodies in many countries, including the Food and Agriculture Organization (FAO)/the World Health Organization (WHO). Non-nutritive sweeteners are here to stay, as it is an effective strategy to reduce sugar and caloric intake which is a public health priority today. It is a tool to increase dietary compliance in the management of obesity and diabetes and is a partner for fitness seekers. However, the debate on its safety and efficacy continues, including several myths associated with its usage. This review has evaluated the scientific literature in-depth and concludes that NNSs are safe to use within an acceptable daily intake (ADI). Non-nutritive sweeteners are beneficial for their intended use, including weight management and diabetes control when consumed as a part of a dietary management program. The current data do not provide sufficient evidence that NNSs can affect the gut microbiome, and more research, particularly at relevant doses, is required. We also need more randomized control trials (RCTs) among the Indian population on the impact of sugar reduction with NNSs and its health benefits to strengthen the evidence for its use in medical nutrition management and preventive health, helping the individual make an informed choice.

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INTRODUCTION

Non-nutritive/noncaloric sweeteners are defined as food additives that are used to replace sugar and give food a sweet taste, thus helping in decreasing caloric and sugar intake. The tabletop sweeteners are products that consist of or include permitted NNSs approved by regulatory bodies like the United States Food and Drug Administration (USFDA) Joint FAO/WHO Expert Committee on Food Additives (JECFA), country-specific regulatory bodies, etc.) and are intended for use as an alternative to sugar, to their ultimate customers. Predominantly there are two kinds of sweeteners—caloric sweeteners and noncaloric/NNSs/low-caloric sweeteners (LCSSs). Sucrose, glucose, and fructose are the foremost bulk caloric sweeteners used in food and beverages or packed in small containers for retail sale. Caloric sweeteners add bulk and calories to the food. These sweeteners are generally carbohydrates or sugar alcohols that have a similar sweetness to sugar, for example, sorbitol, sorbitol syrup, mannitol, isomalt, polyglycitol syrup, maltitol, maltitol syrup, lactitol, xylitol, etc. Sugars add 4 kcal/gm to foods, while sugar alcohols add calories ranging from 0.2 to 2.6 kcal/gm. Conversely, high-intensity sweeteners/NNSs have a sweet taste, are noncaloric, do not provide bulk to the food, have multifold sweetness than sugar, and are consequently used in small amounts. These include steviol glycoside, thaumatin, aspartame, sucralose, neotame, acesulfame potassium, saccharin, etc.1

Sugar is deemed as the major contributing factor for the increased risk of obesity since it adds caloric value to the food.1–3 Obesity is a major public health concern worldwide,2–4 and its prevalence has increased evidently over the past few decades.5 It is considered as the major cause of comorbidities leading to diabetes mellitus, cardiovascular disorders, hypertension, certain cancers, and other health problems.3,5 Owing to a high burden of the disease, the WHO has recommended that the total added sugars should be restricted to below 10% (preferably 5%) of the total energy intake.4–7 Therefore the regulatory bodies around the world have recommended reducing the intake of sugar to combat the issue of obesity and related comorbidities.2 The use of NNSs is one of the most important strategies that may help in substituting the sugar due to their sweetness, palatability, and addition of none or few calories to food.2–5

Several studies have demonstrated that substituting sugars with NNSs has been useful in preventing and managing obesity and associated disorders.2,3 In 2011, the European Food Safety Authority (EFSA) concluded that there was sufficient scientific evidence to support the claims that NNSs like sucralose reduced postprandial blood sugar levels and maintained tooth mineralization by decreasing tooth demineralization.8

Despite the consistent reassurances from food safety authorities, there exists some distrust regarding the use of NNSs among healthcare professionals.2 The present succinct review focuses on busting the myths surrounding the efficacy and safety of NNSs in humans by deliberating their safety and efficacy on health outcomes.

NON-NUTRITIVE SWEETENERS: THE JOURNEY FROM DISCOVERY TO HUMAN USE

Non-nutritive sweeteners have an intensely sweet taste that provides very low or zero calories. These agents are used in minimal quantities as they have greater sweetness than sugar.1,3 Non-nutritive sweeteners have been used safely in food and drinks all over the world for over a century. Saccharin was the first NNS to be discovered in 1879 by Remsen and Fahlberg. This was followed by the discovery of stevia, cyclamate, aspartame, acesulfame potassium, sucralose, and neotame. Non-nutritive sweeteners differ from each other in terms of their sweetness, unique structure, metabolic fate, and technical characteristics.3 The properties of the most used NNSs are summarized in Table 1.

HEALTH OUTCOMES OF NNSs

Several studies have established the effectiveness of NNSs in the maintenance of body weight, treatment of obesity, management of diabetes, and prevention/reduction of dental caries.1 However, there

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Clearing the Myths around non-nutritive/noncaloric Sweeteners

Explain how the findings in evidence-based medicine are biased. Unintended weight gain due to NNS consumption and its impact on obesity and metabolic syndrome.

Table 1: Characteristics of various NNSs

<table>
<thead>
<tr>
<th>NNS</th>
<th>Saccharin</th>
<th>Stevia</th>
<th>Cyclamate</th>
<th>Aspartame</th>
<th>Acesulfame potassium</th>
<th>Sucralose</th>
<th>Neotame</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chemical composition</td>
<td>As sodium salt of an organic acid</td>
<td>Consists of steviol glycosides</td>
<td>Exists as calcium or sodium salts of cyclamic acid</td>
<td>Consists of a methyl ester of two amino acids, aspartic acid, and phenylalanine</td>
<td>Potassium salt of an organic acid</td>
<td>Disaccharide made from sucrose</td>
<td>Derived from aspartic acid and phenylalanine</td>
</tr>
<tr>
<td>Relative sweetness to sucrose</td>
<td>300–600</td>
<td>250–300</td>
<td>30</td>
<td>160–220</td>
<td>150–200</td>
<td>400–800</td>
<td>7000–13,000</td>
</tr>
<tr>
<td>Calories (kcal/gm)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>4*</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Metabolic and biological properties</td>
<td>Not metabolized; excreted unchanged</td>
<td>Staviosides are metabolized to steviol; excreted in the urine as steviol glucuronide</td>
<td>Generally not metabolized; excreted unchanged</td>
<td>Metabolized to its constituent amino acids and methanol</td>
<td>Not metabolized; excreted unchanged</td>
<td>Minimally metabolized; excreted unchanged</td>
<td>Extensively metabolized to phenylalanine and methanol; excreted via feces and urine</td>
</tr>
<tr>
<td>ADI (mg/kg bodyweight) as per JECFA</td>
<td>5</td>
<td>4 mg of steviol equivalents or 12 mg of high purity stevia extracts</td>
<td>11</td>
<td>40</td>
<td>15</td>
<td>15</td>
<td>2</td>
</tr>
<tr>
<td>Global status (Codex approval for use in food, beverages, and tabletop sweeteners)</td>
<td>Approved in over 100 countries</td>
<td>Approved in nearly 49 countries</td>
<td>Permitted in more than 100 countries</td>
<td>Approved in over 100 countries</td>
<td>Approved in approximately 90 countries</td>
<td>Approved in nearly 80 countries</td>
<td>Approved in more than 40 countries</td>
</tr>
<tr>
<td>Indian regulatory approval</td>
<td>Allowed as non-caloric sweetener in some of the food product categories specified in Food Safety and Standard Regulations</td>
<td>Allowed as non-caloric sweetener in some of the food product categories specified in Food Safety and Standard Regulations</td>
<td>Not permitted</td>
<td>Allowed as non-caloric sweetener in some of the food product categories specified in Food Safety and Standard Regulations</td>
<td>Allowed as non-caloric sweetener in some of the food product categories specified in Food Safety and Standard Regulations</td>
<td>Allowed as non-caloric sweetener in some of the food product categories specified in Food Safety and Standard Regulations</td>
<td>Allowed as non-caloric sweetener in some of the food product categories specified in Food Safety and Standard Regulations</td>
</tr>
</tbody>
</table>

a Although aspartame provides 4 kcal/gm, due to its high sweetness, it is used in very small amounts thus providing practically no calories. b Methanol is formed in small quantities lesser than that equivalent to commonly found in many foods.

Effect on Body Weight/Body Mass Index

Subjects with obesity commonly replace caloric sweeteners with NNSs to maintain the pleasure of sweet taste and reduce energy intake. However, the effect of NNSs on weight gain and reduction is debatable with evidence suggesting weight loss or otherwise. Epidemiological studies in rodent models and human observational studies have recognized that NNSs promote weight gain by altering taste and metabolic signaling, increasing appetite, hunger, sweets cravings, and decreasing satiety. On the contrary, RCTs and human interventional or experimental trials have demonstrated that NNSs assist in weight management by promoting weight loss and maintenance by reducing intake of sugar-containing foods, thereby reducing the net energy intake. Randomized control trials are at the highest level of evidence in evidence-based medicine as these are designed to be unbiased and have less risk of systematic errors. Tables 2 and 3 display the effect of NNSs on body weight.

The variation in the results of different studies may be due to the following reasons:

- Observational studies are known to have significant limitations, including the possibility of reverse causality in studies...
Clearing the Myths around non-nutritive/noncaloric Sweeteners

**Table 2: Effect of NNSs on body weight/BMI**

<table>
<thead>
<tr>
<th>Author (year)</th>
<th>Study type</th>
<th>Study population</th>
<th>Study duration</th>
<th>LCS used</th>
<th>Comparator</th>
<th>Conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stamatakis et al. (2020)</td>
<td>Randomized, controlled, open-label, two-parallel-arm trial</td>
<td>28 healthy individuals</td>
<td>12 weeks</td>
<td>Stevia</td>
<td>Control</td>
<td>Weight maintenance observed with daily stevia consumption</td>
</tr>
<tr>
<td>Peters et al. (2016)</td>
<td>Randomized, equivalence trial</td>
<td>303 weight-stable people with overweight and obesity</td>
<td>1 year</td>
<td>Not specified</td>
<td>Water</td>
<td>NNS beverages were superior to water beverages for weight loss and weight maintenance</td>
</tr>
<tr>
<td>Sørensen et al. (2014)</td>
<td>Sub-study of a single-blind, parallel design, intervention trial</td>
<td>24 healthy, overweight subjects</td>
<td>10 weeks</td>
<td>Aspartame, acesulfame potassium, cyclamate, saccharin</td>
<td>Sucrose</td>
<td>Bodyweight and fat mass decreased with the use of artificial sweeteners and increased with sucrose</td>
</tr>
<tr>
<td>Koyuncu and Balci (2014)</td>
<td>Crossover study</td>
<td>54 prediabetic patients</td>
<td>6 months</td>
<td>Aspartame</td>
<td>–</td>
<td>Aspartame effectively reduced body weight</td>
</tr>
<tr>
<td>Maersk et al. (2012)</td>
<td>Randomized parallel intervention trial</td>
<td>60 healthy, nondiabetic subjects</td>
<td>6 months</td>
<td>Aspartame</td>
<td>Sucrose</td>
<td>Increased ectopic fat accumulation, triglycerides, and total cholesterol levels with sucrose-sweetened soft drinks compared with aspartame-sweetened drinks</td>
</tr>
<tr>
<td>Reid et al. (2007)</td>
<td>Long-term study</td>
<td>133 normal-weighted women</td>
<td>5 weeks</td>
<td>Aspartame</td>
<td>Sucrose</td>
<td>The weight loss was observed with aspartame, while weight gain observed with sucrose</td>
</tr>
<tr>
<td>Raben et al. (2002)</td>
<td>Parallel design, intervention trial</td>
<td>41 healthy, overweight subjects</td>
<td>10 weeks</td>
<td>Aspartame, acesulfame potassium, cyclamate, saccharin</td>
<td>Sucrose</td>
<td>Gain in weight and fat mass was observed with sucrose, while the loss in weight and fat mass observed with artificial sweeteners</td>
</tr>
<tr>
<td>Blackburn et al. (1997)</td>
<td>Prospective, randomized, stratified, two-parallel-arm design trial</td>
<td>163 obese women</td>
<td>Intervention: 16 weeks Maintenance: 1 year</td>
<td>Aspartame</td>
<td>Control</td>
<td>Aspartame may facilitate long-term maintenance of reduced body weight</td>
</tr>
<tr>
<td>Parker et al. (1997)</td>
<td>Community-based cohort study</td>
<td>465 individuals</td>
<td>4 years</td>
<td>Saccharin</td>
<td>–</td>
<td>Weight gain with use of saccharin</td>
</tr>
<tr>
<td>Colditz et al. (1990)</td>
<td>Questionnaires-based cohort study</td>
<td>31,940 healthy women</td>
<td>8 years</td>
<td>Saccharin</td>
<td>–</td>
<td>Continuing weight gain over time with saccharin use</td>
</tr>
<tr>
<td>Stellman and Garfinkel (1986)</td>
<td>Prospective mortality study</td>
<td>78,694 women</td>
<td>1 year</td>
<td>Saccharin (n = 17,016)</td>
<td>Control (n = 61,678)</td>
<td>Long-term use of artificial sweeteners does not help in losing weight or prevent weight gain</td>
</tr>
</tbody>
</table>

where overweight individuals may choose to consume NNS beverages to reduce their risk of weight gain.

- Residual confounding may be another issue with observational studies where insufficient factors about subject characteristics and behaviors were adjusted for in the data analysis.
- The questionnaire-based cohort studies lacked specific information about the use of specific NNSs in the target population.

**Effect on Metabolic Health: A Focus on Diabetes**

In a 2013 position statement and a 2019 consensus report, the American Diabetes Association stated that “the use of nonnutritive sweeteners has the potential to reduce overall calorie and carbohydrate intake if substituted for caloric sweeteners and without compensation by intake of additional calories from other food sources.” The committee further added that “substituting sugar-sweetened beverages in people with diabetes mellitus.” However, there exist some discrepancies as certain studies report a positive association between intake of LCSs and increased risk of obesity, type II diabetes, hypertension, and cardiovascular events. This association may be due to several limitations, including potential reverse causation bias, substantial heterogeneity among the cohorts, potential publication bias, use of different types of low-calorie sweeteners, different outcome measures, and different lengths of follow-up times that resulted in exorbitant variability to pool the results.

**Effect on Taste Receptor and Incretin Secretion**

Taste receptors are involved in the modulation of multiple metabolic processes like satiation, glucose homeostasis, and gut motility. Activation of sweet-taste receptors in the gut plays a role in the regulation of glucose absorption and promoting insulin release. Exposure to food, sugars, or nutrients
Clearing the Myths around non-nutritive/noncaloric Sweeteners

## Effect on Dental Health

Frequent consumption of free sugars is associated with the development of dental caries. A systematic review that appraised the relationship between the amount of free sugar intake and the development of dental caries across age groups revealed that limiting free sugar intake to <10% of daily energy intake diminishes the risk of dental caries throughout the life course. Evidence has revealed that the use of NNSs influences the microbial composition of the oral mucosa that may be utilized to reduce the risk of the development of dental caries. Furthermore, in vitro studies have uncovered that aspartame, saccharin, and sucralose have antimicrobial activity against common periodontal pathogens.

## Association of NNSs with Cancer

The NNSs have undergone a comprehensive safety assessment by the global regulators before their approval in human use. The USFDA, JECFA, and EFSA have confirmed the safety of all approved LCSs as food additives. These bodies have suggested that NNSs should be taken in an amount of ADI. Acceptable daily intake is defined as the estimated amount of NNS that a person can safely consume on an average every day over a lifetime without risk. It is usually set at 1/100 of the no-observed-adverse-effect-level maximum level at which no adverse effects were seen in animal experiments. The levels of NNSs in food ingredients are set to ensure that the actual daily intakes do not exceed the ADIs. However, there are some ongoing debates that NNSs pose health risks like the development of cancer, renal toxicity, genotoxicity, and neurotoxicity, and adversely affect the gut microbiota.

**Bursting the Myths Around the Safety of NNSs**

The NNSs have undergone a comprehensive safety assessment by the global regulators before their approval in human use. The USFDA, JECFA, and EFSA have confirmed the safety of all approved LCSs as food additives. These bodies have suggested that NNSs should be taken in an amount of ADI. Acceptable daily intake is defined as the estimated amount of NNS that a person can safely consume on an average every day over a lifetime without risk. It is usually set at 1/100 of the no-observed-adverse-effect-level maximum level at which no adverse effects were seen in animal experiments. The levels of NNSs in food ingredients are set to ensure that the actual daily intakes do not exceed the ADI.
Table 4: Effect of NNSs on glycemia and glucose hemostasis

<table>
<thead>
<tr>
<th>Author (year)</th>
<th>Study type</th>
<th>Study population</th>
<th>Study duration</th>
<th>LCS used</th>
<th>Comparator</th>
<th>Conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kim et al. (2020)</td>
<td>Randomized, crossover trial</td>
<td>39 healthy individuals</td>
<td>2 weeks intervention</td>
<td>Acesulfame potassium + aspartame</td>
<td>Mineral water</td>
<td>No effect on glucose, insulin, and insulin sensitivity</td>
</tr>
<tr>
<td>Higgins et al. (2018)</td>
<td>Parallel-arm design</td>
<td>100 healthy, lean adults</td>
<td>12 weeks</td>
<td>Aspartame</td>
<td>–</td>
<td>No effect on glycemia, appetite, or bodyweight</td>
</tr>
<tr>
<td>Engel et al. (2018)</td>
<td>Secondary analysis</td>
<td>60 overweight and obese subjects</td>
<td>6 months</td>
<td>Aspartame</td>
<td>Sucrose</td>
<td>No effect of aspartame on long-term glycemic (fasting glucose and insulin) or on insulin sensitivity</td>
</tr>
<tr>
<td>Tey et al. (2017)</td>
<td>Randomized, crossover study</td>
<td>10 healthy males</td>
<td>24 hours</td>
<td>Aspartame, stevia</td>
<td>Sucrose</td>
<td>Minimal effect on 24-hour glucose profiles with LCS</td>
</tr>
<tr>
<td>Grotz et al. (2017)</td>
<td>Double-blind, parallel, randomized clinical trial</td>
<td>47 healthy males</td>
<td>12 weeks</td>
<td>Sucralose</td>
<td>Placebo</td>
<td>Sucralose does not affect glycemic control</td>
</tr>
<tr>
<td>Sylvestsky et al. (2016)</td>
<td>Four-period, crossover study</td>
<td>61 healthy adults</td>
<td>24 hours</td>
<td>Diet soda with sucralose, acesulfame potassium, aspartame</td>
<td>Water with sucralose</td>
<td>Diet sodas augmented GLP-1 responses to oral glucose</td>
</tr>
<tr>
<td>Temizkan et al. (2015)</td>
<td>Prospective study</td>
<td>8 healthy volunteers and 8 newly diagnosed, drug-naive T2DM patients</td>
<td>Not specified</td>
<td>Sucralose, aspartame</td>
<td>Water</td>
<td>Sucralose lowers blood glucose in healthy subjects by enhancing GLP-1 release; however, this is not observed in newly diagnosed T2DM patients</td>
</tr>
<tr>
<td>Hazali et al. (2014)</td>
<td>Prospective study</td>
<td>32 healthy subjects</td>
<td>24 hours</td>
<td>Stevia</td>
<td>Sucrose</td>
<td>Stevia maintained blood glucose even when consumed in a short length of time</td>
</tr>
<tr>
<td>Bryant et al. (2014)</td>
<td>Prospective study</td>
<td>10 healthy subjects</td>
<td>Not specified</td>
<td>Aspartame, saccharin, acesulfame potassium</td>
<td>–</td>
<td>No additional effect of aspartame or saccharin on blood glucose</td>
</tr>
<tr>
<td>Pepino et al. (2013)</td>
<td>Randomized crossover design</td>
<td>17 obese subjects</td>
<td>2 days with 7 days washout period</td>
<td>Sucralose</td>
<td>Water</td>
<td>Sucralose increased peak plasma glucose concentrations, C-peptide, and insulin concentrations, and total insulin AUC after an oral glucose load</td>
</tr>
<tr>
<td>Brown et al. (2009)</td>
<td>Prospective study</td>
<td>22 healthy subjects</td>
<td>24 hours</td>
<td>Sucralose and acesulfame potassium</td>
<td>Carbonated water</td>
<td>Increase in GLP-1 secretion</td>
</tr>
</tbody>
</table>

GLP, Glucagon-like peptide; T2DM, Type II diabetes mellitus; AUC, Area under curve

Table 5: Meta-analysis demonstrating the effect of NNSs on glycemia and glucose hemostasis

<table>
<thead>
<tr>
<th>Author (year)</th>
<th>Study type</th>
<th>LCSs involved</th>
<th>Conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nichol et al. (2018)</td>
<td>Meta-analysis</td>
<td>Aspartame, saccharin, stevia, sucralose</td>
<td>• No increase in blood glucose level</td>
</tr>
<tr>
<td>Greyling et al. (2020)</td>
<td>Meta-analysis</td>
<td>Acesulfame potassium, saccharin, stevia, sucralose, aspartame, stevioside, erythritol</td>
<td>No acute effects on insulminemic responses or the mean change in postprandial glucose levels compared with a control group</td>
</tr>
<tr>
<td>Lohner et al. (2017)</td>
<td>Meta-analysis</td>
<td>ASs (aspartame, acesulfame potassium, advantame, allatame, cyclamate, neotame, neohesperidin dihydrochalcone, saccharin, sucralose) or NNCSs (stevioside, thaumatin, rebaudioside A, brazzein) or NNSs (defined as any combination of AS and NNCS)</td>
<td>• Systematic reviews reported an increased risk of diabetes with the intake of artificially sweetened soft drinks</td>
</tr>
</tbody>
</table>

BMI, Body mass index; ASs, Artificial sweeteners; NNCSs, Natural, noncaloric sweeteners
of high doses of saccharin in one generation of rats. Only one study reported an increased incidence of bladder cancer, while none of the remaining studies found significantly more neoplasia in the saccharin-fed animals than in controls. In the positive study, August Copenhagen Irish rats were used that are susceptible to saccharin-induced bladder cell proliferation due to frequent bladder infection with *Trichosomoides crassicanda* parasite. Further reports on animal studies have revealed that the high urine osmolality in rodents enhances the precipitation of cytotoxic calcium phosphate-containing crystals in the bladder leading to regenerative hyperplasia and tumors.63

A few earlier human epidemiological studies reported an increased risk of bladder cancer with extremely high doses of saccharin. However, further human epidemiological studies failed to reproduce these findings since it was observed that saccharin metabolism varied in different species. This led to the affirmation that saccharin was not associated with the formation of either urinary tract stones or epithelial lesions in humans. Similarly, a few case-control studies revealed an increased risk of bladder cancer in nonsmokers and men consuming artificial sweeteners; however, the largest case-control study analyzing the issue found no relation between the cancer risk and the use of artificial sweeteners. An ecological study reported that aspartame use was associated with an increased risk of breast cancer which might have been a result of increased aspartame use. However, these studies had limitations of inadequate sample size. Overall, the results of this review do not support that aspartame use is associated with an increased risk of cancer in humans. Yet, the largest case-control study reported that daily consumption of pure sucralose or aspartame in doses reflective of typically high consumption has minimal effect on the composition of gut microbiota, including human cells and nonhuman mammalian cells.64

Evidence from animal models has demonstrated that NNSs alter the gut microbiota. A study conducted on mice proved that the exposure of saccharin and aspartame was associated with alterations in the gut microbiota and glucose intolerance.65 However, a recent human study reported that daily consumption of pure sucralose or aspartame in doses reflective of typically high consumption has minimal effect on the composition of gut microbiota, including human cells.66

Table 6 summarizes the evidence to show the association between NNSs and risk of cancer development.

**Effect of NNSs on Gut Microbiota**

Evidence from animal models has demonstrated that NNSs alter the gut microbiota. A study conducted on mice proved that the exposure of saccharin and aspartame was associated with alterations in the gut microbiota and glucose intolerance.65 However, a recent human study reported that daily consumption of pure sucralose or aspartame in doses reflective of typically high consumption has minimal effect on the composition of gut microbiota, including human cells.
Association of NNSs with Renal Toxicity

The increasing rates of obesity and diabetes mellitus have contributed to the rise in the prevalence of chronic kidney diseases (CKDs) worldwide. Several studies have reported that sugar-sweetened beverages, as well as artificially sweetened beverages, are associated with CKDs. On the contrary, some other studies have shown no association between CKD and these beverages.60 However, due to the benefits of artificial sweeteners, the National Kidney Foundation’s guide, Planning for Emergencies, A Guide for People with Chronic Kidney Diseases recommends adding an artificial sweetener as a part of an emergency diet plan.75

Cheungpasitporn et al. conducted a meta-analysis of RCTs and observational studies to evaluate the association between sugar or artificially sweetened beverages with CKD. The results showed that sugar-sweetened beverages increased the risk of CKD by 1.58-fold. Though the study showed an association between the risk of CKD and the consumption of artificially sweetened beverages, this association was not statistically significant. The discrepancies in the result may be due to the following reasons:

- Misclassification of sugar-sweetened and artificially sweetened beverages in some questionnaire-based studies lacking a structured interview.
- Statistical heterogeneities in the study due to differences in methods of CKD diagnosis, type and amount of beverage consumed, and duration of follow-up.
- The observational studies in the analysis inherent the limitations of observational studies which can demonstrate an association, but not a causal relationship.56

Safety of NNSs in Special Population

The safety of NNSs in pregnancy and children has been evaluated and accepted in some countries, but its usage is not permitted in other countries. A full risk assessment report on aspartame published in 2013 by EFSA concluded that aspartame and its by-products are safe for the use in general population (including infants, children, and pregnant women).79 Similarly, the Academy of Nutrition and Dietetics states that the consumption of NNSs is safe during pregnancy and childhood.77 Health Canada had approved the use of stevia in the general population including pregnant women and children.76 de Ruyter et al. evaluated the effects of a sugar-free, artificially sweetened beverage in normal-weight children from 4 to 11 years of age. He reported that the replacement of sugar-containing beverages with noncaloric beverages significantly reduced the occurrence of weight gain and fat accumulation in normal-weight children.79 Clinical studies on the use of NNSs in pregnancy and its effect on long-term outcomes in offspring are the need of the hour, however, its use should be clinically evaluated for the dietary management of gestational diabetes and reducing the sugar intake.79

Table 7: Effect of NNSs on gut microbiota

<table>
<thead>
<tr>
<th>Author (year)</th>
<th>Study type</th>
<th>Study population</th>
<th>Study duration</th>
<th>LCS used</th>
<th>Conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serrano et al. (2021)58</td>
<td>Randomized</td>
<td>46 healthy adults</td>
<td>10 weeks</td>
<td>Saccharin</td>
<td>No change in microbial diversity or composition at any taxonomic level in humans. Therefore, intake of saccharin for a short period at maximum acceptable levels does not induce glucose intolerance or alter gut microbiota in healthy individuals.</td>
</tr>
<tr>
<td>Ahmad et al. (2020)62</td>
<td>double-blind, placebo-controlled, parallel-arm study</td>
<td>17 healthy participants</td>
<td>12 weeks in a crossover design</td>
<td>Sucralose and aspartame</td>
<td>Daily repeated intake of pure aspartame or sucralose has minimal effect on the composition of gut microbiota or production of short-chain fatty acids.</td>
</tr>
</tbody>
</table>

LIMITATIONS

The present review might be limited due to the following factors. Some relevant studies might have been missed inadvertently despite the extensive literature search. Furthermore, the efficacy and safety of NNSs could not be evaluated from an Indian perspective due to the lack of sufficient Indian trials. However, the outcomes of various ongoing trials registered at Clinical Trials Registry–India (CTRI/2019/12/022470, CTRI/2021/04/032809, and CTRI/2021/04/032686) on the use of various NNSs as food additives are awaited.

CONCLUSION

Several regulatory bodies have deemed the safe use of NNSs in adults (including pregnancy) and children when consumed within the ADI. Mere replacement of sugars in daily beverages or as tabletop sweeteners hardly increases the chance to exceed the ADI. Systematic reviews and RCTs, along with interventional and observational trials, have demonstrated the efficacy and safety of various NNSs in human trials bursting the myths around them. These trials have testified that the replacement of sugars with NNSs is an effective strategy for weight loss and maintenance in obese adults. Clinicians and dietitians may explore the arena of replacing caloric sugars with NNSs in their patients due to their safety and efficacy in weight management and reducing postprandial blood sugar levels. The present review attempted to resolve the negative perception with the use of NNSs by evaluating the efficacy and safety profile of various NNSs.

ACKNOWLEDGMENTS

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Influence of Serum Levels of Vitamin D on Insulin Resistance in Patients with Type II Diabetes Mellitus

BN Raghvendra Prasad¹, Tameem Imran², Rumaisa Ahmed³, Sumathi ME⁴, Prasanna Kumar⁵, Chaitra C⁶

Received: 13 October 2019; Accepted: 18 January 2022

Abstract

Background: Vitamin D plays an important role in bone and modulates mineral metabolism and immune function with probable link to several chronic and infectious conditions. In vivo studies have revealed that vitamin D deficiency reduces insulin secretion capacity of the islet beta cells in pancreas. Several studies have shown a correlation between vitamin D levels and insulin resistance, nonetheless, extensive studies showing the relationship between the two are lacking especially among southern Indian population. So the present study was aimed at evaluating the relationship between vitamin D and insulin resistance by using homeostatic model assessment-insulin resistance (HOMA-IR).

Materials and methods: In a cross-sectional study, 184 people among which 92 were diabetic and 92 were nondiabetic were recruited at RL Jalappa Hospital, Kolar in the Department of Medicine between May 2018 and April 2019. Fasting serum insulin (I₀), fasting plasma glucose (G₀), hemoglobin A1c (HbA1C), renal function test, liver function test (LFT), lipid profile, and vitamin D levels were estimated. IBM SPSS version 22 was used for statistical analysis.

Results: The prevalence of vitamin D deficiency in our study was (72) 78.2% among diabetic cases and (59) 64.1% among the nondiabetic controls, with the diabetic cases showing lower levels of vitamin D than the controls, however, it was not statistically significant.

There was no significant difference in homeostatic model assessment-beta-cell function (HOMA-B) and HOMA-IR between vitamin D deficient and nondeficient groups among cases and controls.

Conclusion: Vitamin D deficiency is prevalent in both type II diabetes mellitus (T2DM) as well as nondiabetic. Furthermore, there is no association between vitamin D deficiency and insulin resistance or beta-cell function.

Introduction

Around 50.9 million Indians suffer from diabetes, and this figure will rise up to 80 million by 2025, making India the “diabetes capital” of the world. Type II diabetes is a metabolic syndrome that is characterized by hyperglycemia, insulin resistance, and relative lack of insulin. Several factors including genetic, lifestyle, environmental, and nutritional conditions are important in its development. Out of which recent nutritional factors such as vitamin D status have been shown to play a major role in insulin resistance. Vitamin D plays an important role in bone and mineral metabolism. However, vitamin D has been found to have a major link in many disease conditions such as cancer, cardiovascular disease, and diabetes mellitus. In vivo studies have revealed that vitamin D deficiency reduces insulin secretion capacity of the islet beta cells in pancreas. Moreover, epidemiological studies have demonstrated that vitamin D deficiency is closely related to obesity and increased risk of T2DM. Several studies have shown a correlation between vitamin D levels and insulin resistance, nonetheless, extensive studies showing the relationship between the two are lacking especially among southern Indian population. So the present study is aimed at evaluating the relationship between vitamin D and insulin resistance by using HOMA-IR.

Objectives

• To estimate vitamin D deficiency among diabetic and nondiabetic.
• To calculate insulin resistance between diabetic and nondiabetic.
• To correlate insulin resistance in vitamin D deficient and nondeficient among the diabetic cases.

Materials and Methods

Study Design

This cross-sectional study was carried out by the Department of Medicine in RL Jalappa Hospital, Kolar, between May 2018 and April 2019.

Ethical Considerations

Ethical approval for this study was obtained from Sri Devaraj Ura University as well as the Institutional Review Board of the Hospital. Aims and objectives were explained to the participants and informed consent was taken after patients were willing to participate in the study.

Study Population

A total of 184 people were recruited into the study, among which 92 were diabetic and 92 were nondiabetic population.

Inclusion Criteria

• Age >40 years.
• Newly diagnosed T2DM
• Type II diabetes already on oral hypoglycemic drugs.

Exclusion Criteria

• Patients with hepatic, pancreatic, renal, and bone diseases, malignancy, any history of the use of drugs such as insulin, anticonvulsants, calcium, and vitamin D.

Measurements (Anthropometric and Biochemical)

• Participants underwent general physical examination.
• Height, weight, body mass index (BMI), and systolic and diastolic blood pressure were documented.
• Fasting serum insulin (I₀), fasting plasma glucose (G₀), and HbA1C were measured by enzymatic and chromatographic methods using commercial kits, respectively.
• Serum creatinine, serum electrolytes (sodium and potassium), LFT, and lipid profile.
• Serum 25(OH) vitamin D was measured by radioimmunoassay.
• Table 1.

Materials and methods: In a cross-sectional study, 184 people among which 92 were diabetic and 92 were nondiabetic were recruited at RL Jalappa Hospital, Kolar in the Department of Medicine between May 2018 and April 2019. Fasting serum insulin (I₀), fasting plasma glucose (G₀), hemoglobin A1c (HbA1C), renal function test, liver function test (LFT), lipid profile, and vitamin D levels were estimated. IBM SPSS version 22 was used for statistical analysis.

Results: The prevalence of vitamin D deficiency in our study was (72) 78.2% among diabetic cases and (59) 64.1% among the nondiabetic controls, with the diabetic cases showing lower levels of vitamin D than the controls, however, it was not statistically significant.

There was no significant difference in homeostatic model assessment-beta-cell function (HOMA-B) and HOMA-IR between vitamin D deficient and nondeficient groups among cases and controls.

Conclusion: Vitamin D deficiency is prevalent in both type II diabetes mellitus (T2DM) as well as nondiabetic. Furthermore, there is no association between vitamin D deficiency and insulin resistance or beta-cell function.
Results of Serum Levels of Vitamin D on Insulin Resistance

• Surrogate markers were used to calculate insulin resistance and sensitivity.
  • Homeostatic model assessment-insulin resistance is used to calculate insulin resistance.
  • HOMA-IR = \( \frac{G_0 (\text{mg/dL}) \times I_0 (\mu U/mL)}{405} \)
  • Homeostatic model assessment-beta-cell function is used to assess the beta-cell function.
  • HOMA-B = \( 360 \times I_0 (\mu U/mL)/G_0 (\text{mg/dL}) – 63 \)

Table 1: 25(OH) vitamin D levels and significance

<table>
<thead>
<tr>
<th>Grading of severity</th>
<th>Vitamin D levels</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severe deficiency</td>
<td>&lt;10 nmol/L</td>
</tr>
<tr>
<td>Mild–moderate</td>
<td>10–24 nmol/L</td>
</tr>
<tr>
<td>Optimal</td>
<td>25–80 nmol/L</td>
</tr>
<tr>
<td>Toxicity</td>
<td>&gt;80 nmol/L</td>
</tr>
</tbody>
</table>

Table 2: Gender distribution comparison between two groups

<table>
<thead>
<tr>
<th>Group</th>
<th>Count</th>
<th>%</th>
<th>Count</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cases</td>
<td></td>
<td></td>
<td>Controls</td>
<td></td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td>Female</td>
<td>54</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Male</td>
<td>38</td>
</tr>
</tbody>
</table>

\( \chi^2 = 1.771, \text{df} = 1, p = 0.183 \)

Among cases, 58.7% were females and 41.3% were males and among controls, 51.1% were males and 48.9% were females. There was no significant difference in gender distribution between two groups.

Table 3: Vitamin D distribution comparison between two groups

<table>
<thead>
<tr>
<th>Vitamin D levels</th>
<th>Diabetic (N = 92)</th>
<th>Nondiabetic (N = 92)</th>
<th>Chi-square</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Optimal (25–80 nmol/L)</td>
<td>20 (21.73%)</td>
<td>33 (35.86%)</td>
<td>4.496</td>
<td>0.106</td>
</tr>
<tr>
<td>Mild–moderate (10–24.9 nmol/L)</td>
<td>37 (40.21%)</td>
<td>31 (33.69%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Severe (&lt;10 nmol/L)</td>
<td>35 (38.04%)</td>
<td>28 (30.43%)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Among cases 38.04% had severe, 40.2% had mild or moderate deficiency, and 21.7% had optimal vitamin D levels. Among controls, 30.4% had severe, 33.6% had mild or moderate deficiency, and 37% had optimal vitamin D levels. There was no significant difference in vitamin D levels between two groups.

\[ p \text{-value} < 0.05 \text{ was considered statistically significant.} \]
Table 4: Age, FIL, FBS, HOMA-B, and HOMA-IR comparison between two groups

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Diabetic Median (IQR)</th>
<th>Non-diabetic Median (IQR)</th>
<th>Mann–Whitney U test (p-value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>FIL (mIU/L)</td>
<td>7.85 (4.97, 14.475)</td>
<td>4 (3.1, 5.075)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>FBS (mg/dL)</td>
<td>121 (100, 188)</td>
<td>96.5 (86, 110)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>HOMA 1-B</td>
<td>49.97 (23.21, 97.13)</td>
<td>44.37 (31.29, 79.97)</td>
<td>0.932</td>
</tr>
<tr>
<td>HOMA 1-IR</td>
<td>2.73 (1.53, 5.03)</td>
<td>0.94 (0.72, 1.36)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Among cases, mean age was 51.46 ± 9.59 years, median FIL was 7.85 (mIU/L), median FBS was 121 mg/dL, median HOMA 1-B was 49.97, and HOMA 1-IR was 2.73. Among controls mean age was 50.17 ± 9.70 years, median FIL was 4 (mIU/L), FBS was 96.5 mg/dL, HOMA-B was 44.37, and HOMA-IR was 0.94. There was significant difference in median FBS, FIL, and HOMA-IR between cases and controls.

Table 5: Comparison of anthropometric parameters between the two groups (N = 184)

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Diabetic Median (IQR) (N = 92)</th>
<th>Non-diabetic Median (IQR) (N = 92)</th>
<th>Mann–Whitney U test (p-value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Height (in inches)</td>
<td>1.62 (1.56, 1.67)</td>
<td>1.61 (1.56, 1.67)</td>
<td>0.832</td>
</tr>
<tr>
<td>Weight (in kg)</td>
<td>65 (60, 69)</td>
<td>60 (56, 66)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>BMI</td>
<td>24.61 (23.58, 25.61)</td>
<td>23.43 (21.74, 24.64)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>WHR</td>
<td>1 (0.85, 1.19)</td>
<td>0.87 (0.7, 1)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

There was significant difference in median weight, BMI, and WHR between cases and controls.

Table 6: Comparison of median of lipid profile between the two groups (N = 184)

<table>
<thead>
<tr>
<th>Lipid profile</th>
<th>Diabetic Median (IQR) (N = 92)</th>
<th>Non-diabetic Median (IQR) (N = 92)</th>
<th>Mann–Whitney U test (p-value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cholesterol (mg/dL)</td>
<td>210 (190, 250)</td>
<td>200 (180, 217.5)</td>
<td>0.001</td>
</tr>
<tr>
<td>Triglyceride (mg/dL)</td>
<td>200 (150, 230)</td>
<td>180 (142.5, 210)</td>
<td>0.034</td>
</tr>
<tr>
<td>Low-density lipoproteins (mg/dL)</td>
<td>125 (110, 140)</td>
<td>120 (106.25, 135)</td>
<td>0.167</td>
</tr>
<tr>
<td>High-density lipoprotein (mg/dL)</td>
<td>45 (35, 65)</td>
<td>55 (40, 70)</td>
<td>0.040</td>
</tr>
</tbody>
</table>

There was significant difference in median cholesterol, triglyceride, and high-density lipoprotein between cases and controls.

Table 7: WHR and BMI comparison between Vitamin D deficient and nondeficient groups

<table>
<thead>
<tr>
<th>Vitamin D</th>
<th>Deficient</th>
<th>Nondeficient</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>WHR</td>
<td>Mean Standard deviation</td>
<td>Mean Standard deviation</td>
<td></td>
</tr>
<tr>
<td>0.98</td>
<td>0.229</td>
<td>0.89</td>
<td>0.18</td>
</tr>
<tr>
<td>BMI</td>
<td>24.05</td>
<td>3.83</td>
<td>23.775</td>
</tr>
</tbody>
</table>

*highly significant p-value. WHR was significantly elevated in deficient group compared to nondeficient.

Table 8: HOMA-B and HOMA-IR comparison between vitamin D deficient and nondeficient groups among cases

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Nondeficient Median (IQR) (N = 20)</th>
<th>Deficient Median (IQR) (N = 72)</th>
<th>Mann–Whitney U test (p-value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HOMA 1-B</td>
<td>50.84 (24.62, 87.49)</td>
<td>62.24 (39.45, 100.85)</td>
<td>0.131</td>
</tr>
<tr>
<td>HOMA 1-IR</td>
<td>2.86 (1.37, 5.72)</td>
<td>1.8 (0.96, 3.54)</td>
<td>0.085</td>
</tr>
</tbody>
</table>

Among cases, there was no significant difference in HOMA-B and HOMA-IR between vitamin D deficient and nondeficient groups.
Influence of Serum Levels of Vitamin D on Insulin Resistance

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and Buttriss reported vitamin D deficiency of 2–30% in European adults. Vitamin D though prevalent across the globe shows wide variation in percentages.

Indians are neither overclothed nor they are excessively dark. Experts pin down the deficiency to improper dietary habits, changing lifestyle, and rising pollution levels.

Obesity also leads to vitamin D deficiency due to excess adiposity; vitamin D is stored in adipose tissues and due to increased storage, obese individuals have lower circulating vitamin D concentrations. In our study, waist–hip ratio (WHR) and BMI were significantly elevated in the diabetic study participants as compared to controls. Additionally, only WHR was significantly higher in the vitamin D deficient diabetics as compared to the nondeficient diabetics.

Rodriguez-Rodriguez et al., in a cross-sectional study on Spanish women, reported that overweight and obese women are at higher risk of vitamin D deficiency, principally due to excess adiposity. Vimaleswaran et al. have proved genetically that higher BMI leads to lower vitamin D status among both sexes of different ages, providing substantial evidence for the role of obesity as an important risk factor for the development of hypovitaminosis D.

In our study, there was no significant difference in mean age, F1L, FBS, HOMA-B, HOMA-IR, and gamma-hydroxybutyrate between vitamin D deficient and nondeficient groups in diabetic cases. Some studies have shown association between vitamin D deficiency and T2DM, others have reported no association. Furthermore, some studies have also suggested that vitamin D supplementation improves glucose homeostasis, insulin resistance, and glucose control.

We did not observe any significant association of HOMA-IR and HOMA-B between vitamin D deficient and sufficient groups in both diabetics and nondiabetics. Sheth et al. and Luo et al. also showed no association between vitamin D deficient and HOMA-IR and glycemic control. In addition, Witham et al. and Kampmann et al. reported that improving vitamin D status had no effect on insulin resistance in diabetic patients.

However, in our study, we noted that the severity (<10 nmol/L) of vitamin D deficiency was more in diabetic cases than nondiabetic controls. This was similar to a study which says that the risk of severe vitamin D deficiency (<25 nmol/L) was significantly higher in cases than in controls.

We have not gathered the current information of patient’s medication use. Observed levels of vitamin D can be due to their routine medications like thiazide diuretics and some hypertension medications that are known to increase vitamin D levels.

Since no significant association was noted between vitamin D and insulin resistance as well as HOMA-B in the diabetic participants compared to controls, we need larger studies and further evaluation of the role of vitamin D in T2DM, insulin resistance, and glucose homeostasis.
Influence of Serum Levels of Vitamin D on Insulin Resistance

**Conclusion**

Vitamin D deficiency is prevalent in both T2DM as well as nondiabetic. Furthermore, there is no association between vitamin D deficiency and insulin resistance or beta-cell function.

**References**

INTRODUCTION

Any critical illness is defined as a serious condition requiring support of failing organ functions. Any condition which is life-threatening, caused by trauma, surgery, and severe medical illness, is a classic example of acute and extreme physical stress. Stressful situation affects all the endocortical axes and shows difference in response to acute and chronic phases of stress. The physiological reason behind all these alterations is to change internal environment of organism which helps in fighting the external threat to homeostasis. Thyroid hormones have a crucial role in adapting the metabolic function during stress and critical illness. The changes in thyroid hormone levels occur during starvation and acute or chronic critical illness. In hospital admitted patients, thyroid hormone changes occur frequently, particularly in increasing age or in critical illness.

In patients with no prior history of intrinsic thyroid disease, critical illness can cause profound changes in thyroid hormone metabolism. Such changes have been named as euthyroid sick syndrome (ESS). ESS is the most common change in critically ill patients. Most common hormone pattern is a fall in T3 and FT3 levels with normal T4 and TSH. Patients in intensive care unit (ICU) usually present with low plasma T3, low T4, and normal or minimal fall in TSH. This ensemble of changes is collectively and recently called non-thyroidal illness syndrome (NTIS). Among the patients in ICU, low T3 syndrome or ESS is seen more commonly than true hypothyroidism. Low T3 levels are responsible for elevated deiodination of T4 to reverse triiodothyronine than T3 and elevation in catabolism of T3 to 3,3'-diodothyronine.

Acute Physiology and Chronic Health Evaluation II (APACHE II) score was first developed by Knauss et al. for assessing severity of disease classification system. It is useful in assessing the patients presenting in 24 hours of ICU admission. Higher score corresponds to increased severity of disease and increased risk of death. In 1985, APACHE II was developed and was used commonly, which was later revised and improved in 1991, that is, APACHE III as one of several ICU scoring systems.

METHODS

After taking clearance from the Institutional Ethical Committee, a 2-year study was carried out between September 2017 and August 2019 in the Department of General Medicine, 100 patients admitted in MICU were assessed who fulfilled the selection criteria.

Inclusion Criteria

• Age more than 12 years,
• All patients admitted in MICU were included,
• All critically ill patients in MICU with sepsis,
• Immunocompromised patients were included.

Exclusion Criteria

• Age less than 12 years,
• All pregnant patients,
• Patients with pre-existing thyroid disorders with other endocrinopathies,
• Patients having connective tissue disorders,
• Patients having diabetes mellitus,
• Drugs altering thyroid hormones (like patients on amiodarone, lithium, interferon alpha, and iodine contrast dyes).

Procedure

Proper consent was taken from all the participants. Strict confidentiality was maintained about the personal details of the participants and information related to the study. A detailed clinical history of illness and thorough physical examination was

Abstract

Background: Thyroid hormones have a crucial role in adapting the metabolic functions during stress and critical illness. Patients who are critically ill may have profound changes in thyroid hormone metabolism. Non-thyroidal illness syndrome (NTIS) is one among them, in which there is marked abnormality seen in the thyroid hormone levels. Hence this study is to understand the alterations of the thyroid function tests (TFTs) encountered in critically ill patients admitted in medical intensive care unit (MICU) without primary thyroid disease and to correlate with the severity of Acute Physiology and Chronic Health Evaluation (APACHE III) scoring.

Methods: The study was conducted on 100 critically ill patients with no previous thyroid disorders, admitted in MICU in the Department of General Medicine in a tertiary care hospital between September 2017 and August 2019 who fulfilled the inclusion and exclusion criteria.

Results: Out of 100 critically ill patients the abnormal thyroid function prevalence was seen in 78% patients. Most common abnormality seen in our study was low total triiodothyronine (T3) (61%) followed by low free triiodothyronine (FT3) (36%), low total thyroxine (TT4) (29%), high thyroid-stimulating hormone (TSH) (18%), and low free thyroxine (FT4) (12%). Low TT3, TT4, and FT3 values had a significant correlation with increasing critical severity score of APACHE III with a p value which was statistically significant (p < 0.05).

Conclusions: With increase in severity of critical illness assessed by APACHE III, TFT, that is, TT3, TT4, and FT3 levels were decreasing, suggestive of increasing non-thyroidal illness in critically ill patients.

Study of Thyroid Functions in critically ill Patients admitted in Medical Intensive Care Unit and its Correlation with Critical Care Scoring Acute Physiology and Chronic Health Evaluation III

Madhulika Mahashabde, Sonika R Murukoti, Gaurav Chaudhary, Gangadharam Kanchi, Rahul Patil

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Study of Thyroid Functions in critically ill Patients admitted in MICU

Table 1 shows the distribution of the critically ill patients’ cases in 100 subjects. Infectious cases were the majority followed by neurological cases, gastrointestinal cases, renal cases, poisoning, respiratory, cardiovascular, miscellaneous, and hematological cases.

Table 1: Distribution of cases in MICU

<table>
<thead>
<tr>
<th>Critically ill cases</th>
<th>No. of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infectious cases</td>
<td>23</td>
</tr>
<tr>
<td>Neurological cases</td>
<td>19</td>
</tr>
<tr>
<td>Cardiovascular cases</td>
<td>6</td>
</tr>
<tr>
<td>Gastrointestinal cases</td>
<td>16</td>
</tr>
<tr>
<td>Respiratory cases</td>
<td>6</td>
</tr>
<tr>
<td>Renal cases</td>
<td>14</td>
</tr>
<tr>
<td>Poisoning</td>
<td>9</td>
</tr>
<tr>
<td>Hematological cases</td>
<td>2</td>
</tr>
</tbody>
</table>

Table 2: APACHE III scoring

<table>
<thead>
<tr>
<th>APACHE III</th>
<th>Mean ± standard deviation</th>
</tr>
</thead>
<tbody>
<tr>
<td>APS</td>
<td>42.29 ± 22.79</td>
</tr>
<tr>
<td>CHE</td>
<td>0.52 ± 1.34</td>
</tr>
<tr>
<td>Age</td>
<td>0.52 ± 1.34</td>
</tr>
<tr>
<td>GCS</td>
<td>13.48 ± 2.74</td>
</tr>
<tr>
<td>Total</td>
<td>48.96 ± 24.58</td>
</tr>
</tbody>
</table>

These statistical analyses were done by Epi Info (version 7) provided by CDC Atlanta. Categorical data were shown in percentages and proportions and numerical data in mean and standard deviation. Bar diagrams, pie charts, and others graphs were used to depict the results wherever necessary. Appropriate statistical tests such as Student’s t-test and analysis of variance (ANOVA) were used for numerical data and Chi-square test for categorical variables with significance level kept at 5% (p < 0.05 considered as statistically significant). Correlations were assessed using Pearson’s correlation coefficient. ‘r’ value ranges from –1.0 and +1.0. A high value of +1.00 indicates a strong direct relationship, whereas a low negative value of –1.00 indicates a strong inverse relationship, and values near 0.00 indicate little significance.

RESULTS

This study was conducted among 100 cases. Following tables and figures show observations of the study.

Fig. 1: Bar diagram of thyroid function abnormalities

Fig. 2: Normal and abnormal TFTs in the study population
The Table 3 shows the number of patients with abnormal thyroid functions with mean values and the mean APACHE III score 48.96 ± 24.58.

The Figure 3 depicts the number of blood samples drawn in 24, 48, and 72 hours respectively from the patients admitted in medical ICU.

Table 4 shows the correlation between the number of patients admitted on 1st day, 2nd day, and 3rd day and APACHE III score. Though on day 1 admission, mean APACHE III score shows an increase than on day 2 and day 3; p-value turned out to be not significant statistically (>0.05) by ANOVA method.

Figure 4 depicts a negative correlation (downward sloping pattern) between APACHE III score (y-axis) and low TT3 (x-axis). As the APACHE III score is increasing, TT3 levels are decreasing. Whereas Figure 5 depicts a negative correlation (inverse) between TT4 levels and APACHE III score means the APACHE III score increases, TT4 levels decrease.

Table 5 shows that TSH has no correlation with APACHE III score. p-value being not significant (0.1). Table 6 shows FT4 has no correlation with APACHE III score. p-value is statistically not significant (0.08).

Figure 6 depicts a downward sloping pattern from left to right, that is, negative correlation between FT3 and APACHE III score. As APACHE III score increases, FT3 values decrease showing a linear correlation.

**Discussion**

In a study conducted by Kumar et al., the mean age was 58.7 ± 16.9 years was mean age of study population of 100 patients; cardiovascular diseases in 32 patients constituted majority, infectious diseases in 18 patients, and neurological disorders in 17 patients. The distribution of thyroid hormone abnormalities had isolated low T3 in 45 patients, low T3 and low T4 in 13 patients, low TT3, TT4, and TSH in three patients, mixed pattern in 16 patients, and normal thyroid profile in 23 patients. The most common abnormality was low T3 seen in 61% followed by low T4 in 14% and low TSH in 7%.

In our study the mean age was 44.34 ± 17.41 years, the commonest cases were infectious in 23 patients followed by neurological cases in 19 patients, gastrointestinal cases in 16 patients, renal cases in 14 patients, poisoning in 9 patients, and cardiovascular and respiratory cases in 6 patients. Thyroid function abnormalities in the present study showed low TT3 in 61 patients, low FT3 in 36 patients, low TT4 in 29 patients, high TSH in 18 patients, low FT4 in 12 patients, and no subject showed concomitant reduction of TT3, TT4, and TSH. In a study done by Suresh et al., the mean age was 59 years belonging to the geriatric age group majorly, male subjects were 55%. About 39% patients had APACHE II score 20–24 and 4% patients had a score of above 34.

About 51% patients had normal TT3 followed by low TT3 in 49% patients. About 78% patients had normal TT4 levels followed by reduced TT4 levels in 22%. About 80% patients had normal TSH levels followed by increased TSH levels in 14% patients and reduced TSH levels in 6%. There was no significant difference in distribution of TT3 TT4, and TSH in males and females. Cardiovascular disorders constituted the major morbidity followed by infections and neurological disorders with no significant difference in the thyroid profile among different diseases.

Among 49 patients who had low TT3, 14 also had low TT4, six had low TSH, and isolated decrease TT3 was seen in 29% patients. Twenty-two patients had low TT4 in which 14 have low TT3, three have low TSH, eight have increased TSH, 11 have normal TSH, and isolated low TT4 was seen in three patients.

**Table 4:** Association between day of admission vs APACHE III score

<table>
<thead>
<tr>
<th>Day of admission</th>
<th>No. of patients</th>
<th>APACHE III score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day 1 (within 24 hours)</td>
<td>36</td>
<td>56.69 ± 24.85</td>
</tr>
<tr>
<td>Day 2 (within 48 hours)</td>
<td>39</td>
<td>45.69 ± 24.3</td>
</tr>
<tr>
<td>Day 3 (within 72 hours)</td>
<td>25</td>
<td>42.92 ± 21.49</td>
</tr>
</tbody>
</table>

ANOVA test applied; p = 0.7 (not significant statistically)
Fig. 5: Correlation between TT4 vs APACHE III

Fig. 6: Correlation between FT3 vs APACHE III

Table 5: Correlation between TSH vs APACHE III

<table>
<thead>
<tr>
<th>TSH</th>
<th>APACHE III</th>
<th>Coefficient of correlation (r)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>5.43 ±</td>
<td>48.96 ±</td>
<td>−0.13</td>
<td>0.1</td>
</tr>
<tr>
<td>15.6</td>
<td>24.58</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 6: Correlation between FT4 vs APACHE III

<table>
<thead>
<tr>
<th>FT4</th>
<th>APACHE III</th>
<th>Coefficient of correlation (r)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.11 ±</td>
<td>48.96 ±</td>
<td>−0.17</td>
<td>0.08</td>
</tr>
<tr>
<td>0.33</td>
<td>24.58</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Thyroid-stimulating hormone levels show mixed pattern with no significant correlation with APACHE II score; 80 had normal TSH, 14 had increased TSH, and six had low TSH level. This study concluded that in those who had increased APACHE II, showed increased number of patients with decreased TT3 levels but no significant relation of low TT4 and TSH levels with APACHE II score.

In our study 20 patients belonged to the geriatric age group, males comprised 65 patients and females 35 patients. Fifty-one patients had APACHE III score >50, 49 patients had a score of ≤50. Sixty-one patients had low TT3, 29 patients had low TT4, 36 patients had low FT3, 12 patients had low FT4, and 18 patients had increased TSH. Low FT4 had a significant correlation with critical severity score of APACHE III. In our study there was no concomitant reduction in TSH, FT3, and FT4 levels in any patient and 36% patients had FT3 levels below normal range. FT3 showed a significant correlation. In a study conducted by Tognini et al., 96 of 301 patients (31.9%) had FT3 levels below the normal levels. No patient had associated reduction in serum TSH, FT3, and FT4 values. In our study there was no concomitant reduction in TSH, FT3, and FT4 levels in any patient and 36% patients had FT3 levels below normal range. FT3 showed a significant correlation. In a study conducted by Tognini et al., 96 of 301 patients (31.9%) had FT3 levels below the normal levels. No patient had associated reduction in serum TSH, FT3, and FT4 values. In our study there was no concomitant reduction in TSH, FT3, and FT4 levels in any patient and 36% patients had FT3 levels below normal range.

**Conclusion**

Prevalence of abnormal thyroid dysfunction in critically ill patients admitted in MICU was seen among 78 cases. The TT3, TT4, and FT3 levels had a significant correlation with critical severity score of APACHE III. With increase in severity score of APACHE III score TT3, TT4, and FT3 levels were decreasing. With this, we found high thyroid dysfunction in critically ill patients (NTIS) which possibly contributes to the morbidity and mortality of multi-organ failure. Table 6: Correlation between FT4 vs APACHE III

**References**

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Study of the Role of Plasma NT-proBNP in the Diagnosis of Heart Failure

Bahaar Athavale1, Jaya Pathak2

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Abstract

Background: The diagnosis of heart failure (HF) remains essentially clinical-Based. However, the history, physical examination, and chest radiograph findings are often inadequate in the diagnosis because multiple other conditions that affect the cardiopulmonary system mimic the symptoms of HF. N-terminal pro-BNP (NT-proBNP) has long been used for diagnosing HF. N-terminal pro-BNP values vary with different patient parameters. There is a scarcity of Indian studies on this topic. Especially with the use of newer drugs like angiotensin receptor nephrilsin inhibitor (ARNI), it is important to have data from our own population on the same.

Aims and objectives: (i) To assess the role of NT-proBNP in the diagnosis of HF. (ii) Achieve diagnostic clarity in cases having cardiorespiratory symptoms and signs like acute onset dyspnea, pedal edema, and basal crepitations. (iii) To study the effect of various factors like age, body mass index (BMI), and creatinine on NT-proBNP. (iv) Establish a relation between NT-proBNP levels and left ventricular ejection fraction (LVEF), disease severity, and etiology of HF.

Materials and methods: An observational prospective study of 50 patients presenting with acute onset breathlessness was carried out, fulfilling inclusion and exclusion criteria over a period of 10 months. Detailed history and examination of the patients were obtained. Venous sample for the measurement of NT-proBNP was collected within 24 hours of onset of symptoms. Other relevant blood and radiographic investigations were obtained. The NT-proBNP “cut-offs” set forth by the American Heart Association (AHA)/American College of Cardiology (ACC) were used to “rule in” or “rule out” HF. Two-dimensional echocardiography (2D Echo) was used to confirm the diagnosis. The correlation between NT-proBNP and various parameters like age, BMI, creatinine, and LVEF was obtained. Sensitivity and specificity tests were applied as well.

Results: Out of the 50 patients presenting with acute onset dyspnea, the most common cause was ischemic heart disease (IHD) (44%) followed by dilated cardiomyopathy (DCM) (32%), chronic obstructive pulmonary disease (COPD) (10%), anemia (4%), followed by other causes. The median NT-proBNP value was the highest for IHD patients (9485 pg/mL), followed by COPD (8969 pg/mL), followed by COPD (2846 pg/mL), and followed by anemia (850 pg/mL). There is a significant positive correlation between NT-proBNP and age (coefficient of correlation r = 0.4007, significance level p = 0.009, and class interval = –0.58 to –0.09). Higher LVEF is associated with lower NT-proBNP values. There is significant negative correlation between creatinine clearance and NT-proBNP (coefficient of correlation r = –0.372, significance level p = 0.0389, and class interval = 0.137–0.61). There is a significant negative correlation between creatinine clearance and NT-proBNP (coefficient of correlation r = –0.36, significance level p = 0.009, and class interval = –0.58 to –0.09). Higher LVEF is associated with lower NT-proBNP values. There is marked heterogeneity in the values though.

Conclusion: It is seen that the values of NT-proBNP vary with factors like age, BMI, and creatinine clearance in addition to LVEF. This may lead to falsely positive or falsely negative diagnosis of HF. With the above observations in mind, it can be concluded that NT-proBNP can help diagnose HF but only in addition to clinical findings.

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Introduction

Heart failure is a common cause of cardiovascular mortality and morbidity, especially among the elderly and poses a significant burden on the healthcare resources of our country. Huffman and Prabhakar in their projections, based on disease-specific estimates projected that a conservative estimate of the prevalence of HF in India is in the range from 1.3 to 4.6 million, with an annual incidence of 0.4–1.8 million. Indian patients are younger than those in high-income countries, the mean age at presentation being 60 years. They also have a high in-hospital mortality and 1-year mortality, which are significantly higher than that in the high-income countries.1

There are a few cardinal symptoms of HF, namely shortness of breath or dyspnea, paroxysmal nocturnal dyspnea, orthopnea, swelling of lower extremities, abdominal distension, right upper quadrant pain, fatigue, and some essential signs such as tachycardia, pedal edema, increased jugular venous pressure, abnormal lung sounds (crackles), and 53 gallop. There is not a single clinical feature with both high sensitivity and specificity. Hence a lot of cases cause a diagnostic dilemma while presenting with acute shortness of breath, like those of asthma, pulmonary edema, COPD, pneumonia, and myocardial ischemia. Rapid and accurate assessment of acute HF is a priority in emergency setting. Hence the role of a biomarker which can help diagnose the condition is instrumental.

Heart failure can be classified in various ways:

- Location of deficit: left or right or biventricular failure,
- Time of onset: acute or chronic HF,
- Left ventricular ejection fraction3:
  - Heart failure with reduced ejection fraction (HFrEF) (EF ≤ 40%, also called systolic HF).
  - Heart failure with preserved ejection fraction (HFrEF) (EF > 50%, also called diastolic HF).
  - Heart failure with preserved ejection fraction borderline (EF between 41 and 49%),
  - Heart failure with preserved ejection fraction improved (EF > 40%).

The 2016 European Society of Cardiology guidelines4 also defines a new class of patients with EF between 40 and 49% viz heart failure with mid-range ejection fraction (HFrEF). They represent the “gray area” as this group of patients warrants further research and targeted treatment to halt disease progression as they have mild systolic dysfunction but also features of diastolic dysfunction.

The precursor of the natriuretic peptides (NPs) is pro-BNP, a 134 amino acid peptide that is synthesized in the myocytes and

1Resident, Department of Nephrology, Bombay Hospital and Medical Research Centre, Mumbai, Maharashtra.
2Associate Professor, Medical College Baroda and Sir Sayajirao General Hospital, Vadodara, Gujarat, India.
3Corresponding Author

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cleaved to the prohormone BNP of 108 amino acids. The prohormone is released during hemodynamic stress, that is, when the ventricles are dilated, hypertrophic, or subject to increased wall tension. proBNP is further cleaved into biologically active BNP (32 amino acids) and NT-proBNP (76 amino acids) by a circulating endopeptidase. N-terminal pro-BNP is functionally inert. Stimulation of the NP receptor by BNP triggers natriuresis, diuresis, vasodilatation, inhibition of renin and aldosterone, and inhibition of fibrosis. BNP is removed from circulation by a receptor-mediated mechanism as well as degradation by neutral endopeptidases such as neprilysin. N-terminal pro-BNP is cleared by renal excretion.

Normally, circulating BNP and NT-proBNP levels are quite low, but in the setting of HF, their concentrations rise dramatically. The ProBNP Investigation of Dyspnea in the Emergency Department (PRIDE) study demonstrated that elevated NT-proBNP concentrations were the strongest predictor of HF compared with traditional assessment. N-terminal pro-BNP has a greater sensitivity for detecting HFpEF.

Our main source of knowledge about NT-proBNP has been foreign studies and data. In addition to being a valuable diagnostic test, it is used to monitor treatment with the advent of ARNI like sacubitril + valsartan (formerly LCZ696). It is being increasingly used in prognostic assessment of patients with heart transplant and acute coronary syndrome. Noncardiac uses of this biomarker are also on the rise. With this applicability and relevance in practice, Indian studies on this particular biomarker are needed.

**Materials and Methods**

An observational prospective study of 50 patients was carried out on the patients presenting to the Medicine Department of Sir Sayajirao General Hospital, Vadodara during a 10-month period from January 2018 to October 2018 and fulfilling inclusion and exclusion criteria.

**Study Sample**

It comprised adult patients aged more than 18 years presenting with acute onset of breathlessness and having cardinal signs of HF like pedal edema, basal crepitations, and neck vein distention as per the definition of HF given by ACCF/AHA 2013 guidelines. Those having sepsis, acute respiratory distress syndrome, pulmonary embolism, lower respiratory tract infection (LRTI), renal failure, hyperthyroidism, and liver cirrhosis were excluded from the study. On receiving approval for the study from the Institutional Ethics Committee, enrollment was commenced. A total of 50 patients were included in the study, after taking proper written and informed consent.

**Data Collection**

Each patient underwent a detailed medical history and examination. Serum sample for the measurement of NT-proBNP was collected in plain vacuette within 24 hours of onset of symptoms. Investigations like complete blood count, blood urea, serum creatinine, random blood sugar, NT-proBNP levels, electrocardiogram, chest X-ray, and 2D Echo were obtained. Creatinine kinase–MB levels and Tropon-I levels were sent when required. All the patients were managed as per the standard protocol. Laboratory analysis for NT-proBNP was done using the Immunoassay Roche Cobas e 411 machine and the technique used was electrochemiluminescence. The serum sample was processed within 4 hours of collection with maintenance of proper cold chain facility.

In our study, the patients of HF were divided into three groups as per the ejection fraction according to the ESC guidelines viz EF < 40% was HFrEF; EF 41–49% was HFmEF; and EF > 50% was HFpEF.

In the current study, the median NT-proBNP for the each age group was: <40 years = 3439 pg/mL, 41–50 years = 3809 pg/mL, 51–60 years = 5526.5 pg/mL, 61–70 years= 10,492 pg/mL, 71–80 years = 8489 pg/mL, and >80 years= 17937.5 pg/mL.

**Interpretation**

Assessment of NT-proBNP levels in patients presenting with acute onset dyspnea was done using the age-specific “cut-off” points set forth by the American College of Cardiology guidelines (Table 1).

**Data Analysis**

Correlation analysis was done between NT-proBNP and various factors like age, creatinine clearance, BMI, and LVEF. Pearson’s correlation coefficient was used for the same. A p-value of <0.05 was considered significant.

**Table 1: American College of Cardiology “cut-offs” for NT-proBNP**

<table>
<thead>
<tr>
<th>Age</th>
<th>NT-proBNP</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;300 ng/mL</td>
<td>HF unlikely</td>
<td></td>
</tr>
<tr>
<td>&lt;50 years</td>
<td>&gt;450 pg/mL</td>
<td>HF likely</td>
</tr>
<tr>
<td>50–75 years</td>
<td>&gt;900 pg/mL</td>
<td>HF likely</td>
</tr>
<tr>
<td>&gt;75 years</td>
<td>&gt;1800 pg/mL</td>
<td>HF likely</td>
</tr>
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</table>

**Table 2: Age- and sex-wise distribution of patients**

<table>
<thead>
<tr>
<th>Age group (years)</th>
<th>Males</th>
<th>Females</th>
<th>Total</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;40</td>
<td>2</td>
<td>5</td>
<td>7</td>
<td>14</td>
</tr>
<tr>
<td>41–50</td>
<td>9</td>
<td>3</td>
<td>12</td>
<td>24</td>
</tr>
<tr>
<td>51–60</td>
<td>8</td>
<td>6</td>
<td>14</td>
<td>28</td>
</tr>
<tr>
<td>61–70</td>
<td>4</td>
<td>6</td>
<td>10</td>
<td>20</td>
</tr>
<tr>
<td>71–80</td>
<td>3</td>
<td>2</td>
<td>5</td>
<td>10</td>
</tr>
<tr>
<td>&gt;80</td>
<td>2</td>
<td>0</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>Total</td>
<td>28</td>
<td>22</td>
<td>50</td>
<td>100</td>
</tr>
</tbody>
</table>

**Results**

In our study of 50 patients, the mean age of the population was 55.4 years, the range being 20–88 years. About 72% of the study population was in the range 40–70 years. Twenty-eight patients (56%) were males and 22 patients (44%) were females (Table 2, Fig. 1). Of the total 50 patients, 22 patients (44%) had IHD, 16 patients (32%) had DCM, five patients (10%) had COPD, two patients (4%) had anemic HF, and 2% had congenital heart disease, rheumatic heart disease (RHD), and hypertensive HF each. Two patients (4%) had breathlessness due to unknown etiology. The cause of DCM needs further evaluation.

In the current study, the median NT-proBNP increased with advancing age. There was a significant positive correlation between NT-proBNP and age with a correlation coefficient r = 0.4007, significance p = 0.0389 with class interval of 0.137–0.61 (Table 3, Fig. 2).

The study population was classified into different BMI categories according to the revised consensus guidelines for Asian Indians, namely underweight, healthy weight, overweight, and obese. No significant correlation was found between BMI and NT-proBNP values.

The study population was classified according to the estimated glomerular filtration rate (eGFR) (creatinine clearance) as per the Cockcroft–Gault equation and the median NT-proBNP for each group was determined. The median NT-proBNP for each group was: eGFR > 60 mL/min = 3455 pg/mL, eGFR 45–60 mL/min = 14,329 pg/mL, eGFR 30–45 mL/min = 8489 pg/mL, and eGFR < 30 mL/min = 22,285 pg/mL. There was a rise
in the NT-proBNP with declining creatinine clearance with a significant negative correlation between the two (correlation coefficient $r = -0.372$, significance level $p = 0.007$, with class interval of $-0.58$ to $-0.105$) (Table 4, Fig. 3).

Patients were classified into three groups according to LVEF as per the ESC guidelines. The median NT-proBNP for each group was HFpEF (LVEF $\geq 50\%$) = 1017 pg/mL, HfEF (LVEF 40–49%) = 9125.5 pg/mL, and HFrEF (LVEF < 40%) = 2846 pg/mL. The increased wall stress in the NT-proBNP with declining creatinine clearance with a significant negative correlation between LVEF and NT-proBNP (correlation coefficient $r = -0.36$, significance level $p = 0.009$, with class interval of $-0.58$ to $-0.09$) (Table 5, Fig. 4).

However, there is a marked heterogeneity in NT-proBNP levels among individuals with the same LVEF. Also, individuals with varying LVEF may have the same NT-proBNP values (Fig. 5).

After classifying patients as per the New York Heart Association (NYHA) functional classification, patients of NYHA class III having the highest median NT-proBNP had the maximum average duration of hospital stay, that is, 8.3 days, followed by NYHA class IV (6.87 days), NYHA class II (5.3 days), and lastly NYHA class I (3.5 days). This was in trend with the median NT-proBNP values for each class but a consistent relation was not observed.

Four patients required intensive care unit (ICU) stay in the present study, with two requiring invasive mode of ventilation and two requiring noninvasive (BiPAP). Both patients on invasive mode of ventilation expired during course of the stay and had NT-proBNP of 25,000 pg/mL and 22,285 pg/mL. This is only an observation in two patients and no significance was derived.

In the current study, 2D Echo was used to confirm the diagnosis of HF. The use of NT-proBNP as a screening test yielded a sensitivity of 97% but a low specificity of 58% (Table 6). The accuracy of the test is 86%. However, the positive predictive value and negative predictive value are 86% and 85%, respectively.

**DISCUSSION**

In our study of 50 patients, the most common cause of HF was IHD (44%), followed by DCM (32%) and then COPD (10%). This was comparable to the Trivandrum Heart Registry the first organized heart registry in India which enrolled patients with HF, in which the most common HF etiology was IHD (72%), followed by DCM (13%) and then RHD (8%).

The median NT-proBNP value was the highest for IHD patients (9485 pg/mL) followed by DCM (8969 pg/mL) followed by COPD (2846 pg/mL) followed by others (684 pg/mL). The increased wall stress caused by left ventricular systolic or diastolic dysfunction in IHD leads to increased values...
of NT-proBNP. Nevertheless, some of the experimental studies suggest a direct release of NPs from cardiomyocytes in response to myocardial ischemia independent of ventricular wall stress.5

It was observed that the NT-proBNP values increased with advancing age. There is a significant positive correlation between NT-proBNP and age with a correlation coefficient $r = 0.4007$, significance $p = 0.0389$ with class interval 0.137–0.61. Similarly in another study by Amrane et al.9 on the prognostic value of NT-proBNP in patients attending an Asian hospital cardiac service, significant positive correlation was established between age and NT-proBNP ($r = 0.27$ and $p = 0.02$). The effect of age on NT-proBNP values is multifactorial. In addition to renal dysfunction and alterations in the secretion of NT-proBNP with increasing age, diastolic dysfunction is responsible for the change.

The median NT-proBNP of the underweight, healthy weight, overweight, and obese categories of patients were 4459 pg/mL, 7375 pg/mL, 8489 pg/mL, and 8176 pg/mL, respectively. It is observed that there is a fall in the median NT-proBNP in obese patients, but no significant correlation was found. Although the exact reason for lower NT-proBNP values in obese patients is not known, the adipose tissue is said to have a high concentration that promotes clearance of NPs.

There was a rise in the NT-proBNP with declining renal function, that is, inverse relation with creatinine clearance (correlation coefficient $r = –0.372$, significance level $p = 0.007$, with class interval of –0.58 to –0.105). In the PRIDE study6 it was noted that with lower GFR, log-transformed NT-proBNP levels increased among all patients in the study ($r = –0.55$, $p < 0.001$) and in those without acute congestive heart failure ($r = –0.41; p < 0.001$). The NP elevations in patients of renal disease may reflect concurrent LV hypertrophy or coronary disease.

The median NT-proBNP according to LVEF was: HFpEF (LVEF ≥ 50%) = 1017 pg/mL, HFrEF (LVEF 40–49%) = 5921 pg/mL, and HFrEF (LVEF < 40%) = 9125.5 pg/mL. There was significant negative correlation between LVEF and NT-proBNP (correlation coefficient $r = –0.36$, significance level $p = 0.009$, and class interval $= –0.58$ to $–0.09$). Similarly in an Indian study of

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**Table 5: Correlation of LVEF with NT-proBNP**

<table>
<thead>
<tr>
<th>LVEF</th>
<th>No. of patients</th>
<th>Percent</th>
<th>Max NT-proBNP (pg/mL)</th>
<th>Min NT-proBNP (pg/mL)</th>
<th>Median NT-proBNP (pg/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤40%</td>
<td>38</td>
<td>76</td>
<td></td>
<td></td>
<td>25,000</td>
</tr>
<tr>
<td>40–49%</td>
<td>3</td>
<td>6</td>
<td>25,000</td>
<td>173</td>
<td>9125.5</td>
</tr>
<tr>
<td>≥50%</td>
<td>9</td>
<td>18</td>
<td>10,875</td>
<td>32</td>
<td>1017</td>
</tr>
</tbody>
</table>

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**Table 6: Sensitivity and specificity**

<table>
<thead>
<tr>
<th>HF as per 2D Echo</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>NT-proBNP</td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>37</td>
</tr>
<tr>
<td>Negative</td>
<td>1</td>
</tr>
<tr>
<td>Total</td>
<td>38</td>
</tr>
</tbody>
</table>

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**Fig. 3:** Median NT-proBNP (pg/mL) as per creatinine clearance

**Fig. 4:** Median NT-proBNP (pg/mL) as per LVEF

**Fig. 5:** NT-proBNP (pg/mL) as per LVEF (%). (NT-proBNP values of COPD patients are highlighted above)
serial NT-proBNP levels to prognosticate HF by Kabi et al., the mean NT-proBNP levels were inversely proportional to the EF: LVEF < 40% (11,374.8 pg/dL), LVEF 40–49% (7175.7 pg/dL), and LVEF > 50% (3685 pg/dL). In another study on NT-proBNP to differentiate patients with normal and reduced LV systolic function by Bay et al., it was noted that the median NT-proBNP varied inversely with LVEF with p-value of <0.05. The results of our current study were corresponding to the above studies.

As seen in Figure 5, there is a marked heterogeneity in NT-proBNP levels among individuals with the same LVEF. Also, individuals with varying LVEF may have the same NT-proBNP values. Here comes the role of confounding factors like age, GFR, BMI, etc. Thus, we can clearly deduce that clinical judgment on the part of the physician is the most important clue to diagnosis of HF.

All patients of the study population were classified according to the NYHA functional classification. Two patients (4%) had presented with NYHA class I breathlessness, three patients (6%) with class II, 28% with class III, and 62% with class IV. The maximum value of NT-proBNP across all NYHA classes was 25,000 pg/mL. A significant relation between NYHA class and NT-proBNP was not observed and results need to be tested on larger sample size.

Four patients required ICU stay in the present study, with two requiring invasive mode of ventilation and two requiring noninvasive (BiPAP). Out of those four patients, three had NT-proBNP level >22,000 pg/mL whereas one patient had NT-proBNP of 451 pg/mL. The lower value in the last case could be attributed to the presence of LRTI with congenital heart disease. Both the patients requiring invasive ventilation expired during the course of stay and had NT-proBNP of 25,000 pg/mL and 22,285 pg/mL.

Two-dimensional echocardiography was used as the diagnostic test for HF. The use of NT-proBNP as a screening test yielded a sensitivity of 97% but a low specificity of 58%. A systematic review and meta-analysis by Taylor and Verbakel on the diagnostic accuracy of point-of-care NP testing reported a sensitivity of 0.99 (0.57–1.00) and specificity of 0.60 (0.44–0.74) at 135 pg/mL for NT-proBNP. This implies that NT-proBNP when used as a screening test would falsely identify those without HF as disease positive owing to the lower specificity.

The accuracy of the test was 86%. The positive predictive value and negative predictive values of NT-proBNP were 86% and 85%, respectively. This implies that NT-proBNP can be used to rule out HF. In another study by Januzzi JL Jr et al., the age-independent cut off of NT-proBNP <300 pg/mL had a negative predictive value of 98% and specificity of 71.7%.

**Conclusion**

There is a significant negative correlation between NT-proBNP and LVEF. However, it also varies significantly with age and renal function. These confounding factors may lead to falsely positive or negative diagnoses of HF. Hence we conclude that NT-proBNP can help rule in or rule out HF, only in addition to clinical findings.

Although NT-proBNP has a well-established role as a diagnostic marker, prospective studies on the same as a prognostic marker in the area of HF are desirable.

**References**

Noninvasive Measurement of Aortic Pressure and Evaluation of Arterial Stiffness in Patients with Hypertension: An Observational Study

Sunil Sathe1*, MK Inamdar2, Archana Sathe3, Mangesh Tiwaskar4

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Abstract

Aim: Arterial stiffness, a major marker of vascular impedance, has been identified as a predictor of adverse cardiac outcomes. The present study determined the relationship between blood pressure (BP) and arterial stiffness measured noninvasively using a periscope in hypertensive patients. It has also evaluated the usefulness of indices of arterial stiffness in cardiovascular (CV) risk stratification and the necessity to implement these aortic pressure parameters in clinical practice.

Methods: The prospective, observational study involved patients with hypertension between the age of 18 and 80 years. The demographic and anthropometric measurements of all the participants were recorded and various central and peripheral (brachial) arterial pressure parameters were measured using a periscope. The clinical variables were compared separately for different CV risk grades and arterial stiffness index (ASI) using Spearman’s correlation method. The agreement of different ASI indices with CV risk grades was assessed using Kappa method.

Results: The study recruited a total of 3,032 patients with hypertension. Classification of the subjects for CV risk grades had demonstrated that major proportion of the patients (n = 713) had moderate and severe CV risks (n = 708). The classification of hypertension patients for arterial stiffness had shown that 1,037 subjects had severe arterial stiffness. Classification of arterial stiffness based on BP levels had demonstrated that 623 patients with severe arterial stiffness and 315 with borderline arterial stiffness had stage II hypertension, and 480 patients with normal BP had no arterial stiffness. Brachial ASI had a strong correlation with systolic BP (SBP). A very good agreement with K value 0.871 was noted for Kappa agreement of arterial stiffness indices with CV risk.

Conclusion: The present study corroborates the use of central BP parameters as indicators of arterial stiffness in hypertensive subjects. Noninvasive measurement of these indices has wider implications in personalized risk assessment of CV risk in subjects with hypertension.

Introduction

Arterial stiffness, a common feature associated with aging, is accentuated by the presence of several disorders such as diabetes, renal disease, and hypertension.1 It has been identified as the root cause of target organ damage and as a predictor of adverse cardiac events.1 Literature evidence has corroborated the use of regulating arterial stiffness in the successful outcome of various therapeutic and surgical interventions.1 The 2003 European Society of Hypertension guidelines on the management of hypertension has highlighted the key role of arterial stiffness in the clinical management of hypertension.2 The expert consensus document published in 2006 by the European Network for Non-invasive Investigation of Large Arteries has reported that, despite several studies addressing the methodological issues, it is difficult for clinicians and investigators to choose the most appropriate technology for assessing arterial stiffness.3 The position statement has recommended the use of arterial stiffness and central pressure parameters for the CV risk assessment, especially in subjects whose target organ damage is not detected by routine tests.4

Recent years have witnessed greater acceptance of noninvasive techniques for measuring arterial stiffness, particularly of large arteries.5 Periscope, which can be used for measuring both brachial BPs and pulse wave velocity (PWV), has been validated through various clinical studies. Although such techniques have several advantages such as ease of use, low cost, and wider acceptability among patients, the full clinical impact of these measurements has not been clearly investigated. A review by Oliver and Webb has underscored the need of larger studies involving greater number of at-risk population for evaluating the complete prognostic value of such noninvasive technologies, especially PWV.6

The present study was intended to evaluate the association of BP and arterial stiffness measured using a periscope in patients with hypertension. It has also assessed the usefulness of indices of arterial stiffness in CV risk stratification and the necessity to introduce these aortic pressure parameters in clinical practice.

Methods

The prospective, observational study recruited patients with hypertension attending the outpatient department of a clinical setting, as a part of a routine checkup. The inclusion criteria considered were: subjects between 18 and 80 years of age and patients with hypertension (newly and/or already diagnosed and treated). The study excluded subjects requiring hospitalization due to other ailing conditions and pregnant or lactating women. Duly signed consent form was obtained from all the study participants.

The demographic characteristics of all the participants were recorded. Anthropometric measurements included the measurement of weight, height, and body mass index (BMI). The subjects were asked to lie down comfortably in supine position. After resting for 10 minutes, the BP indices of all the selected subjects were recorded using a periscope. This noninvasive, PC-based arterial health assessment analysis system is clinically validated, as per international guidelines, and it is devoid of any operator bias. The cuffs tied to the four limbs of the subjects were used to measure the BP values at brachium and ankle by oscillometric method. The two
Noninvasive Measurement of Aortic Pressure

The following pressure parameters were documented: peripheral (brachial) arterial pressure parameters: SBP, diastolic BP (DBP), pulse pressure (PP), and heart rate (HR). Central (aortic) pressure parameters: right brachial PWV (RbaPWV), left brachial PWV (LbaPWV), right ankle ASI (R ANK ASI), left ankle ASI (L ANK ASI), right ankle-brachial index (R ABI), left ankle-brachial index (L ABI), carotid-femoral PWV (CF PWV), augmentation index (AIX), aortic systolic pressure (AORTIC SYS), aortic diastolic pressure (AORTIC DYS), aortic pulse pressure (AORTIC PP), aortic augmentation pressure (AOAUGP). The CV risk was classified as negligible, borderline, mild, moderate, and severe. Arterial stiffness was classified as no, borderline, mild, moderate, and severe. Arterial stiffness groups were classified on the basis of BP levels as: normal (<120 mm Hg), elevated (120–129 mm Hg), stage I hypertension (130–139 mm Hg), and stage II hypertension (≥140 mm Hg).

Statistics

The data were presented as mean ± standard deviation (SD) or median (range) for continuous data and as counts for categorical data. The clinical variables were compared separately for different CV risk grades and ASI using Kruskal–Wallis test for non-normal data and chi-square test for count data. The correlation of different vital parameters with CV risk grade and arterial stiffness indices was verified using Spearman’s correlation method.7 The agreement of different arterial stiffness indices with CV risk grades was verified using Kappa method. p < 0.05 was considered significant for all analyses. The MedCalc software was used for statistical analysis.

Results

A total of 3,032 patients with hypertension attending the outpatient department were enrolled. One hundred and thirty patients with extreme values for different variables were excluded and 2,902 patients were included. The median years of age of the selected participants was 62 (19–96) and the male-to-female ratio noted was 2.7:1. The average BMI, HR, SBP, DBP, and PP noted were 27.1 (15.43–66.44), 66.65 (34.4–125.4), 135 (82–239), 73 (40–150), and 58 (31–144), respectively (Table 1).

The median (range) of other central pressure parameters were as follows: RbaPWV 1610.2 (25.0–6304.9), LbaPWV 1747.20 (32.10–3941.20), CF PWV 1211.70 (47.1–3069.40), R BRA ASI 39.92 (3.50–116.00), L BRA ASI 39.34 (3–117.8), R ANK ASI 55.81 (0–146), L ANK ASI 56.76 (0.5–140), R ABI 0.91 (0.03–2.15), L ABI 1.08 (0.03–2.38), AORTIC SYS 124.12 (75–227), AORTIC DYS 75 (52–136), AORTIC PP 45.70 (16–109), AOAUGP 13.93 (0–81).

Table 1: Descriptive statistics for demographic and clinical variables of the study subjects

<table>
<thead>
<tr>
<th>Variables</th>
<th>Values (n = 2,902)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>59.21 ± 10.58</td>
</tr>
<tr>
<td>Gender M/F</td>
<td>2119/783</td>
</tr>
<tr>
<td>BMI</td>
<td>27.06 ± 3.93</td>
</tr>
<tr>
<td>HR</td>
<td>71.28 ± 12.40</td>
</tr>
<tr>
<td>SBP</td>
<td>140.14 ± 23.08</td>
</tr>
<tr>
<td>DBP</td>
<td>77.50 ± 10.87</td>
</tr>
<tr>
<td>PP</td>
<td>62.72 ± 18.67</td>
</tr>
<tr>
<td>RbaPWV</td>
<td>1746.28 ± 567.81</td>
</tr>
<tr>
<td>LbaPWV</td>
<td>1703.62 ± 350.40</td>
</tr>
<tr>
<td>CF PWV</td>
<td>1211.70 ± 328.61</td>
</tr>
<tr>
<td>R BRA ASI</td>
<td>39.92 ± 14.85</td>
</tr>
<tr>
<td>L BRA ASI</td>
<td>39.34 ± 14.77</td>
</tr>
<tr>
<td>R ANK ASI</td>
<td>55.81 ± 18.00</td>
</tr>
<tr>
<td>L ANK ASI</td>
<td>56.76 ± 17.14</td>
</tr>
<tr>
<td>R ABI</td>
<td>0.91 ± 0.12</td>
</tr>
<tr>
<td>L ABI</td>
<td>1.08 ± 0.11</td>
</tr>
<tr>
<td>AORTIC SYS</td>
<td>124.12 ± 22.46</td>
</tr>
<tr>
<td>AORTIC DYS</td>
<td>77.79 ± 10.59</td>
</tr>
<tr>
<td>AORTIC PP</td>
<td>45.70 ± 15.01</td>
</tr>
<tr>
<td>AOAUGP</td>
<td>13.93 ± 7.86</td>
</tr>
<tr>
<td>AIX</td>
<td>28.86 ± 8.66</td>
</tr>
</tbody>
</table>

M, Male; F, Female

Fig. 1: Classification of hypertensive patients for various CV risk grades

Table 2: All the variables demonstrated statistically significant differences across the CV risk groups.

Fig. 2: The least number of patients (n = 178) was noted for moderate stiffness. The number of subjects with no, borderline, and mild arterial stiffness were 623, 542, and 524, respectively (Fig. 2).
very good agreement with K value 0.871 (Table 5, 95% confidence interval 0.861–0.882).

Results of correlation studies of SBP and DBP are given in Tables 6 and 7. The correlation of age and all vital parameters with DBP showed low effect size. Age and ABI were inversely correlated with DBP. Brachial ASI had strong correlation with SBP; whereas RbaPWV, CfPWV, R and L ANK ASI, R and L ASI, R and L ABI, and AIX demonstrated moderate correlation. Left brachial PWV had weak correlation. Age did not correlate with SBP.

**Discussion**

The current study has corroborated the use of BRA ASI, RbaPWV, CfPWV, R and L ANK ASI, R and L ASI, R and L ABI, and AIX as reliable indicators of arterial stiffness in hypertensive subjects. Augmentation index, a measure of pulse wave reflection, has been identified as a surrogate measure of arterial stiffness. Studies have demonstrated that the AIX correlates well with the incidence of left ventricular mass in hypertensive subjects.8 Higher ASI measurements have been identified as an independent predictor of all-cause and cardiovascular disease (CVD) mortality, and severe arterial stiffness noted with normal elevated (120–129 mm Hg) and stage I hypertension (130–139 mm Hg) were 30, 273, and 102.

Classification of arterial stiffness based on BP levels had demonstrated that 632 patients with severe arterial stiffness had stage II hypertension (≥140 mm Hg), indicating a direct association between arterial stiffness and hypertension. In addition, no arterial stiffness was noted in 480 patients with normal BP and 315 with borderline arterial stiffness had stage II hypertension (Table 3). The corresponding number of subjects belonging to the class of arterial stiffness is given in Table 2. All the variables, except BMI, were statistically significantly different across the ASI groups. Kappa agreement of arterial stiffness indices with CV risk grades showed

<table>
<thead>
<tr>
<th>Variables</th>
<th>Negligible CV risk (n = 519)</th>
<th>Borderline CV risk (n = 463)</th>
<th>Mild CV risk (n = 500)</th>
<th>Moderate CV risk (n = 712)</th>
<th>Severe CV risk (n = 708)</th>
<th>p-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>65 (25–96)</td>
<td>63 (23–90)</td>
<td>59 (19–86)</td>
<td>55 (22–94)</td>
<td>63 (25–83)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Gender</td>
<td>M/F</td>
<td>478/41</td>
<td>250/213</td>
<td>371/129</td>
<td>520/192</td>
<td>500/208</td>
</tr>
<tr>
<td>BMI</td>
<td>27.10 (16.42–37.09)</td>
<td>27.10 (16.23–45.18)</td>
<td>26.66 (17.04–66.44)</td>
<td>28.73 (17.3–62.03)</td>
<td>25.74 (15.43–43.24)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>HR</td>
<td>63.6 (46.10–115.20)</td>
<td>66.80 (48.20–105.3)</td>
<td>73.10 (34.40–117.80)</td>
<td>66.75 (38.20–125.40)</td>
<td>71.45 (38.30–122.40)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>SBP</td>
<td>118 (94–134)</td>
<td>125 (102–163)</td>
<td>140 (100–195)</td>
<td>137 (100–219)</td>
<td>168 (82–239)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>DBP</td>
<td>73 (53–88)</td>
<td>73 (45–130)</td>
<td>74 (40–103)</td>
<td>73 (54–150)</td>
<td>87 (40–145)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>PP</td>
<td>45 (33–51)</td>
<td>54 (33–84)</td>
<td>63 (33–115)</td>
<td>57 (36–135)</td>
<td>82 (31–144)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>RbaPWV</td>
<td>1417.3 (38.80–1914.90)</td>
<td>1417.3 (39.40–100.70)</td>
<td>1557.55 (25.00–3065.0)</td>
<td>1929.6 (41.60–3604.90)</td>
<td>2191.9 (29.20–6182.90)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>LbaPWV</td>
<td>1747.2 (32.10–2039.80)</td>
<td>1538.1 (84.00–2000.80)</td>
<td>1594.15 (39.60–2850.6)</td>
<td>1784.3 (38.90–3941.20)</td>
<td>1864.7 (259.2–3903.9)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>CIPWV</td>
<td>1085.2 (203.8–1358.30)</td>
<td>1032.4 (66.80–1303.50)</td>
<td>1091.1 (58.20–1530)</td>
<td>1336.15 (47.10–2663.6)</td>
<td>1517.0 (79.20–3069.40)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>R BRA ASI</td>
<td>30.8 (8.0–45.8)</td>
<td>32.30 (10.50–70.5)</td>
<td>38.15 (5.0–100.5)</td>
<td>33.90 (4.30–99.0)</td>
<td>52.50 (3.50–116.0)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>L BRA ASI</td>
<td>28.80 (8.50–47.30)</td>
<td>30.30 (7.80–67.50)</td>
<td>36 (5.50–90.0)</td>
<td>34.50 (6.80–104.80)</td>
<td>53.50 (3.0–117.80)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>R ANK ASI</td>
<td>53.0 (3.0–89.80)</td>
<td>53.0 (0–86.50)</td>
<td>54.30 (1.30–121.80)</td>
<td>49 (4–127)</td>
<td>69 (0–146.80)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>L ANK ASI</td>
<td>56 (8.30–66.50)</td>
<td>56 (5.30–99.30)</td>
<td>53.80 (0.5–126.80)</td>
<td>47.50 (5.0–128.80)</td>
<td>72.30 (1.0–140.0)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>R ABI</td>
<td>0.92 (0.01–1.2)</td>
<td>0.92 (0.2–2.1)</td>
<td>0.92 (0.52–2.15)</td>
<td>0.92 (0.5–1.32)</td>
<td>0.88 (0–1.79)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>L ABI</td>
<td>1.15 (0.90–1.35)</td>
<td>1.13 (0.65–2.38)</td>
<td>1.08 (0.58–1.86)</td>
<td>1.13 (0.68–1.59)</td>
<td>1.09 (0.03–1.5)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>AORTIC SYS</td>
<td>102 (75–119)</td>
<td>106 (85–143)</td>
<td>119 (87–180)</td>
<td>123 (90–183)</td>
<td>153 (95–227)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>AORTIC DYS</td>
<td>69 (52–84)</td>
<td>69 (53–103)</td>
<td>76 (52–95)</td>
<td>76 (60–122)</td>
<td>89 (60–136)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>AORTIC PP</td>
<td>32 (16–41)</td>
<td>35 (16–62)</td>
<td>42 (18–94)</td>
<td>43 (25–95)</td>
<td>65 (23–109)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>AOAUGP</td>
<td>8 (0–14)</td>
<td>8 (0–19)</td>
<td>11 (0–67)</td>
<td>14 (0–35)</td>
<td>24 (2–51)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>AIX</td>
<td>24 (0–72)</td>
<td>24 (0–81)</td>
<td>26 (0–61)</td>
<td>33 (0–71)</td>
<td>37 (4–73)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

*For not normal data Kruskal–Wallis test and count data chi-square test were performed; M, Male; F, Female
new-onset adverse CVD outcomes. The 2018 study by Said et al., involving 169,613 UK Biobank participants, has concluded ASI and PP as independent predictors of adverse CVD outcomes and mortality. The researchers have noted that addition of ASI to Framingham Risk Score had enhanced the 5.9-year risk prediction model of incident CV events by 2.3%.9 Pulse wave velocity has been considered as gold standard for the evaluation of arterial stiffness due to enhanced accuracy, reproducibility, reduced cost, and ease of measurement.4 The 2010 study published in European Heart Journal has established the normal and reference values of PWV. The study has standardized the findings of different methodological approaches used for the determination of PWV after gathering the data from a sizable European population.10 A 2010 meta-analysis by Vlachopoulos et al. has concluded arterial stiffness, measured as aortic PWV, is a major predictor of CV events and all-cause mortality. The study has noted that the increase of PWV by 1 m/s had resulted in the corresponding increase of CV events, CV mortality, and all-cause mortality by 14%.

### Table 3: Classification of arterial stiffness groups based on BP levels (systolic)

<table>
<thead>
<tr>
<th>Classification</th>
<th>No arterial stiffness (n = 623)</th>
<th>Borderline arterial stiffness (n = 540)</th>
<th>Mild arterial stiffness (n = 524)</th>
<th>Moderate arterial stiffness (n = 178)</th>
<th>Severe arterial stiffness (n = 1,037)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal (&lt;120 mm Hg)</td>
<td>480</td>
<td>33</td>
<td>152</td>
<td>14</td>
<td>30</td>
</tr>
<tr>
<td>Elevated (120–129 mm Hg)</td>
<td>87</td>
<td>74</td>
<td>67</td>
<td>22</td>
<td>273</td>
</tr>
<tr>
<td>Stage I Hypertension (130–139 mm Hg)</td>
<td>43</td>
<td>118</td>
<td>95</td>
<td>28</td>
<td>102</td>
</tr>
<tr>
<td>Stage II Hypertension (≥140 mm Hg)</td>
<td>13</td>
<td>315</td>
<td>210</td>
<td>114</td>
<td>632</td>
</tr>
</tbody>
</table>

### Table 4: Comparison of arterial stiffness groups for different clinical variables

<table>
<thead>
<tr>
<th>Variables</th>
<th>No arterial stiffness (n = 623)</th>
<th>Borderline arterial stiffness (n = 540)</th>
<th>Mild arterial stiffness (n = 524)</th>
<th>Moderate arterial stiffness (n = 178)</th>
<th>Severe arterial stiffness (n = 1,037)</th>
<th>p-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>65 (25–96)</td>
<td>60 (19–94)</td>
<td>60 (23–82)</td>
<td>61 (46–80)</td>
<td>58 (25–86)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Gender M/F</td>
<td>556/67</td>
<td>362/178</td>
<td>327/197</td>
<td>135/43</td>
<td>739/298</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>27 (20–45.18)</td>
<td>26.45 (16.23–41.23)</td>
<td>27.10 (17.04–66.44)</td>
<td>26.29 (19.10–51.94)</td>
<td>27.14 (15.43–42.57)</td>
<td>0.0829</td>
</tr>
<tr>
<td>HR (bpm)</td>
<td>63.6 (46.10–115.20)</td>
<td>72.50 (36.0–125.40)</td>
<td>69.80 (34.40–117.80)</td>
<td>75.55 (38.20–117.90)</td>
<td>65 (38.30–122.40)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>SBP (mm Hg)</td>
<td>118 (94–163)</td>
<td>142 (102–219)</td>
<td>134 (100–219)</td>
<td>146 (82–212)</td>
<td>149 (101–239)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>DBP (mm Hg)</td>
<td>73 (47–130)</td>
<td>73 (42–123)</td>
<td>75 (51–150)</td>
<td>78 (40–124)</td>
<td>80 (40–145)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>PP (mm Hg)</td>
<td>45 (33–60)</td>
<td>70 (34–135)</td>
<td>55 (35–140)</td>
<td>68 (33–130)</td>
<td>66 (31–144)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>RbaPWV (cm/s)</td>
<td>1417.3 (38.80–1984.70)</td>
<td>1458.80 (25–6304.90)</td>
<td>1555.75 (32.20–3993.70)</td>
<td>1811.30 (44.30–4162.20)</td>
<td>2253.80 (29.20–6182.90)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>LbaPWV (cm/s)</td>
<td>1447.2 (32.10–2381.70)</td>
<td>1492.45 (39.60–2850.60)</td>
<td>1694.8 (50.80–2339.80)</td>
<td>1794.75 (38.90–2223.80)</td>
<td>1784.3 (185.30–3941.20)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>CfPWV (cm/s)</td>
<td>998.2 (197.10–1585.90)</td>
<td>1085.7 (47.10–1516.60)</td>
<td>1191.80 (195.50–2405.50)</td>
<td>1276.8 (102.20–1679.50)</td>
<td>1449.2 (79.20–3069.40)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>R BRA ASI (mm Hg)</td>
<td>30.80 (8–56.30)</td>
<td>43.90 (5.50–99)</td>
<td>33 (4.30–116)</td>
<td>40 (12.50–114)</td>
<td>40.80 (3.50–105.30)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>L BRA ASI (mm Hg)</td>
<td>28.80 (7.80–49.50)</td>
<td>39.80 (6.30–104.80)</td>
<td>31.80 (5.50–115.50)</td>
<td>41.40 (11.80–111.0)</td>
<td>39 (3.0–117.80)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>R ANK ASI (mm Hg)</td>
<td>53 (1.80–89.80)</td>
<td>56.30 (0.127)</td>
<td>53 (1.30–121.80)</td>
<td>59.55 (6.80–119.50)</td>
<td>59.80 (0–146.80)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>L ANK ASI (mm Hg)</td>
<td>56 (8.30–76.50)</td>
<td>56 (0.5–128.80)</td>
<td>56 (5–126.80)</td>
<td>59.65 (8.50–119.80)</td>
<td>57.50 (1–140)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>R ABI</td>
<td>0.92 (0.01–1.45)</td>
<td>0.90 (0–2.11)</td>
<td>0.92 (0.57–2.15)</td>
<td>0.90 (0.50–1.17)</td>
<td>0.91 (0–1.79)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>L ABI</td>
<td>1.15 (0.65–2.38)</td>
<td>1.04 (0.58–1.86)</td>
<td>1.13 (0.75–1.59)</td>
<td>1.08 (0.76–1.33)</td>
<td>1.10 (0.03–1.5)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>AORTIC SYS (mm Hg)</td>
<td>102 (75–143)</td>
<td>120 (85–183)</td>
<td>117 (87–197)</td>
<td>130 (88–196)</td>
<td>136 (86–227)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>AORTIC DYS (mm Hg)</td>
<td>69 (52–103)</td>
<td>74 (52–122)</td>
<td>76 (58–105)</td>
<td>80 (52–136)</td>
<td>82 (59–132)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>AORTIC PP (mm Hg)</td>
<td>32 (16–45)</td>
<td>45 (21–95)</td>
<td>39 (22–107)</td>
<td>49 (27–100)</td>
<td>52 (18–109)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>AOAUGP (mm Hg)</td>
<td>8 (0–18)</td>
<td>11 (0–67)</td>
<td>10 (0–38)</td>
<td>16 (1–34)</td>
<td>19 (0–51)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>AIX (%)</td>
<td>24 (0–81)</td>
<td>25 (0–55)</td>
<td>26 (0–58)</td>
<td>32 (4–40)</td>
<td>36 (3–73)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

*For not normal data Kruskal–Wallis test and count data chi-square test were performed; M, Male; F, Female
Noninvasive Measurement of Aortic Pressure

Our study also showed that there was significant correlation with 1,037 patients who had severe aortic stiffness and the mean RbaPWV, LbaPWV, and CFPWV was 2253.80 cm/s (29.20–6182.90), 1784.3 cm/s (185.30–3941.20), and 1449.2 cm/s (79.20–3069.40), respectively which was significantly higher.

The predictive potential of clinical markers has gained wider recognition for stratifying the high-risk subjects with CVD. Implementation of assessment of the central BP parameters in routine clinical practice assists in getting a comprehensive picture of the patients’ CV status. The current study has noted a very good agreement between arterial stiffness and CV risk grades in patients with hypertension. In concurrence with these findings, the Rotterdam study by Mattace-Raso et al. has concluded that the inclusion of aortic PWV to known factors such as measures of atherosclerosis and PP improved the prediction of CVD. An Indian study by Shanker et al. has reported that combining carotid intima-media thickness with periscope markers assists in the evaluation of atherosclerotic burden in Asian Indians. The Framingham heart study has noted higher incidence of arterial stiffness in a major proportion of hypertensive subjects. In addition, a significant association was noted between the trend toward CVD risk and high PWV in both hypertensive and nonhypertensive subjects. There is very limited evidence on the use of indices of arterial stiffness in CVD risk stratification in hypertensive subjects. A cohort study conducted in a representative sample of individuals from UK has found that noninvasive measurement of arterial stiffness may assist in optimal CVD risk stratification in apparently healthy subjects. The study has reported ASI as the best parameter for stratifying between low- to medium-risk and high-risk groups.

Hypertension increases the risk of transient and sustained stiffening of arteries. The association between BP and vascular stiffness is appeared to be bidirectional. The elevated BP may gradually lead to collagen degradation, elastin degradation, vascular hypertrophy and hyperplasia, atherosclerosis, and fixed increase in arterial stiffness. The present study has also noted a direct association between arterial stiffness and hypertension. The study has found that majority of the patients with severe arterial stiffness had stage II hypertension (≥140 mm Hg). In concurrence with these findings, a 2017 cross-sectional study by Muela et al. has noted that worsening of arterial stiffness and cerebral vasoreactivity is in line with the severity of hypertension. The Atherosclerosis Risk in Communities Study has attempted to describe the association between arterial stiffness and hypertension. The large, population-based study has suggested that hypertension-related increase in arterial stiffness might be due to the effect of distending pressure rather than structural alterations in the arterial wall.

The present study has noted a significant correlation between BRA ASI and SBP. This finding corroborates the potential of arterial stiffness in assessing arterial health and its complementary role in BP evaluation. A 2015 study published in The Journal of Clinical Hypertension has reported baPWV as an independent predictor of incident hypertension. The researchers have found a positive association between baPWV during baseline examination and higher SBP, DBP, PP, and mean arterial pressure during the first follow-up examination.

The 2015 scientific statement from American Heart Association recommends the following regarding arterial stiffness measurement: (1) noninvasive techniques

### Table 5: Agreement of ASI with CV risk grades

<table>
<thead>
<tr>
<th>Variables</th>
<th>Kappa</th>
<th>95% confidence interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arterial stiffness</td>
<td>0.871</td>
<td>0.861–0.882</td>
</tr>
<tr>
<td>Value of K</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;0.20</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.21–0.40</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.41–0.60</td>
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<td></td>
</tr>
<tr>
<td>0.61–0.80</td>
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</tr>
<tr>
<td>0.81–1.00</td>
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</tbody>
</table>

### Table 6: Correlation coefficient of variables with DBP

<table>
<thead>
<tr>
<th>Variables</th>
<th>Correlation coefficient</th>
<th>p-value</th>
<th>95% confidence interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>-0.207</td>
<td>&lt;0.0001</td>
<td>-0.241 to -0.172</td>
</tr>
<tr>
<td>RbaPWV</td>
<td>0.305</td>
<td>&lt;0.0001</td>
<td>0.272–0.338</td>
</tr>
<tr>
<td>LbaPWV</td>
<td>0.239</td>
<td>&lt;0.0001</td>
<td>0.204–0.273</td>
</tr>
<tr>
<td>CFPWV</td>
<td>0.3</td>
<td>&lt;0.0001</td>
<td>0.267–0.334</td>
</tr>
<tr>
<td>R BRA ASI</td>
<td>0.167</td>
<td>&lt;0.0001</td>
<td>0.131–0.202</td>
</tr>
<tr>
<td>L BRA ASI</td>
<td>0.196</td>
<td>&lt;0.0001</td>
<td>0.160–0.230</td>
</tr>
<tr>
<td>R ANK ASI</td>
<td>0.247</td>
<td>&lt;0.0001</td>
<td>0.212–0.281</td>
</tr>
<tr>
<td>L ANK ASI</td>
<td>0.231</td>
<td>&lt;0.0001</td>
<td>0.197–0.266</td>
</tr>
<tr>
<td>R ABI</td>
<td>-0.12</td>
<td>&lt;0.0001</td>
<td>-0.157 to -0.0848</td>
</tr>
<tr>
<td>L ABI</td>
<td>-0.0881</td>
<td>&lt;0.0001</td>
<td>-0.124 to -0.0518</td>
</tr>
<tr>
<td>AIX</td>
<td>0.306</td>
<td>&lt;0.0001</td>
<td>0.273–0.339</td>
</tr>
</tbody>
</table>

### Table 7: Correlation coefficient of variables with SBP

<table>
<thead>
<tr>
<th>Variables</th>
<th>Correlation coefficient</th>
<th>p-value</th>
<th>95% confidence interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>-0.0154</td>
<td>0.4084</td>
<td>-0.0517 to 0.0210</td>
</tr>
<tr>
<td>RbaPWV</td>
<td>0.4</td>
<td>&lt;0.0001</td>
<td>0.369–0.430</td>
</tr>
<tr>
<td>LbaPWV</td>
<td>0.218</td>
<td>&lt;0.0001</td>
<td>0.183–0.252</td>
</tr>
<tr>
<td>CFPWV</td>
<td>0.378</td>
<td>&lt;0.0001</td>
<td>0.347–0.409</td>
</tr>
<tr>
<td>R BRA ASI</td>
<td>0.662</td>
<td>&lt;0.0001</td>
<td>0.641–0.682</td>
</tr>
<tr>
<td>L BRA ASI</td>
<td>0.689</td>
<td>&lt;0.0001</td>
<td>0.670–0.708</td>
</tr>
<tr>
<td>R ANK ASI</td>
<td>0.468</td>
<td>&lt;0.0001</td>
<td>0.440–0.496</td>
</tr>
<tr>
<td>L ANK ASI</td>
<td>0.421</td>
<td>&lt;0.0001</td>
<td>0.391–0.450</td>
</tr>
<tr>
<td>R ABI</td>
<td>-0.315</td>
<td>&lt;0.0001</td>
<td>-0.348 to -0.282</td>
</tr>
<tr>
<td>L ABI</td>
<td>-0.467</td>
<td>&lt;0.0001</td>
<td>-0.495 to -0.438</td>
</tr>
<tr>
<td>AIX</td>
<td>0.499</td>
<td>&lt;0.0001</td>
<td>0.472–0.526</td>
</tr>
</tbody>
</table>

0.1 to < 0.3: small/weak correlation; 0.3 to < 0.5: medium/moderate correlation; 0.5 and above: large/strong correlation; The direction of the relationship between variables is represented by the sign of the coefficient; + indicates positive linear relationship; 0 indicates no relationship; *Correlation coefficient effect size

0.1 to < 0.3: small/weak correlation; 0.3 to < 0.5: medium/moderate correlation; 0.5 and above: large/strong correlation; The direction of the relationship between variables is represented by the sign of the coefficient; + indicates positive linear relationship; 0 indicates no relationship; *Correlation coefficient effect size
should be used for the assessment of arterial stiffness by measuring CfPWV, (2) PWVs measured in other vascular segments such as ankle-brachial and the cardiac-ankle vascular stiffness index are effective in predicting CV outcome in Asian populations, and (3) single-point estimates of PWV are not advocated for CV outcome prediction due to the lack of evidence from longitudinal studies. The statement has also underscored the need of standardizing arterial stiffness measurement and its wider application in clinical medicine and research. Future research should also focus on developing targeted therapeutic interventions to treat established aortic stiffness and prevention strategies. The sample size in the current study was adequate enough to analyze the results for possible associations through correlation studies. One of the major limitations of the study was that the BP parameters were assessed only once time. Comparison of periscope markers noted in hypertensive patients with unaffected population would have given a clear picture on the clinical utility of these vascular indices in predicting future CV risk.

**Conclusion**

The present study validates the use of central BP parameters such as RbaPWV, CfPWV, ANK ASI (R and L), ABI (R and L) and AIX as good indicators of arterial stiffness in hypertensive patients. Noninvasive measurement of these clinical indices, in conjunction with classic and molecular markers, may add a newer dimension to personalized risk assessment of CV risk in subjects with hypertension.

**References**

Noninvasive Measurement of Aortic Pressure

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Still progressing towards T2DM despite lifestyle changes for 3 to 6 months
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No additional safety concerns
Recommendations from National and International Guidelines: ADA, ICMR, RSSDI, AACE

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*English, Hindi, Bengali, Gujarati, Marathi, Punjabi, Tamil, Assamese, Kannada, Malayalam, Oriya and Telugu.
Retrospective Cohort Observational Study to compare the Effect of Mycobacterium w along with Standard of Care vs Standard of Care alone in critically ill COVID-19 Patients

Subhal Dixit1, Kapil Zipre2, Prasad Suryawanshi3, Kapil Borawake4, Sayi Prasad5, Sourabh Ambapkar6, Saavni Ambapkar7, Ameya Joshi8, Mukund Joshi9

Received: 30 January 2022; Revised: 05 April 2022; Accepted: 13 April 2022

Abstract

Background: COVID-19 has created enormous health crisis in India due to limited available treatments. Majority of the physicians use sepsis as a prototype to understand the pathophysiology of COVID-19 as there are similarities. Heat-killed Mycobacterium w (Mw) (Inj. Mw*) is a known immunomodulator, which is approved for the treatment of gram-negative sepsis. This observational study was aimed to evaluate the role of Mw along with standard of care (SOC) in critically ill COVID-19 patients.

Methods: Total 448 patients’ data (intervention group: 298 in Mw plus SOC vs 150 in SOC alone) with reverse transcriptase-polymerase chain reaction (RT-PCR) confirmed critically ill COVID-19 patients who were admitted at five tertiary care centers were evaluated. They were observed for changes in laboratory (C-reactive protein (CRP), D-dimer, ferritin, lactate dehydrogenase (LDH), and interleukin-6 (IL-6)) parameters, hospital stay, intensive care unit (ICU) stay, and discharge status after giving 0.3 mL intradermal Mw for 3 consecutive days along with SOC during hospitalization. Standard of care included injectable steroids, remdesivir, and heparin. Data were analyzed using STATA 14.2 (StataCorp., College Station, Texas, USA).

Results: In baseline characteristics, Mw plus SOC arm had more critically ill patients as seen by higher high-resolution computed tomography (HRCT) score, higher lab values (CRP, ferritin, D-dimer, LDH, creatinine, alanine aminotransferase (ALT)), and more oxygen requirement as compared to SOC alone. Mycobacterium w arm had significantly higher mortality rate in ICU and hospital. Both hospital stay and ICU stay were longer in Mw arm. However, subgroup analysis found that early initiation of Mw (<3 days vs >3 days) was associated with significantly lesser odds of mortality and lesser odds of intubation requirement. Early initiation of Mw (<3 days vs >3 days) also resulted in significantly lesser duration of stay in the ICU along with reduction of CRP, D-dimer, and LDH. Moreover, further analysis of early initiation of Mw (<3 days vs control) resulted in significant reduction in lab values (procalcitonin, CRP, ferritin, LDH, and D-dimer).

Conclusion: Mw when added to SOC was found to associate with significantly increased risk of mortality and increased length of hospital stay. However, time since admission to administration of Mw was a significant predictor of in-ICU deaths in multivariate analysis. Early initiation of Mw (<3 days) was observed to be a protective factor against ICU deaths from the multivariate logistic regression model. However, large randomized controlled trials are required to support the same.

Introduction

COVID-19 – a recent pandemic declared by the World Health Organization on 11th March 2020 – posed a significant challenge as far as human health is concerned. The condition is aggravated by the highly contagious nature of the virus because of its rapidly spreading human-to-human transmission.

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has already infected nearly 271,963,258 people worldwide, resulting in deaths of 5,331,019, as of 20th December 2021.2 Because of hospitalizations, COVID-19 has become a public health issue, affecting the health as well as the economy.3

Majority of the physicians use sepsis as a prototype of severe illness to understand COVID-19 pathogenesis. This is due to hypercytokinemia, associated with severe COVID-19.4,5 In addition to that, the early immunological picture of COVID-19 shares many similarities with bacterial sepsis.6 Cytokine levels seem to play a significant role in morbidity and mortality in patients with COVID-19. This clinical situation is similar to what is seen in patients with gram-negative sepsis. Also, it is well known that an individual’s immune response to the virus is responsible for clearance as well as associated with the severity of illness. The innate immune response is the initial and prompt body mechanism for resistance against pathogenic organisms. This is done by recognition of pathogen-associated molecular patterns of an infectious agent by pathogen-recognition receptors like toll-like receptors (TLRs). This immune response is the first protection against infection and is considered relevant to COVID-19 as well. Inj. Mw* (heat-killed Mw, Cadila Pharmaceuticals Limited, Ahmedabad, Gujarat, India) has undergone thorough preclinical and clinical studies and is now approved as an adjunct therapy for the management of gram-negative sepsis in India.7 It modulates T cell responses of the host cells by acting through TLRs pathway and is a known immunomodulator.8
without use of Mw from five tertiary care centers were taken.

Clinical laboratory and radiological parameters were evaluated at baseline. Levels at the time of admission were considered as baseline and levels at discharge/dead status were considered as last.

Our primary objective was to compare effect of addition of Mw to SOC on mortality reduction. Secondary objectives were reduction of length of hospital stay, ICU stay, and reduction of laboratory (CRP, D-dimer, ferritin, procalcitonin, IL-6), in critically ill patients. All the patients on admission received standard pharmacological treatment as per institutional protocol, including antipyretic medication (paracetamol), corticosteroid (dexamethasone/methylprednisolone), anticoagulant (low molecular weight heparin), and remdesivir. Compassionate usage of Mw was as 0.3 mL (0.1 mL × three injections at three different sites) for 3 consecutive days via intradermal route was given in intervention arm along with SOC.

All statistical analyses were performed using STATA 14.2 (StataCorp., College Station, Texas, USA). Changes from baseline to end of study visit values for efficacy variables at various time points were analyzed using generalized estimating equations with robust standard error accounting for time points for clustering. A two-tailed p-value of less than 0.05 (p < 0.05) was considered as statistically significant. Analysis was performed on the data available at different time points. The primary outcomes, that is, death in different settings, were modeled with logistic regression (with robust standard error), taking Mw as the main intervention. A p-value of <0.05 (two-tailed) was considered statistically significant. On the contrary, the secondary outcome, that is, the duration of stay in ICU Mw was taken as the key intervention. Among the exposure group (i.e., those who received Mw) a subgroup analysis was conducted to understand the usefulness of early initiation of Mw (within 3 days of admission). Similar models were prepared and statistical significance was set at 0.05 (two-tailed).

Study Centers
Total five tertiary care centers participated in this study from Maharashtra.

Study Parameters
Clinical and laboratory data of all patients were available at baseline and discharge. Values at admission, before and after completion of Mw therapy were retrieved for these patients along with data on symptoms, demographic characteristics, diagnostic workup, laboratory values and concomitant medications, and day of hospitalization and status of discharge/mortality.

Results
Results are summarized in Tables 1 to 6.

Table 1: Baseline characteristics

<table>
<thead>
<tr>
<th>Study group</th>
<th>N</th>
<th>Mean</th>
<th>Standard deviation</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>HRCT score</td>
<td>Intervention (Mw plus SOC) 295</td>
<td>14.37</td>
<td>6.96</td>
<td>0.000</td>
</tr>
<tr>
<td></td>
<td>Control 150</td>
<td>11.78</td>
<td>4.57</td>
<td></td>
</tr>
<tr>
<td>SpO2 on admission (%)</td>
<td>Intervention (Mw plus SOC) 261</td>
<td>69.11</td>
<td>36.10</td>
<td>0.000</td>
</tr>
<tr>
<td></td>
<td>Control 148</td>
<td>92.97</td>
<td>41.37</td>
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</tr>
<tr>
<td>Procalcitonin (ng/mL)</td>
<td>Intervention (Mw plus SOC) 151</td>
<td>0.83</td>
<td>6.59</td>
<td>0.000</td>
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<tr>
<td></td>
<td>Control 149</td>
<td>1.99</td>
<td>9.06</td>
<td></td>
</tr>
<tr>
<td>CRP (mg/L)</td>
<td>Intervention (Mw plus SOC) 287</td>
<td>36.35</td>
<td>35.85</td>
<td>0.000</td>
</tr>
<tr>
<td></td>
<td>Control 146</td>
<td>10.24</td>
<td>14.49</td>
<td></td>
</tr>
<tr>
<td>Ferritin (ng/mL)</td>
<td>Intervention (Mw plus SOC) 275</td>
<td>370.99</td>
<td>334.72</td>
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<tr>
<td></td>
<td>Control 150</td>
<td>487.51</td>
<td>652.36</td>
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<tr>
<td>D-dimer (ng/mL)</td>
<td>Intervention (Mw plus SOC) 284</td>
<td>989.04</td>
<td>2179.87</td>
<td>0.000</td>
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<tr>
<td></td>
<td>Control 130</td>
<td>723.16</td>
<td>1712.15</td>
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<tr>
<td>IL-6 (pg/mL)</td>
<td>Intervention (Mw plus SOC) 254</td>
<td>53.43</td>
<td>136.75</td>
<td>0.793</td>
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<tr>
<td></td>
<td>Control 140</td>
<td>50.13</td>
<td>77.18</td>
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<tr>
<td>LDH (U/L)</td>
<td>Intervention (Mw plus SOC) 269</td>
<td>509.15</td>
<td>301.68</td>
<td>0.020</td>
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<tr>
<td></td>
<td>Control 148</td>
<td>442.68</td>
<td>232.53</td>
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<tr>
<td>Creatinine (mg/dL)</td>
<td>Intervention (Mw plus SOC) 290</td>
<td>1.20</td>
<td>0.78</td>
<td>0.000</td>
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<td></td>
<td>Control 147</td>
<td>0.93</td>
<td>0.35</td>
<td></td>
</tr>
<tr>
<td>ALT (IU/L)</td>
<td>Intervention (Mw plus SOC) 254</td>
<td>49.06</td>
<td>43.96</td>
<td>0.038</td>
</tr>
<tr>
<td></td>
<td>Control 149</td>
<td>40.49</td>
<td>31.70</td>
<td></td>
</tr>
<tr>
<td>Aspartate aminotransferase (IU/L)</td>
<td>Intervention (Mw plus SOC) 254</td>
<td>51.08</td>
<td>56.55</td>
<td>0.489</td>
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<tr>
<td></td>
<td>Control 149</td>
<td>47.39</td>
<td>42.08</td>
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</tbody>
</table>

Table 2: Comparative assessment of mortality in both groups

<table>
<thead>
<tr>
<th>Study group</th>
<th>Total</th>
<th></th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Intervention (Mw plus SOC)</td>
<td>Control</td>
</tr>
<tr>
<td>Death during ICU stay</td>
<td>Survived 180</td>
<td>132</td>
</tr>
<tr>
<td></td>
<td>Death 94</td>
<td>10</td>
</tr>
<tr>
<td>Total</td>
<td>274</td>
<td>142</td>
</tr>
</tbody>
</table>
Retrospective Cohort Observational Study to compare the Effect of Mycobacterium w

**Table 3:** Hospital stay and ICU stay in both arms

<table>
<thead>
<tr>
<th>Study group</th>
<th>N</th>
<th>Mean</th>
<th>Standard deviation</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Duration of hospital stay (days)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intervention (Mw plus SOC)</td>
<td>298</td>
<td>15.02</td>
<td>8.07</td>
<td>0.001</td>
</tr>
<tr>
<td>Control</td>
<td>147</td>
<td>12.24</td>
<td>7.61</td>
<td></td>
</tr>
<tr>
<td><strong>Length of ICU stay (days)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intervention (Mw plus SOC)</td>
<td>274</td>
<td>11.17</td>
<td>6.73</td>
<td>0.000</td>
</tr>
<tr>
<td>Control</td>
<td>142</td>
<td>8.20</td>
<td>5.44</td>
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</tr>
</tbody>
</table>

**Table 4:** Effect of early administration of Mw <3 days vs >3 days administration on mortality

<table>
<thead>
<tr>
<th>Mw administration</th>
<th>Odds ratio</th>
<th>Lower</th>
<th>Upper</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;3 days</td>
<td>0.32</td>
<td>0.14</td>
<td>0.74</td>
<td>0.007</td>
</tr>
</tbody>
</table>

Time since admission to Mw is a significant predictor of in-ICU deaths in multivariate analysis
Early initiation of Mw was observed to be a protective factor against ICU deaths from the multivariate logistic regression model

**Table 5:** Effect of early administration of Mw (<3 days) on length of ICU stay

<table>
<thead>
<tr>
<th>Mw time &lt;3 days</th>
<th>N</th>
<th>Mean</th>
<th>Standard deviation</th>
<th>Standard error mean</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Length of ICU stay (days)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>81</td>
<td>7.31</td>
<td>5.01</td>
<td>0.56</td>
<td>0.000</td>
</tr>
<tr>
<td>No, &gt;3 days</td>
<td>102</td>
<td>13.93</td>
<td>5.84</td>
<td>0.58</td>
<td></td>
</tr>
</tbody>
</table>

**Table 6:** Effect of early administration (<3 days) of Mw along with SOC on lab parameters

<table>
<thead>
<tr>
<th>Coefficient</th>
<th>Lower bound</th>
<th>Upper bound</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>LDH post-Mw</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mw given within 3 days</td>
<td>−116.29</td>
<td>−212.66</td>
<td>−19.93</td>
</tr>
<tr>
<td>LDH baseline</td>
<td>1.05</td>
<td>0.74</td>
<td>1.36</td>
</tr>
<tr>
<td><strong>IL-6 post-Mw</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mw given within 3 days</td>
<td>−12.56</td>
<td>−41.58</td>
<td>16.46</td>
</tr>
<tr>
<td>IL-6 baseline</td>
<td>0.00</td>
<td>−0.05</td>
<td>0.04</td>
</tr>
<tr>
<td><strong>D-dimer post-Mw</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mw given within 3 days</td>
<td>−1119.28</td>
<td>−2031.26</td>
<td>−207.30</td>
</tr>
<tr>
<td>D-dimer baseline</td>
<td>0.12</td>
<td>0.03</td>
<td>0.20</td>
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<tr>
<td><strong>Ferritin post-Mw</strong></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Mw given within 3 days</td>
<td>−93.39</td>
<td>−328.13</td>
<td>141.35</td>
</tr>
<tr>
<td>Ferritin baseline</td>
<td>0.53</td>
<td>0.02</td>
<td>1.04</td>
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<tr>
<td><strong>Procalcitonin post-Mw</strong></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Mw given within 3 days</td>
<td>3.35</td>
<td>−1.88</td>
<td>8.58</td>
</tr>
<tr>
<td>Procalcitonin baseline</td>
<td>0.75</td>
<td>−0.01</td>
<td>1.51</td>
</tr>
<tr>
<td><strong>CRP post-Mw</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mw given within 3 days</td>
<td>−10.67</td>
<td>−20.79</td>
<td>−0.54</td>
</tr>
<tr>
<td>CRP baseline</td>
<td>0.41</td>
<td>0.22</td>
<td>0.60</td>
</tr>
</tbody>
</table>

Interpretation: early initiation of Mw (<3 days) has a statistically significant effect on reducing CRP, D-dimer, and LDH

**DISCUSSION**

We found that Mw when added to SOC was noninferior to SOC alone in critically ill patients in terms of mortality benefit. However, this could be due to baseline imbalance (Table 1) wherein more critically ill patients in Mw plus SOC arm. This could have led to higher mortality in Mw plus SOC arm.

Mycobacterium w has been shown to induce apoptosis of activated macrophages by suppressing IL-β, thus subduing the hyperinflammatory response. This is supported by our observation, where we could demonstrate a fall in inflammatory markers (like CRP) in critically ill COVID-19 patients using Mw.

Cytokine storm is the umbrella term that includes several immune dysregulation disorders characterized by constitutional symptoms, systemic inflammation, and multiorgan dysfunction and, if not adequately treated, leads to multiorgan failure. The role of “cytokine storm” or “cytokine cascade” apart from COVID-19 is well established in the pathophysiology of bacterial sepsis too. COVID-19 and bacterial sepsis share many similarities in cytokine profiles.

Mycobacterium w is known to induce type II interferon (IFN-gamma) through TLR2. Modulation of innate immune response by TLR2 has been demonstrated to be effective in providing protection against various respiratory virus infections in preclinical studies. Type II interferon is also known to provide protection against coronavirus.

Mycobacterium w is a potent TLR2 agonist which induces IFN-gamma secretion. This suggests Mw can modulate the immunity by suppressing the overexpressed inflammatory cytokines while at the same time inducing adaptive immune response for effective clearing of the virus. During early part of COVID-19 pandemic morbidity and mortality were suggested to be associated with upregulation of cytokines and control of cytokine upregulation was suggested for management to reduce morbidity and mortality. With this background, we explored the role of Mw when added to SOC in critically ill COVID-19 patients.

Mycobacterium w is a potent TLR2 agonist and poly TLR antagonist (4,5,7,9) and a potent inducer of Th1 response. The reduction of dendritic cell function is observed in the COVID-19 infection, and it suggests that strategies that reverse this negative effect might be useful in COVID-19 therapy. Mycobacterium w activates dendritic cells through TLR2 and increases dendritic cell survival, translating into a reduction in the viral load.
In the present study, we found that significantly more number of patients in Mw arm reported symptoms like fever, sore throat, weakness, and shortness of breath as compared to control arm. This could be due to more severe nature of clinical presentation in Mw plus SOC arm. We also found that addition of Mw to SOC was associated with increased mortality in critically ill patients (Table 2). Both ICU stay and overall hospital stay were significantly longer in Mw plus SOC arm. This could be due to more severe nature of the disease as seen in baseline characteristics (Table 3).

However, in subgroup analysis we found that time since admission to Mw was a significant predictor of in-ICU deaths in multivariate analysis.

Early initiation of Mw (<3 days) was observed to be a protective factor against ICU deaths from the multivariate logistic regression model (Table 4). Early initiation of Mw resulted in significantly lesser duration of stay in the ICU (Table 5), and significant reduction of CRP, D-dimer, and LDH (Table 6). This result was consistent with the previous study by Ingale et al., which also showed that inflammatory markers started reducing soon after a single dose of Mw.

Initial safety and efficacy of Mw in COVID-19 were reported by Sehgal et al. in case series wherein Mw added to treatment protocol resulted in clinical and radiological improvement in all the cases. The CRP levels improved gradually, and all the patients could be successfully managed without the need for mechanical ventilation.

Sehgal et al. demonstrated the compassionate usage of Mw in COVID-19 patients to stop the progression of the disease and faster recovery in terms of significantly better distribution of clinical status on days 14 and 21. They showed clinical and radiological improvement in all the cases, and Mw did not cause any adverse events.

Another retrospective observational study on 117 patients of COVID-19 showed that the usage of Mw was associated with rapid recovery and improvement in patients’ condition. C-reactive protein and IL-6 levels were also found to be decreased in the study.

We observed a significant reduction in D-dimer, LDH, and CRP when Mw was given early (<3 days vs >3 days) in this study. Severe cases of COVID-19 have been associated with infection-induced coagulopathy and secondary hyperfibrinolysis. A higher D-dimer level at admission was associated with a worse prognosis of COVID-19. Changes in D-dimer level are positively associated with the prognosis of COVID-19.

We also did further analysis of the effect of early administration (<3 days vs control) wherein Mw resulted in a significant reduction in lab values (procalcitonin, CRP, ferritin, LDH, and D-dimer) (Table 7).

Usage of Mw in COVID-19 patients was found to be well-tolerated and safe, without any major safety concerns.

**Study Limitations**

Though this is the largest and one of the first study from five tertiary care centers which has evaluated the effect of addition of Mw in critically ill patients, it has its own limitations.

Our study is retrospective in nature. Also, the imbalance in baseline characteristics in both arms could have impacted the outcome.

**Conclusion**

In COVID-19, control of the exaggerated cytokine production is seemingly an effective modality in critically ill patients. Mycobacterium w when added to SOC was found to associate with significantly increased mortality and increased length of hospital stay. However, time since admission to administration of Mw was a significant predictor of in-ICU deaths in multivariate analysis. Early initiation of Mw (<3 days) was observed to be a protective factor against ICU deaths from the multivariate logistic regression model. Early initiation of Mw (<3 days) also resulted in significantly lesser duration of stay in the ICU along with reduction of CRP, D-dimer, and LDH.

The larger randomized controlled trials are recommended to generate data on larger population.

**Acknowledgment**

We would like to thank Dr Pratik Patel (Medical Affairs Department, Cadila Pharmaceuticals Ltd.) for his assistance and help in writing the manuscript.

**ORCID**

Subhal Dixit [https://orcid.org/0000-0002-1441-0807]
Kapil Zirpe [https://orcid.org/0000-0002-8140-727X]
Prasad Suryawanshi [https://orcid.org/0000-0001-7306-8434]
Sayi Prasad [https://orcid.org/0000-0003-0077-0513]
Sourabh Ambapkar [https://orcid.org/0000-0002-0636-3879]
Saavni Ambapkar [https://orcid.org/0000-0003-2758-9073]
Ameya Joshi [https://orcid.org/0000-0001-5383-9668]
Mukund Joshi [https://orcid.org/0000-0002-8602-1632]

**Table 7:** Mw <3 days vs control; impact on lab parameters

<table>
<thead>
<tr>
<th>Control vs Mw</th>
<th>Robust Coefficient</th>
<th>Lower limit</th>
<th>Upper limit</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mw given procalcitonin</td>
<td>–16.52</td>
<td>–25.35</td>
<td>–7.70</td>
<td>0.000</td>
</tr>
<tr>
<td></td>
<td>0.05</td>
<td>–0.27</td>
<td>0.37</td>
<td>0.746</td>
</tr>
<tr>
<td>Mw given CRP</td>
<td>–2423.70</td>
<td>–3259.13</td>
<td>–1588.28</td>
<td>0.000</td>
</tr>
<tr>
<td></td>
<td>0.07</td>
<td>–0.25</td>
<td>0.39</td>
<td>0.666</td>
</tr>
<tr>
<td>Mw given ferritin</td>
<td>331.85</td>
<td>59.76</td>
<td>603.95</td>
<td>0.017</td>
</tr>
<tr>
<td></td>
<td>0.41</td>
<td>–0.09</td>
<td>0.90</td>
<td>0.105</td>
</tr>
<tr>
<td>Mw given D-dimer</td>
<td>722.71</td>
<td>181.13</td>
<td>1264.28</td>
<td>0.009</td>
</tr>
<tr>
<td></td>
<td>0.18</td>
<td>0.13</td>
<td>0.22</td>
<td>0.000</td>
</tr>
<tr>
<td>Mw given IL-6</td>
<td>–53.35</td>
<td>–108.86</td>
<td>2.16</td>
<td>0.059</td>
</tr>
<tr>
<td></td>
<td>0.05</td>
<td>–0.08</td>
<td>0.17</td>
<td>0.455</td>
</tr>
<tr>
<td>Mw given LDH</td>
<td>–43.89</td>
<td>–151.88</td>
<td>64.10</td>
<td>0.423</td>
</tr>
<tr>
<td></td>
<td>0.73</td>
<td>0.35</td>
<td>1.11</td>
<td>0.000</td>
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</table>
Retrospective Cohort Observational Study to compare the Effect of Mycobacterium w

References


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Dr. Agam C Vora
Hon. General Secretary
Management of Hypertension in Patients with Diabetes: A Comprehensive Review of the Perceptions and Practices of Health Care Providers in India

C Venkata S Ram1*, V Mohan2, Kaushik Pandit3, Surender Kumar4, Rakesh Sahay5, Mathew John6, Shehla Shaikh7, Santosh Revankar8, Neeraj Kumar9

Accepted: 24 February 2022; Accepted: 15 May 2022

ABSTRACT

Objectives: This study evaluated the perception and practices of health care providers (physicians, diabetologists, and endocrinologists) regarding the treatment of hypertension in patients with diabetes in India.

Methods: Health care providers throughout India who treated patients with diabetes and hypertension were invited to participate in an online survey and periodic 21 virtual meetings. They were questioned about their perception and practices in managing these patients, and strategies to improve blood pressure (BP).

Results: The online survey was completed by 2,513 health care providers, and 344 participated in virtual meetings. More than 50% reported that 31–50% of their patients with diabetes also had hypertension. Home BP monitoring was recommended by 88%, and lifestyle modifications were consistently recommended. Choice of antihypertensive treatment varied based on comorbidities, and a renin–angiotensin system blocker plus a calcium channel blocker (CCB) was the most common combination for dual antihypertensive therapy. Suggested strategies to improve BP control included patient awareness/education, lifestyle modifications, better follow-up/monitoring, and optimization of therapy.

Conclusion: Indian health care providers were aware of clinical recommendations and practices regarding treatment of patients with diabetes and hypertension, and generally make clinical decisions consistent with current guidelines. Optimization of care for these patients is essential to reduce cardiovascular disease risk and improve patient outcomes.

Introduction

High BP is one of the most important risk factors for global morbidity and mortality. Recent epidemiological studies reported that there are 100–110 million people with hypertension in India. According to Global Burden of Diseases (GBD) 2016 and 2017 reports, hypertension was responsible for 1.63 million deaths in India, and high systolic BP (SBP) contributed to 10.2 million deaths worldwide. Also, GBD data showed that more than half of all deaths were due to coronary heart disease (54.2%), stroke (56.2%), and chronic kidney disease (CKD; 54.5%) were associated with high SBP. A study investigating the effects of socioeconomic variables on hypertension awareness, treatment, and control showed that low household wealth index and low educational status were associated with poor control of hypertension.

The International Diabetes Federation estimates that approximately 537 million adults (age 20–79 years) worldwide had been diagnosed with diabetes, and this number will increase to 643 million by 2030 and to 783 million by 2045. In India, the 2021 age-adjusted prevalence of diabetes is 9.6%, and more than 39 million people may have undiagnosed diabetes.

In addition to hypertension, diabetes is a risk factor for mortality in both developing and developed countries. The prevalence of hypertension in patients with diabetes is 1.5–2.0 times higher than that in individuals without diabetes. In addition, patients with hypertension and diabetes mellitus share well-known metabolic abnormalities such as abdominal obesity, hyperinsulinemia, insulin resistance, and hypertriglyceridemia. The presence of hypertension in patients with diabetes can accelerate the risk of vascular complications, and the coexistence of diabetes and hypertension is considered to be a significant risk factor for atherosclerotic cardiovascular disease (ASCVD) and heart failure.

In India, rapid urbanization and improved standards of living have resulted in increased obesity and cardiovascular disease risk factors. The presence of hypertension in individuals with type 2 diabetes mellitus also increases cardiovascular risk markers, including microalbuminuria, insulin resistance, and left ventricular hypertrophy. The presence of uncontrolled hypertension and diabetes may lead to endothelial dysfunction, arteriosclerotic cardiovascular diseases, acute hypertensive encephalopathy, retinopathy, stroke, myocardial infarction, heart failure proteinuria, and renal failure.

Although the association between hypertension and diabetes is well established, attitudes of health care professionals in India regarding these comorbid conditions in routine clinical practice have not been elucidated. Therefore, this study investigated the perception and practices of health care providers regarding the treatment of hypertension in patients with diabetes.

Methods

Study Design and Participants

This study consisted of a cross-sectional survey and 21 periodic virtual round table meetings (RTMs). Surveys were conducted

1 Director, Apollo Institute for Blood Pressure Management and Apollo Blood Pressure Clinics, Apollo Hospitals, Hyderabad, Telangana; 2Chairman and Chief Diabetologist, Dr. Mohan’s Diabetes Specialities Centre, Chennai, Tamil Nadu; 3Consultant Endocrinologist and Diabetologist, Fortis Hospital and Belle Vue Clinic, Kolkata, West Bengal; 4Chairman, Department of Endocrinology, Sir Ganga Ram Hospital, New Delhi, Delhi; 5Professor of Endocrinology, Department of Endocrinology, Osmania Medical College, Hyderabad, Telangana; 6Consultant Endocrinologist, Providence Endocrine and Diabetes Specialty Centre, Trivandrum, Kerala; 7Consultant Endocrinologist, Prince Aly Khan Hospital and Saifee Hospital, Mumbai, Maharashtra; 8Deputy General Manager; 9Assistant Manager, Scientific Services, USV Private Limited, Mumbai, Maharashtra, India; *Corresponding Author

Management of Hypertension in Patients with Diabetes

according to the globally accepted standards of good clinical practice (as defined in the International Conference on Harmonisation E6 Guidelines for Good Clinical Practice, 1st May 1996), in agreement with the latest version of the Declaration of Helsinki and in accordance with the local internal and external regulations. Health care providers managing for patients with hypertension and diabetes were recruited using random sampling, with a focus on a mix of doctors from different regions and major cities in India.

Survey
A web-based survey was designed by a collaborative team of diabetologists and endocrinologists. It included questions relating to the following parameters:

- Prevalence and diagnosis of hypertension
- Blood pressure thresholds and targets
- Treatment
- Compliance and BP control

Virtual RTMs
Total 21 virtual RTMs were conducted. During the meeting, all the questionnaire responses were discussed. Entire session was recorded and feedback was taken from expert health care providers.

Statistical Methods
Data were entered in a Microsoft Excel spreadsheet, and statistical analysis was done using SPSS (version 28). All responses to the survey and expert comments from all health care providers in the virtual RTMs were included in the analyses. Qualitative variables were compared using the chi-square test.

Results
Study Sample
A total of 2,857 health care providers participated in the study, 2,513 participated in survey and 344 participated in 21 virtual RTMs (Table 1).

Prevalence and Diagnosis of Hypertension
More than 50% of health care providers reported that 31–50% of their patients with diabetes also had hypertension.

The average duration of diabetes was stated to be 6–10 years by 42% of health care providers, while the average duration of hypertension in their patients with diabetes was 1–5 years for 41% of health care providers.

The majority of health care providers (88%) recommended the use of home BP monitoring in patients with diabetes and hypertension, using an average of three BP readings. Use of ambulatory BP monitoring (ABPM) was less frequent, with nearly all health care providers stating that they were using this in ≤20% of their patients (Fig. 1A). Circadian BP variation, discrepancy between home and office BP readings, and to rule out masked hypertension were the most commonly cited indications for the use of ABPM (Fig. 1B).

Additional diagnostic evaluations in patients with diabetes and hypertension included the lipid profile, renal and hepatic function, and urinary albumin (Fig. 2). Health care providers also advised monitoring of serum electrolytes (e.g., sodium and potassium) in patients being treated with renin–angiotensin–aldosterone system (RAAS) blockers.

Blood Pressure Thresholds and Targets
More than 55% of health care providers recommended initiation of monotherapy in patients with diabetes when BP was ≥140/90 mm Hg and 32% initiated monotherapy when BP was ≥130/80 mm Hg. Dual antihypertensive therapy was initiated when BP was ≥140/90 mm Hg by 26% of health care providers, ≥150/90 mm Hg by 32%, and ≥160/100 mm Hg by 33%; the remaining health care providers used dual therapy at higher BP thresholds (Table 2).

Target BP in patients aged <65 years was <130/80 mm Hg for 42% of health care providers and <140/90 mm Hg for another 30%, while the remainder varied the target based on cardiovascular risk. For those aged ≥65 years, 43% of health care providers used a target of <140/90 mm Hg, and 31% used different targets based on cardiovascular risk. In patients with diabetes and hypertension who also had albuminuria and CKD, target BP was <130/80 mm Hg or <140/90 mm Hg for 40% and 41% of health care providers, respectively (Table 3). Some health care providers suggested that all BP levels below 120/80 mm Hg in patients with diabetes are associated with poor coronary flow and mortality in some cases.

Treatments
The majority of health care providers recommended a range of nonpharmacological methods to control BP in their patients with diabetes and hypertension (Fig. 3). The choice of initial antihypertensive therapy varied based on the presence of other comorbid conditions (Fig. 4). Angiotensin receptor blockers (ARBs) were the most popular agents for patients who also had CKD, albuminuria, cerebrovascular disease, or coronary artery disease, while diuretics were the most commonly used initial agents in the presence of congestive heart failure (Fig. 4). In the presence of coronary artery disease, health care providers preferred ARBs over angiotensin-converting enzyme (ACE) inhibitors based on the adverse event profile, and also noted that an ARB + beta-blocker combination is a good choice in this patient population. In patients with congestive heart failure, mineralocorticoid receptor antagonists were preferred, along with RAAS blockers and beta-blockers, while diuretics provide symptomatic improvement; sodium–glucose cotransporter 2 (SGLT2) inhibitors and angiotensin receptor–neprilysin inhibitors were also an effective choice. In patients with comorbid albuminuria and/or CKD, ARBs were preferred because of their better safety profile.

In normotensive patients with diabetes and albuminuria, 89% of health care providers recommended the use of RAAS blockers, and ARBs (77% of health care professionals) were preferred over ACE inhibitors (23%); SGLT2 inhibitors were also an option in patients with albuminuria. Health care providers noted that there is a good body of evidence for the renal protective effects of ARBs. Just over three-quarters (76%) of them recommended aspirin therapy in patients with diabetes and hypertension. The combination of a RAAS blocker and a CCB was the most popular dual antihypertensive therapy combination, followed by a RAAS blocker and a diuretic (Table 4).

Compliance and BP Control
In RTMs, poor awareness of the complications of untreated hypertension, lack of regular BP monitoring, inadequate access to medical care, and denial of hypertension were the four main reasons cited for noncompliance to medication according to the health care providers.

Four major strategies were recommended by health care providers to control diabetes and

Table 1: specialty of participating health care providers by region

<table>
<thead>
<tr>
<th>Specialty, n (%)</th>
<th>South (n = 1,072)</th>
<th>East (n = 561)</th>
<th>North (n = 642)</th>
<th>West (n = 582)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetologist</td>
<td>936 (87.3)</td>
<td>468 (83.4)</td>
<td>443 (69.0)</td>
<td>507 (87.1)</td>
<td>0.199</td>
</tr>
<tr>
<td>Endocrinologist</td>
<td>77 (7.2)</td>
<td>93 (16.6)</td>
<td>117 (18.2)</td>
<td>31 (5.3)</td>
<td></td>
</tr>
<tr>
<td>Consultantphysician</td>
<td>59 (5.5)</td>
<td>0 (0.0)</td>
<td>82 (12.8)</td>
<td>44 (7.6)</td>
<td></td>
</tr>
</tbody>
</table>
**Discussion**

The results of this study provide an overview of the clinical practice of health care providers with respect to the treatments, challenges, and solutions involved in treating hypertension in patients with diabetes in India.

**Figs 1A and B:** Percentage of patients with diabetes and hypertension who are using ABPM (A) and reasons for using ABPM (B)

**Fig. 2:** Other tests used in patients with diabetes and hypertension. ECHO, Echocardiography; eGFR, Estimated glomerular filtration rate

hypertension: increasing patient awareness (using education, counseling, and screening—recommended by 40% of health care providers); lifestyle modification (diet, stress management, and exercise—recommended by 31% of health care providers); better follow-up and regular monitoring (at home and in the clinic—recommended by 19% of health care providers); and optimization of therapy (including use of fixed-dose combination therapy and improved adherence—recommended by 10% of health care professionals).
Our data showed that the majority of health care providers reported the prevalence of hypertension in patients with diabetes as 31–50%. This is lower than the prevalence reported in a previous study, in which almost 60% of patients with diabetes had hypertension.11 Health care providers in our survey were specialists in a tertiary care setting. They reported that the average duration of diabetes in their patients was 6–10 years, and the average duration of hypertension in these patients was 1–5 years. The duration of diabetes in our study was similar to that reported in the Japan Diabetes Complications and its Prevention prospective study 3 of 5,844 patients with type II diabetes, which reported 9 years as the average duration of diabetes.13 A longer duration of diabetes increases the risk of developing hypertension and microvascular injury, and decreases insulin sensitivity. In our study, the average duration of diabetes and the average duration of hypertension in patients with diabetes appeared to vary depending on the clinical experience, area of practice, and type of health care professional.

It was encouraging to see that the majority of health care providers (88%) recommended home BP monitoring to their patients who had hypertension and diabetes. According to the 2021 American Diabetes Association (ADA) recommendation, all hypertensive patients with diabetes should monitor their BP at home.16 In our study, most health care providers recommended measurement of home BP rather than ABPM, and felt that it was important to properly educate and train patients on how to perform home BP measurement. Ambulatory BP monitoring was not used very often by the Indian health care providers who responded to our survey. However, most health care providers suggested that all diabetic patients with hypertension should undergo ABPM at least once, but that it is important to identify symptoms before referring for ABPM to avoid unnecessary cost. If ABPM is not available, then home BP monitoring is a valid alternative.

The use of lipid profiling, liver and renal function tests, urine albumin, serum electrolytes, electrocardiogram (ECG), 2D echocardiography, and chest X-ray for patients with diabetes and hypertension by health care providers in our survey is consistent with the European Society of Cardiology (ESC)/European Society of Hypertension (ESH) guidelines for the management of arterial hypertension.17 These tests are also important for the detection of hypertension-mediated organ damage.17 Both the International Society of Hypertension Global Hypertension Practice Guidelines18 and ADA guidelines16 state that target BP in patients with diabetes should be ≤140/90 mm Hg. In the present study, health care providers reported that they used a target BP of <130/80 mm Hg and <140/90 mm Hg in patients with diabetes aged <65 and >65 years, respectively.

Table 2: Blood pressure threshold for initiating mono and dual pharmacotherapy

<table>
<thead>
<tr>
<th>Pharmacotherapy</th>
<th>BP threshold, mm Hg</th>
<th>Doctors, n (%)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Monotherapy</td>
<td>≥130/80</td>
<td>186 (32.0)</td>
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</tr>
<tr>
<td></td>
<td>≥140/90</td>
<td>320 (55.1)</td>
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</tr>
<tr>
<td></td>
<td>≥150/90</td>
<td>75 (12.9)</td>
<td></td>
</tr>
<tr>
<td>Dual therapy</td>
<td>≥140/90</td>
<td>151 (26.0)</td>
<td>0.220</td>
</tr>
<tr>
<td></td>
<td>≥150/90</td>
<td>183 (31.5)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>≥160/100</td>
<td>189 (32.5)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>≥170/100</td>
<td>36 (6.2)</td>
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</tr>
<tr>
<td></td>
<td>≥180/100</td>
<td>22 (3.8)</td>
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</tbody>
</table>

Table 3: Blood pressure target and monitoring in patients with diabetes and hypertension

<table>
<thead>
<tr>
<th>Patients with diabetes</th>
<th>Target BP, mm Hg</th>
<th>Doctors, n (%)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &lt;65 years</td>
<td>&lt;130/80</td>
<td>243 (41.8)</td>
<td>0.199</td>
</tr>
<tr>
<td></td>
<td>&lt;140/90</td>
<td>175 (30.1)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>&lt;130/80 (multiple CV risk factors) and &lt;140/90 (low CV risk)</td>
<td>163 (28.1)</td>
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</tr>
<tr>
<td>Age ≥65 years</td>
<td>&lt;130/80</td>
<td>107 (18.4)</td>
<td>0.224</td>
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<td></td>
<td>&lt;140/90</td>
<td>247 (42.5)</td>
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<td></td>
<td>&lt;130/80 (multiple CV risk factors) and &lt;140/90 (low CV risk)</td>
<td>182 (31.3)</td>
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<tr>
<td></td>
<td>&lt;145/90</td>
<td>45 (7.8)</td>
<td></td>
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<tr>
<td>With albuminuria and/or CKD</td>
<td>&lt;130/80</td>
<td>233 (40.1)</td>
<td>0.199</td>
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<tr>
<td></td>
<td>&lt;140/90</td>
<td>237 (40.8)</td>
<td></td>
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<tr>
<td></td>
<td>&lt;120/70</td>
<td>111 (19.1)</td>
<td></td>
</tr>
</tbody>
</table>

CV, Cardiovascular

Fig. 3: Nonpharmacological therapies recommended to patients with diabetes and hypertension
The Kidney Disease Improving Global Outcomes group recommends a BP goal of \( \leq 140/90 \) mm Hg in patients with diabetes, with a lower goal (\( \leq 130/80 \) mm Hg) in those with comorbidities. 16 20 27 Practices of health care providers (13%) stated that their goal (\( \leq 130/80 \) mm Hg) in those with comorbidities is in agreement with ADA 2021 guidelines for patients with diabetes plus CKD and for hypertension management in patients with diabetes and hypertension.16

In terms of initiating antihypertensive therapy, the ADA guidelines state that this should occur when BP is from \( >140/90 \) mm Hg to \( <160/100 \) mm Hg (monotherapy) or \( >160/100 \) mm Hg (dual therapy), both with lifestyle modifications.16 The practice of health care providers in this study was consistent with these recommendations, although they noted that treatment decisions should not be based on a single reading. It is clear that fewer than half of all patients respond to antihypertensive monotherapy, whereas response rates to two or more drugs are much higher (75–80% and 90–95%, respectively).21

The fact that a small proportion of health care providers (13%) stated that their threshold for initiating antihypertensive monotherapy was \( >150 \) mm Hg might have been a consequence of their lack of confidence in the accuracy of BP measurements. However, this is inconsistent with current guideline recommendations.16,27 For some health care professionals, the BP level at which therapy for hypertension was initiated in patients with diabetes was dependent on the presence of other comorbidities, cardiovascular risk, drug tolerance, and other factors.

Angiotensin receptor blockers were the first-choice agents for antihypertensive therapy in patients with diabetes and albuminuria.19,20 Practices of health care providers surveyed in this study, who reported that \( <130/80 \) mm Hg and \( <140/90 \) mm Hg were the BP target in diabetic patients with kidney diseases (albuminuria and CKD), were similar. Clinical practice and the comorbidities present determine the correct BP target in patients with diabetes and hypertension.

In the present study, 54% of the health care providers surveyed selected a RAAS blocker + CCB for dual antihypertensive therapy. This reflects current ESC/ESH guidelines (2018) and ADA guidelines (2021), which recommend the combination of a RAAS blocker with a CCB or a thiazide-like diuretic for the treatment of patients with diabetes and hypertension.16

For patients aged \( \geq 65 \) years, health care providers recommended dual antihypertensive therapy with an ARB + CCB, and noted the risk of hyponatraemia with diuretics in the elderly. In patients with diabetes \( <65 \) years, health care providers preferred the combination of an ARB and a diuretic. Furthermore, health care providers recommended the use of low drug dosages in combination therapy due to the development of tolerance to the effects of higher drug dosages over a few months. It was also suggested that higher dosages of a RAAS blocker + CCB are associated with peripheral edema, meaning that diuretics are an alternative combination drug in this setting.

Although not recommended by specific guidelines, beta-blockers are associated with better outcomes in obese patients with type II diabetes and CAD compared with RAAS blockers. For dual therapy, the antihypertensive effects of a combination of drugs with a different mechanism of action are associated with a two- to five-times greater antihypertensive effect than antihypertensive monotherapy.

More than 75% of health care providers surveyed recommended aspirin therapy in diabetes patients with hypertension to reduce the risk of cardiovascular disease. Use of aspirin in all patients with diabetes is debatable. Age, history of atherosclerosis, and the presence of multiple risk factors are to take into account when deciding whether to use aspirin in patients with diabetes. The ADA 2021 guidelines recommend the use of aspirin (75–162 mg/day) as a secondary prevention strategy in patients with diabetes who have a history of ASCVD.16,28 Therefore, aspirin (75–162 mg/day) may be considered as a primary prevention strategy in patients with diabetes who are at increased cardiovascular risk after a comprehensive discussion with the patient on the benefits of therapy compared with the increased risk of bleeding. Statins are another group of agents that have been shown to be useful for the secondary prevention of cardiovascular disease and for primary prevention in high-risk patients; use in primary prevention should therefore be based on clinical judgement.22

Health care providers reported four main reasons for nonadherence to antihypertensive therapy in patients with diabetes, including poor awareness of the complications of untreated hypertension, inadequate access to medical care, lack of regular health check-ups, and denial of hypertension. Similarly, reasons...
Management of Hypertension in Patients with Diabetes

for nonadherence to antihypertensive pharmacotherapy in previous studies included lack of patient motivation, the incurable nature of the disease, lack of symptoms, use of herbal preparations, physical disability, presence of complications, low level of education, poor knowledge about the disease, and ignorance of the need for long-term treatment. According to ADA 2021 guidelines, strategies for improving antihypertensive medication adherence include the use of home BP monitoring and single-pill antihypertensive combinations.

Health care providers in this study suggested that denial of hypertension and poor awareness were two major reasons for antihypertensive treatment failure. Social media may also play a key role because patients believe social media messages and discontinue medications without the knowledge of health care professionals. Therefore, dissemination of accurate information by health care providers on social media would be helpful.

We acknowledge a few limitations in the present study. This was an observational study and emphasis was on hypertension management, so we have not explored the effect of hemoglobin A1C status, glucose level, nutritional, socioeconomic, and educational status of the patients on the management of hypertension in diabetes patients. Geographic region and ethnicity may also affect the treatment approach which were not discussed. This study was performed on a limited number of health care practitioners; therefore, these observations cannot be generalized to the overall health care practitioners of India.

In conclusion, data from the current survey and RTMs suggest that Indian health care providers are aware of clinical recommendations and practices relating to the care of patients with diabetes and hypertension, and generally make clinical decisions that are consistent with current guidelines. Optimization of care for this important patient group is essential to reduce cardiovascular disease risk and improve patient outcomes.

Acknowledgment
We acknowledge Ms Farida Hussain and Mr Sagar Patil from USV Private Limited for their assistance in the conduct of the project. The content published herein represents the views and opinions of various contributing authors and does not necessarily represent the view or opinions of USV Private Limited.

Compliance with Ethics Guidelines
This article is based on previously conducted studies and does not contain any studies with human participants or animals performed by any of the authors. However, ethical approval was obtained from the ACEAS-Independent Ethics Committee (US/PATTERN/01).

Authors’ Contributions
Dr Venkata S Ram and Dr V Mohan have conceptualized the study format and reviewed the manuscript. Other authors contributed toward the integration of survey questionnaires and their responses in the different sections as given below:

- Dr Kaushik Pandit: prevalence and diagnosis.
- Dr Mathew John: BP target.
- Dr Rakesh Sahay: pharmacological intervention.
- Dr Surender Kumar: management in different comorbidities.
- Dr Shehla Shaikh: adherence and compliance.

All named authors take the responsibility for the integrity of the work as a whole and have given approval for the version to be published.

Other contributors: The contributions of the following individuals in the execution of our research work: Dr A Premkumar, Dr Abhay Kumar Sahoo, Dr Ajish TP, Dr Amey Joshi, Dr Amit Rastogi, Dr Anish Behl, Dr Arundhati Dasgupta, Dr Ashish Sehgal, Dr Ashok Venkata Narasu, Dr Atul Dhingra, Dr Bhartar Sharma, Dr K A V Subramyan, Dr N K Agarwal, Dr N K Narayanay, Dr S K Mathur, Dr Sandeep Julka, Dr Santosh Malpani, Dr Shreerang Godbole, Dr Soumik Goswami, Dr Sunil Mishra, and Dr Vageesh Ayyar.

References
BETA COURSE
BEST ECG TECHNIQUES APPLICATION

An initiative to provide a platform for paramedic staff to upskill the best practices while performing and reading/interpreting ECGs

TABLE OF CONTENTS

1. Introduction to ECG: History, Definition, waves and lines
2. How to record ECG properly: Electrodes - chest and limbs, colour coding of electrodes, preparation of room, patient and machine, correct placement of electrodes, final ECG - what to see
3. Abnormal waves and what do they mean: P, Q, R waves, PR, ST, TP Segments - Abnormalities and Diseases
4. ECG in CAD: ECG changes in ACS and What to do?
5. Abnormal rhythms: Sinus rhythm, Premature beats, Tachycardia, Bradycardia

If you want to enroll your paramedic staff, kindly contact:
Mr. Sagar Patil: sagar.patil@usv.in | 9004687621
Mr. Sumit Kakirde: sumit.kakirde@usv.in | 7718847052
Ms. Siddhi Sawant: siddhi.sawant@usv.in | 9987493753
In patients with hypertension and diabetes,

**Tazloc®-AM 40**
Telmisartan 40 mg + Amlodipine 5 mg

For the Detrimental duo... The Distinctive duo...

**Journal of ACC – Mar’21**

Higher time in Target Range

<table>
<thead>
<tr>
<th>Month</th>
<th>SBP (mmHg)</th>
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<tr>
<td>0</td>
<td>180</td>
</tr>
<tr>
<td>1</td>
<td>160</td>
</tr>
<tr>
<td>2</td>
<td>140</td>
</tr>
<tr>
<td>3</td>
<td>120</td>
</tr>
</tbody>
</table>

Target Range (110-130 mmHg)

If uncontrolled, Up-titrate to

**Tazloc®-AM 80**
Telmisartan 80 mg + Amlodipine 5 mg

- In mild to moderate hypertension, initiate / add
- In elderly hypertensives, uncontrolled on monotherapy
- In hypertensives uncontrolled on dual drug therapy

In hypertension

**Amlopin**
Amlodipine 5 mg

For Intensive BP control with CV safety

**Amlopin®-M**
Amlodipine 5 mg + Metoprolol Succinate ER 25/50 mg

For long-lasting BP control

**Amlopin®-AT**
Amlodipine 5 mg + Atorvastatin 10 mg

Neuroimaging Profile of drug-resistant Epilepsy from a Tertiary Care Center in South India

M Navab1, K Nagarajan2, Pradeep P Nair3, KM Sivasubramaniyan4

Received: 22 October 2021; Accepted: 04 April 2022

ABSTRACT

Background and aims: Drug-resistant epilepsy (DRE) is a common and important neurological problem to identify with scope for curative surgical treatment if underlying cause is delineated. There are very few prospective structured studies in our population. This study aimed to look at the neuroimaging profile of DRE presenting in a tertiary care center in South India.

Materials and methods: All patients diagnosed clinically as DRE as per International League Against Epilepsy (ILAE) criteria and who underwent magnetic resonance imaging (MRI) over a period of 24 months were included in the study. Their clinical and MRI features were documented and analyzed.

Results: A total of 150 patients diagnosed with DRE were included in the study. Clinically, 96 of them presented with generalized tonic-clonic seizures (GTCS), 36 with complex partial seizures (CPS), 14 with simple focal seizures, and two each with atonic seizures and focal seizures with secondary generalization. Magnetic resonance imaging (done in 1.5 T) was normal in 32%. In those with abnormal MRI, mesial temporal sclerosis (MTS) was the commonest pathology seen in 41.3%, followed by cortical malformations (6.7%), tumors (2.6%), vascular malformations (2.7%), and other nonspecific lesions (12%).

Conclusion: The clinical and neuroimaging profile of DRE showed that DRE is more common in younger age (of less than 30 years); presents mainly with GTCS or CPS; mesial temporal sclerosis is the commonest underlying pathology which was bilateral in 8.6%; temporal lobe lesions predominate (49.3% of all DRE); and cortical malformation, low-grade tumors, and vascular lesions are other important causes.

INTRODUCTION

Management of epilepsy has evolved over the last few decades with the advent of new drugs, which is the mainstay of treatment. But, about one in every three epilepsy patients does not respond or is refractory to anticonvulsant therapy.1 International League Against Epilepsy defines DRE as “persistent seizure despite the use of adequate trials of two or more anticonvulsants.”2 As per a recent study from Italy on the prevalence of DRE, it accounts for around 15% of active diseases and 10.5% of newly diagnosed cases.3 Another study from a tertiary care center in Singapore showed prevalence of drug resistance as about 20%.4

An epileptogenic zone is defined as “a part of the cortex that is obligatory and required for initiating seizures and whose removal is necessary for the complete abolition of seizures.”5 Magnetic resonance imaging identifies the underlying structural lesion which forms the “lesional zone” in the patient with DRE. The structural lesions cannot be equated to the epileptogenic zone but gives indirect evidence for the same. Magnetic resonance imaging delineation will help in deciding treatment options, especially surgical management. In India, over 10.2 million people have epilepsy, in which medically refractory or DREs may account for about 1 million.6 For such patients, identifying a structural brain abnormality provides the best potential for surgical cure and improvement in the quality of life. This study was done to evaluate the clinical and neuroimaging profile of patients with DRE presenting in our institution which is a tertiary care center in this part of the country catering to adjacent states. The study aimed for emphasis on the localization, whether in temporal lobe or in extratemporal site, so as to enable further management of these patients with available limited resources.

MATERIALS AND METHODS

This descriptive study was conducted in the Department of Radiodiagnosis in collaboration with Department of Neurology, after approval by the Institute Research Monitoring Committee and Institute Ethics Committee. The patients were recruited according to the inclusion and exclusion criteria as detailed below.

Inclusion Criteria
All cases of DRE diagnosed as per ILAE criteria, who are referred for neuroimaging to rule out, and if present, to localize structural lesion.

Exclusion Criteria
- All patients whose MRI could not be done due to lack of consent or poor cooperation.
- All contraindications for undergoing MRI like metallic implants.
- Those diagnosed as pseudoseizures or drug-induced seizures.

We evaluated 150 consecutive DRE patients over a period of 24 months who satisfied the inclusion and exclusion criteria. Informed consent was obtained from all the patients. The MR images were interpreted with a 1.5 T system (Avanto Magnetom, Siemens, Erlangen, Germany), using standard head coil for the acquisition of images. The patients’ demographic and clinical details were recorded in the proforma. Magnetic resonance imaging was performed with T1-weighted sagittal, gradient T2*-weighted, T2-weighted coronal, fluid attenuated inversion recovery (FLAIR) axial, T2-weighted coronal, 3D T1-weighted sagittal, 3D T2-weighted coronal, 3D T2*-weighted sagittal, gradient T2*-weighted or susceptibility-weighted imaging, and FLAIR and inversion recovery T1 in oblique coronal plane perpendicular to the hippocampus. Depending on the lesion morphology and other features, contrast-enhanced MR was used with T1-weighted axial sequence (with magnetization transfer transfer). After completion of the procedure, the clinical and neuroimaging findings were collected and results were analyzed. The MR images were interpreted by

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Results
A total of 150 patients with DRE underwent MRI of the brain over a period from June 2016 to July 2018. There were 95 male patients and 55 female patients. The commonest age group that presented with DRE was between 10 and 20 years followed by 20 and 30 years (Table 1).

About 10.6% of patients had family history of seizures (first-degree relatives with seizures). Majority of the patients had focal onset seizures (58%) and about 38% of patients had generalized onset of seizures (Table 2).

About 68% of the patients had abnormal MRI findings (Table 3).

Patients were divided based on etiology into the following six groups: (1) normal (32%), (2) mesial temporal sclerosis (MTS) (41.3%), (3) cortical malformations (6.7%), (4) tumors (2.7%), (5) vascular (2.7%), and (6) nonspecific findings (12%). Out of the 68% of the patients with abnormal MRI findings, mesial temporal lobe sclerosis was the main abnormality detected followed by cortical malformation.

Table 1: Patients of DRE in different age groups

<table>
<thead>
<tr>
<th>Age group (years)</th>
<th>No. of patients</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>0–10</td>
<td>29</td>
<td>19.3</td>
</tr>
<tr>
<td>10–20</td>
<td>53</td>
<td>35.3</td>
</tr>
<tr>
<td>20–30</td>
<td>37</td>
<td>24.7</td>
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<tr>
<td>30–40</td>
<td>20</td>
<td>13.3</td>
</tr>
<tr>
<td>40–50</td>
<td>2</td>
<td>1.3</td>
</tr>
<tr>
<td>50–60</td>
<td>5</td>
<td>3.3</td>
</tr>
<tr>
<td>&gt;60 years</td>
<td>4</td>
<td>2.7</td>
</tr>
</tbody>
</table>

Table 2: Type of seizures

<table>
<thead>
<tr>
<th>Type of seizure</th>
<th>No. of patients</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Focal onset seizure</td>
<td>87</td>
<td>58</td>
</tr>
<tr>
<td>Generalized</td>
<td>57</td>
<td>38</td>
</tr>
<tr>
<td>Unclassified</td>
<td>6</td>
<td>4</td>
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Table 3: MRI features in DRE

<table>
<thead>
<tr>
<th>MRI diagnosis</th>
<th>No. of patients</th>
<th>% of abnormal MRIs</th>
<th>% of total DRE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>48</td>
<td>32</td>
<td></td>
</tr>
<tr>
<td>MTS</td>
<td>62</td>
<td>60.8</td>
<td>41.3</td>
</tr>
<tr>
<td>Cortical malformation</td>
<td>10</td>
<td>9.8</td>
<td>6.7</td>
</tr>
<tr>
<td>Tumors</td>
<td>4</td>
<td>2.4</td>
<td>2.7</td>
</tr>
<tr>
<td>Vascular</td>
<td>4</td>
<td>2.4</td>
<td>2.7</td>
</tr>
<tr>
<td>Nonspecific etiology</td>
<td>18</td>
<td>17.6</td>
<td>12</td>
</tr>
<tr>
<td>MTS with cortical malformation</td>
<td>2</td>
<td>1.9</td>
<td>1.3</td>
</tr>
<tr>
<td>MTS with vascular etiology</td>
<td>1</td>
<td>0.9</td>
<td>0.6</td>
</tr>
<tr>
<td>Cortical malformation with nonspecific etiology</td>
<td>1</td>
<td>0.9</td>
<td>0.7</td>
</tr>
</tbody>
</table>

Table 4: Hippocampal involvement in DRE

<table>
<thead>
<tr>
<th></th>
<th>% of abnormal MRI (102)</th>
<th>% of total DRE (150)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Right hippocampus</td>
<td>28</td>
<td>38.9</td>
</tr>
<tr>
<td>Left hippocampus</td>
<td>31</td>
<td>43.1</td>
</tr>
<tr>
<td>Both</td>
<td>13</td>
<td>18.1</td>
</tr>
<tr>
<td>No involvement</td>
<td>78</td>
<td></td>
</tr>
</tbody>
</table>

Figs 1A to C: MRI of brain FLAIR oblique coronal sequences in three different patients with DRE showing right-sided (A), left-sided (B), and bilateral (C) mesial temporal sclerosis, respectively.
extratemporal lobe lesions, and 4% of patients had both temporal and extratemporal lobe involvement (Table 5).

**Type of Seizures and MRI Diagnosis (Fig. 4)**

There were 96 patients who presented with GTCS, among whom 38 had normal MRI, 37 had temporal lobe lesions, 16 had extratemporal lobe lesions, and 5 had both. Thirty-six patients had CPS, of which 30 had temporal lesions, one had extratemporal lobe lesion, and five had normal MRI. Of 14 patients with simple focal seizures, six each had temporal and extratemporal lesions, one had both involved, and one was normal. Two patients with simple focal seizures with secondary generalization had temporal lesions and two with atonic seizures had normal MRI.

Of 46 patients with normal MRI, 38 had GTCS, five had CPS, two had atonic, and one had simple focal seizures. Seventy-five patients had temporal lesions of which 37 presented with GTCS and 30 with CPS. Of 23 extratemporal lesions, 16 presented with GTCS and six had simple focal seizures. Out of six patients who had both temporal and extratemporal lesions, five presented with GTCS.

**DISCUSSION**

Our study involved 150 patients who were included based on the ILAE definition of DRE.² Epilepsy can affect people of all age groups and races. Male predominance was noted in this study (63.3%) similar to the previous studies conducted by Ramos et al. (59%), Tripathi et al. (71%), and Wirrell et al. (51%).⁷⁻⁹ The most common age group was 10–20 years, followed by 20–30 years. In a study conducted by Mukherjee et al. from eastern India, 40% of the patients were in the 1st decade of life compared to 19.33% in ours.¹⁰ This study also reported that 11.5% patients with DRE had family history of epilepsy.¹⁰ A study conducted by Baraitser found 4–10% increased risk of epilepsy in patients with positive family history.¹¹ Boonluksiri et al.¹² in

**Table 5: Temporal vs extratemporal involvement in DRE**

<table>
<thead>
<tr>
<th>Type of MRI</th>
<th>No. of patients</th>
<th>% of abnormal MRIs (102)</th>
<th>% of total DRE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Temporal lobe</td>
<td>74</td>
<td>72.5</td>
<td>49.3</td>
</tr>
<tr>
<td>Extratemporal lobe</td>
<td>22</td>
<td>21.6</td>
<td>14.7</td>
</tr>
<tr>
<td>Both</td>
<td>6</td>
<td>5.9</td>
<td>4</td>
</tr>
</tbody>
</table>
their study on DRE in children found prior global neurological deficits as risk factor for DRE.

Magnetic resonance neuroimaging plays a significant role in the evaluation and management of a patient with DRE for understanding underlying etiology, in management especially for planning epilepsy surgery and for assessing the prognosis. Studies have shown that compared to MRI-positive DRE, the patients with MRI-negative cases have less favorable outcome. Overall 32% patients had normal MRI and 68% patients had abnormal results. In a study conducted on adult patients with DRE, Li et al. found that 74% of patients with DRE had abnormal MRI findings.

The most common etiology found in this study was MTS in which 28 (18.7%) patients had right-sided MTS, 31 (20.7%) had left-sided MTS, and 13 (8.7%) patients had bilateral hippocampal changes. The imaging hallmark of mesial temporal sclerosis is volume loss of hippocampus associated with hyperintense signal apart from loss of internal architecture of the hippocampus. Kurita et al. found that 54% of their patients had right-sided hippocampal changes and 41% had left-sided changes and about 2% of patients had bilateral changes. In our study, 34% patients had increased intensity, 32.67% have altered morphology, and 39.33% have volume loss. A study conducted by Spencer et al. shows 60–70% patients with drug-resistant temporal lobe epilepsy had volume loss of hippocampus. Bilateral hippocampal involvement was noted in 13 patients and this should be considered in the presurgical planning of the patients with DRE to avoid overestimation of complete seizure control. Fornix and mammillary body atrophy were seen in 11.33% each in our study, similar to Ozturk et al. who reported 14% asymmetric mammillary bodies and 13.5% asymmetry in the fornix. Kim et al. in their study of MTS showed 20% involvement of mammillary body, fornix, amygdala, and anterior thalamus.

Among the 102 abnormal MRI findings, mesial temporal sclerosis was identified in 62 patients (41.33%), two (1.33%) patients had MTS with cortical malformation, and another one had MTS with vascular malformation. In their study of 2,000 patients with focal epilepsy, Craven et al. found the major etiology was MTS (53.6%), followed by the cortical malformation in 18.3% and tumors in 5.1% including 1.5% due to phacomatosis showing a similar pattern to the current study. In a study by Granados et al., out of 29 patients with refractory epilepsy the major pathology was mesial temporal sclerosis (45%) followed by tumors (33%). Neuronal or cortical malformations are the second most common etiology of DRE in adult patients after MTS. The malformations reported with DRE include focal cortical dysplasia, hemimegalencephaly, heterotopia, lissencephaly, schizencephaly, tuberous sclerosis, and polymicrogyria. Cortical thickening or abnormal gyral pattern, indistinct gray-white matter junction, architectural changes in the subcortical white matter, and segmental atrophy of the cortex are the imaging findings in these malformations. Cortical malformations identified in our study population include focal cortical dysplasia (one), lissencephaly-pachygryria complex (four), heterotopia (two), polymicrogyria (two), and schizencephaly (one). Craven et al. in their study showed in 72 cases of cortical malformation, 50% had focal cortical dysplasia, 41% had heterotopia, 4% patients had schizencephaly, and 4% patients had polymicrogyria.

Tumors, predominantly low-grade lesions may be associated with pharmacoresistant epilepsy and about 30% of epilepsy caused by the tumors is refractory to pharmacotherapy. The usual causes are glioneuronal tumors like ganglioglioma and dysplastic neuroepithelial tumor (DNET) apart from low-grade gliomas. A previous study showed that about 75% of the ganglioglioma present with epilepsy and 50% are pharmacoresistant and mostly are located in the temporal lobe. Magnetic resonance neuroimaging features of ganglioglioma are varied and nonspecific and are difficult to distinguish from DNET. These tumors can be purely solid or cystic and can be of mixed density/signal intensity on computed tomography/MR imaging. These tumors can be associated with minimal or no peritumoral edema and varying enhancement with predominant temporal lobe involvement. They can coexist with other cortical malformation especially focal cortical dysplasia. Temporal lobe slow-growing low-grade glioma can also present with DRE. In our series, there were three glioneuronal tumors (all proved to be DNET) with one case of low-grade temporal lobe glioma. Glioneuronal tumors formed the bulk of causes of localization-related epilepsy (20%) in the study by Craven et al., apart from cases of hamartoma and meningiomas.

Seizures are the most common presentation of supratentorial vascular malformations. Seizures associated with cavernoma can be refractory to medication. There were three cases of cavernoma (one each in temporal, temporo-occipital, and frontal locations) and one case was developmental venous anomaly (frontal) in our group. Another case with dual pathology had MTS with cavernoma in which cavernoma was located in the frontal lobe.

Nonspecific etiology includes gliosis and cystic encephalomalacia, hypoxic ischemic encephalopathy (HIE) sequelae, inferior vermalian dysplasia, hypothalamic hamartoma, hippocampal inversion, arachnoid cyst, hippocampal cyst, choirod fissural cyst, tuberous sclerosis, prominent hippocampal perivascular space, and porencephalic cyst. In the nonspecific category, gliosis and encephalomalacia changes are the predominant cause of DRE. Shetty showed approximately 9.4% cases of epilepsy in children were due to encephalomalacia and scarring. Two cases of seizures due to HIE sequelae were associated with developmental delay on examination.

Out of 102 (68%) abnormal MRIs, 74 cases (49.3%) were localized in the temporal lobe and 22 (14.7%) cases were extratemporal. Both temporal and extratemporal lesions were
Neuroimaging Profile of drug-resistant Epilepsy

found in six cases (4%). A study conducted by Semah et al. in a tertiary care center found a similar finding.33 Previous studies based on surgical management of epilepsy have shown that 69–73% of patients had temporal lobe involvement.33–35 Recent case-control study by Roy et al.36 found younger age group, CPS, temporal focus, and mesial temporal sclerosis are variables associated with DRE.

Limitations

Our study was done in a tertiary care referral center, where more uncontrolled cases of refractory seizures are referred and it can be a potential cause of bias. Further, this study was done in 1.5 T MRI. Although 3 T MRI has not been shown to improve significantly as far as detection of pathology, but it is possible that few subtle findings of mesial temporal sclerosis and neuronal migration/cortical malformations could have been better seen with 3 T MRI. Electroencephalographic correlation with clinical and MRI findings could have helped to understand the pathogenesis better. We did not use the 2017 ILAE classification for the clinical types as still many clinicians and general physicians are used to the older classification. All the cases of tumors have not been operated yet pending their complete evaluation and diagnosis on MRI was presumptive.

Conclusion

The neuroimaging profile of DRE in a tertiary care center in South India probably reflects the spectrum expected in a developing country setup. The major findings are; it is more common in younger ages of less than 30 years, presents mainly with GTCS or CPS, mesial temporal sclerosis is the commonest underlying pathology which is bilateral in significant numbers, temporal lobe lesions predominate (49.3% of all DRE), cortical malformation, low-grade tumors, and vascular lesions are other important causes.

Declaration of Patient Consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

References

A prospective, multicenter, clinical Study to evaluate the Safety, Pharmacokinetics, and Efficacy of Bleed Outcomes, with HemoRel-A® in severe Hemophilia A Patients

Mayur Mewada1, Subhaprakash Sanyal2, Savita Rangarajan3,4, Prasad Apsangikar5*, Ajay Kumar Yadav6, Manoj Naik7, Santosh Nair8

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ABSTRACT

Purpose: To evaluate efficacy for an on-demand treatment of acute bleeding events, pharmacokinetics, safety, and tolerability of HemoRel-A® in severe hemophilia A.

Methods: A total of 44 male subjects with severe hemophilia A with an annualized bleed rate of 12 while on-demand treatment with factor VIII (FVIII) were enrolled in the study and received HemoRel-A® for bleed treatment. The efficacy of HemoRel-A® was evaluated based on a four-point scale (excellent, good, moderate, or none). Six-point pharmacokinetic (PK) assessment was performed following a single dose of 50 IU/kg in 12 subjects after a 7-day wash-out period. Safety evaluations were performed at each visit and inhibitor testing was performed in all patients at screening and end of study.

Results: Forty-four male subjects received at least a single dose of the study medication and were included in the intent-to-treat (ITT) analysis and safety outcome. In 23 (7.52%) out of the 306 bleeding events, HemoRel-A® efficacy was rated as excellent, in 272 (88.89 %) bleeds it was rated as good, and in 11 (3.68%) bleeding events it was rated as moderate. No failure of efficacy was noted in any of the bleeding events. Thus overall out of 306 bleeding events, 295 (96.41%) showed excellent or good efficacy. Pharmacokinetic assessment based on plasma FVIII activity measured by the chromogenic assay in 12 patients showed comparative results similar to FVIII preparations. A total of 12 adverse events (AEs) were reported in this study. There was no inhibitor development in this previously treated patients (PTP) cohort.

Conclusion: HemoRel-A® was established to be efficacious and safe in the treatment of acute bleeding events in subjects with severe hemophilia A.

Trial registration number: CTRI/2018/05/013790.
Registration date: 9th May 2018.

INTRODUCTION

Hemophilia A is a congenital, X-linked bleeding disorder with a prevalence of 1 in 5,000 male live births. If not treated adequately, frequent bleeding into joints leads to crippling arthropathy and impaired quality of life. Treatment with exogenous FVIII, using either plasma-derived or recombinant FVIII concentrates, restores normal hemostasis, and improves health and lifestyle of hemophilia patients.1 Prophylaxis is widely recommended for the treatment of severe hemophilia A.1 Secondary prophylaxis encompasses prophylactic treatment of children, adolescents, and adults with established progressive arthropathy.1 Although earlier start of prophylaxis results in better joint status, secondary prophylaxis can reduce the number of bleeds and reduce the risk of serious bleeds, delay joint damage, improve functional capacity and quality of life, and reduce pain.1 The most important and often life-threatening side-effect of hemophilia treatment currently is high risk of developing neutralizing antibodies. The risk appears to be even more serious when using recombinant FVIII products, as revealed by recent clinical studies highlighting an immunogenicity risk that was twice as high with some recombinant FVIII products than with some plasma-derived products.2 The recently published Survey of Inhibitors in Plasma-Product Exposed Toddlers (SIPPET) study concluded that the risk of inhibitors was higher with recombinant products as compared to von Willebrand factor (VWF) containing FVIII.3 As a large number of patients were recruited from the Indian subcontinent, the results are even more relevant to the Indian context.1 Experience with country like Slovakia in the treatment of previously untreated patients with severe hemophilia A showed 14% inhibitor formation after plasma-derived FVIII and 67% after recombinant FVIII products.4 Bioengineered FVIII variants, including current extended half-life (EHL) products are still regulated to a large extent by interaction with VWF. Therefore, half-life of VWF is the limiting factor to half-life extension of FVIII with techniques available today. All approaches described above achieve only moderate increase of half-life.5 The World Federation of Hemophilia does not express a preference for recombinant over plasma-derived concentrates.5 Development of neutralizing antibodies against replacement agents administered to prevent or treat various clinical conditions is a longstanding and growing problem faced by patients and medical providers.1

The present study was undertaken as a postmarketing evaluation of an indigenous plasma-derived FVIII for establishing safety, efficacy, bleeding events, and pharmacokinetics with HemoRel-A® in patients with severe hemophilia A on episodic treatment regimen.

METHODS

Study Design and Patients

The study was done as a prospective, multicenter, clinical study to evaluate the efficacy, safety, and PK of HemoRel-A® in severe hemophilia A patients. The study was conducted in compliance with the ethical principles that originated in the Declaration of Helsinki and ICH-GCP protocol, DCGI, and

1 Assistant Professor, Department of Medicine, KJ Somaiya Medical College, Hospital and Research Centre; 2Consultant Hematologist and Hemato-Oncologist, Fortis Hospitals Limited, Mumbai, Maharashtra, India; 3Faculty of Medicine, University of Southampton, United Kingdom; 4KJ Somaiya Super Speciality Hospital, Clinical Trial Unit, Mumbai; 5Head, Department of Medical Affairs and Pharmacovigilance; 6Head, Department of Clinical Research; 7Head Pharmacovigilance; 8Divisional Medical Head, Reliance Life Sciences Pvt. Ltd., Navi Mumbai, Maharashtra, India; *Corresponding Author

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Schedule Y and/or New Drugs and Clinical Trials Rules, 2019. The study was initiated at the sites only after obtaining approval from the EC in writing for the study protocol and other study documents. Similarly, all amendments, except those involving administrative changes, were submitted to the respective EC for approval prior to implementing the changes.

Immunocompetent (CD4 lymphocytes > 200/μL) male subjects aged between 18 and 65 years (both inclusive) with severe hemophilia A (documented FVIII levels < 1%) with history of >12 bleeding events in past 12 months, who were receiving on-demand treatment were included. Number of exposure days (ED) before inclusion was >50 ED. Subjects with history of inhibitors to FVIII, having inherited or acquired bleeding disorder or any major illness were excluded.

**Study Treatment**

Patients were treated for acute bleeds as per predefined criteria based on site of bleeding, body weight, and the clinical status of the patient. Doses and dose intervals were adapted as per site of hemorrhage. Patients did not receive any FVIII product for at least 7 days prior to the bleeding episode. Factor VIII activity in plasma was expressed either as a percentage (relative to normal human plasma) or in IU (relative to an international standard for FVIII in plasma). The study duration for each subject varied depending on the occurrence of bleeding events.

**Outcome Measures**

Primary objective of the study was to evaluate efficacy of HemoRel-A® for an on-demand treatment of acute bleeding events and secondary objective(s) was to evaluate PK, safety, and tolerability of HemoRel-A®. Response of acute bleeding events to treatment based on a four-point scale (excellent, good, moderate, or none) was kept as the primary end-point (Table 1). The details of bleeding events were captured based on type and location of bleeds. Doses and dose intervals were adapted as per site of hemorrhage. The details of bleeding events and consumption of FVIII were documented. Subjects were monitored for bleeding events (muscle or joint bleeds) during the study in order to have evaluable data of at least 300 bleeds. Subjects were treated for acute bleeds (bleeds <24 hours old) as per predefined criteria based on site of bleeding, body weight, and the clinical status of the patient.

Two bleeding events at the same anatomical site were considered as separate events if they occurred at least 2 weeks apart. Bleeding at different anatomical sites was considered as separate bleeding events. Therapeutic response to traumatic and spontaneous bleeding events was evaluated in this study.

The secondary end-points included evaluation of safety with physical examination, vital signs, AEs, abnormal laboratory parameters, and immunogenicity (baseline and end of study). Pharmacokinetic assessments by chromogenic assay were done for the FVIII concentrate. Pharmacokinetic assessment was performed based on plasma FVIII activity measured by the chromogenic assay in 12 out of 44 patients participating in the study after a 7-day wash period. Blood samples were taken at preinfusion (within 15 minutes prior to infusion), and at 10 minutes, 30 minutes, 1, 3, 6, 9, 24, 28, 32 and 48 hours postinfusion. The PK parameters included incremental recovery, in vivo half-life, area under the curve (AUC), and clearance. Incremental recovery was determined as the peak level recorded in the first hour after infusion and reported as [IU/mL]/[IU/kg]. Safety evaluations were performed at each visit to the study center with evaluation of physical examination, vital signs, AEs, and abnormal laboratory parameters. Inhibitor testing was performed in all patients at screening and end of study.

**Statistical Analyses**

Objective of the study was to evaluate at least 300 bleeds. Statistical analysis of HemoRel A® was performed on the PK parameters by using Pharsight Phoenix WinNonLin® version 8.0 or higher. Response of acute bleeding events to treatment was based on a four-point scale (excellent, good, moderate, or none) for evaluation. Doses and dose intervals were adapted as per site of hemorrhage. The details of bleeding events and consumption of FVIII were documented. The incidence of AEs occurring during the study will be summarized by preferred term and body system for each treatment group.

**RESULTS**

**Subject Disposition**

A total of 44 subjects were enrolled in this study. All 44 subjects received at least single dose of the study medication, hence 44 subjects were included in the ITT and safety modified ITT (mITT) population. Out of 44 subjects, one subject participated only in PK assessment and did not contribute to the efficacy assessment. The remaining 43 subjects were included in the per-protocol population for the analysis. All 12 subjects were considered for the PK assessment. Four subjects (9.00%) had early termination due to noncompliance and four subjects were lost to follow-up. All the 44 subjects included in ITT were male subjects. The mean age of these subjects was 28.27 (± 8.23) years, mean weight

<table>
<thead>
<tr>
<th>Table 1: Assessment of response of acute joint/muscle bleeding episodes to treatment category&lt;sup&gt;9&lt;/sup&gt;</th>
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</thead>
<tbody>
<tr>
<td>Category</td>
</tr>
<tr>
<td>----------</td>
</tr>
<tr>
<td>Excellent</td>
</tr>
<tr>
<td>Good</td>
</tr>
<tr>
<td>Moderate</td>
</tr>
<tr>
<td>None</td>
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</table>

<table>
<thead>
<tr>
<th>Table 2: Subject disposition</th>
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<tbody>
<tr>
<td>Variable</td>
</tr>
<tr>
<td>Safety population</td>
</tr>
<tr>
<td>ITT population</td>
</tr>
<tr>
<td>Per-protocol population</td>
</tr>
<tr>
<td>Study completed</td>
</tr>
<tr>
<td>Early termination</td>
</tr>
<tr>
<td>Reason for discontinuation</td>
</tr>
<tr>
<td>The subject was noncompliant with protocol specifications</td>
</tr>
<tr>
<td>The subject was erroneously included in the study</td>
</tr>
<tr>
<td>AEs</td>
</tr>
<tr>
<td>The investigator feels it is in the subject’s best interest to be withdrawn</td>
</tr>
<tr>
<td>The study is terminated by the sponsor</td>
</tr>
<tr>
<td>Lost to follow-up</td>
</tr>
<tr>
<td>The subject withdrew consent</td>
</tr>
<tr>
<td>Subject death</td>
</tr>
<tr>
<td>Other</td>
</tr>
</tbody>
</table>
was 65.01 (± 15.95) kg, while mean body mass index was 23.71 (± 5.79). The details of the patient disposition are shown in Table 2.

**Safety and Immunogenicity Analysis**

In this study, all 44 subjects received at least one dose of the study medication as per study protocol. Hence all 44 subjects were considered for the safety analysis. A total of 323 infusions of HemoRel-A® were administered to 44 subjects. The mean total dose received by each subject per infusion was 2036.38 IU, corresponding to dose of 31.94 IU/kg for each infusion. Adverse events were coded using Medical Dictionary for Regulatory Activities (MedDRA), Version 21.0.

Adverse events were assessed for any impact on safety or efficacy of the study drug. All the TEAEs (12) were mild in severity. All TEAEs were resolved without any sequel.

**Immunogenicity assessment** was performed using Nijmegen–Bethesda modification method. Blood samples were collected for measurement of inhibitor at screening and end of study. The samples with ≥0.4 Nijmegen–Bethesda units antigen level after processing, were considered to be positive for inhibitor. A total of 33 samples were analyzed at the end of study for the development of inhibitor. Only one of these samples was found to be positive for the inhibitor at the end of study. The subject with positive inhibitor result was further assessed for any impact on safety or efficacy of the drug. The subject consistently responded to the study medication as definite, probable, or possible were termed as “related.” Adverse events, which were not related, or unlikely related to the study medication were termed as “unrelated.” Adverse events for which the causality was not known or could not be assessed were termed as “unknown.” In this study, a total of 12 AEs were reported. There were four (9.09%) subjects who had atleast one AE. There were two (4.55%) subjects with at least one AE related to study medication. No serious AEs were reported in this study. No deaths were reported in this study. No subject was discontinued due to AE. Table 3 shows the summary of AEs observed in the study population.

**Table 3: Summary of efficacy response to bleed events**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Number of episodes</th>
<th>Excellent</th>
<th>Good</th>
<th>Moderate</th>
<th>None</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>306</td>
<td>23 (7.52%)</td>
<td>272 (88.89%)</td>
<td>11 (3.59%)</td>
<td>0 (0.00%)</td>
</tr>
<tr>
<td>Muscle/joint bleed</td>
<td>299</td>
<td>23 (7.69%)</td>
<td>265 (88.63%)</td>
<td>11 (3.68%)</td>
<td>0 (0.00%)</td>
</tr>
<tr>
<td>Mucosal bleed</td>
<td>6</td>
<td>0 (0.00%)</td>
<td>6 (100.00%)</td>
<td>0 (0.00%)</td>
<td>0 (0.00%)</td>
</tr>
<tr>
<td>Traumatic</td>
<td>1</td>
<td>0 (0.00%)</td>
<td>1 (100.00%)</td>
<td>0 (0.00%)</td>
<td>0 (0.00%)</td>
</tr>
</tbody>
</table>

**Fig. 1:** Mean linear graph for FVIII concentration against time

**Mean linear graph for FVIII concentration against time**

<table>
<thead>
<tr>
<th>Variable</th>
<th>HemoRel-A® (N = 44)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subjects with AEs</td>
<td>At least one AE</td>
</tr>
<tr>
<td></td>
<td>At least one TEAE</td>
</tr>
<tr>
<td></td>
<td>At least one TEAE related to study drug</td>
</tr>
<tr>
<td></td>
<td>At least one TE serious AE</td>
</tr>
<tr>
<td></td>
<td>Death</td>
</tr>
<tr>
<td>Subjects discontinued due to TEAE</td>
<td>0 (0.00%)</td>
</tr>
</tbody>
</table>
well to the treatment throughout the study and did not report any AE. There were no observations related to any loss of efficacy over period of time. There were no reports of any major immunologically mediated reactions to the drug administration. Thus, HemoRel-A® administration did not raise any concerns related to its immunogenicity during this study.

**Discussion**

Patients with severe hemophilia A (FVIII coagulant activity < 0.01 IU/mL) suffer from repeated and spontaneous bleeding episodes mainly within muscles and joints, resulting in disabling musculoskeletal damage and chronic arthropathy. Prophylaxis with FVIII concentrate is a widely accepted and safe alternative for the bleed treatment for severe hemophilia A patients in order to prevent spontaneous bleeding and subsequent joint damage. However prophylaxis is not widely used in India due to cost constraints. Most patients are on episodic therapy for bleeds. This study evaluated the outcome of bleed treatment using HemoRel-A® based on the response of acute bleeding events to treatment on a four-point scale (excellent, good, moderate, or none). Overall out of 306 bleeding events, 295 (96.41%) showed excellent or good efficacy. The efficacy response remained consistent over multiple bleeding events experienced by the subjects. Similar efficacy responses were noted in the literature, Mahlangu et al. and Konkle et al. In the PK assessment, the $t_{1/2}$ (half-life) was 15.603 hours with a maximum range of 31.298, which can be said to be comparable to modern EHL products which were shown to have range of half-life between 14.3 and 19 hours in one of the comparative literature. It is plausible that given the similarity in PK data with EHL products the efficacy of this product for prophylaxis use maybe similar to EHL products but this needs to be tested in a separate clinical trial setting. All the AEs were mild and resolved completely without any sequelae. No Factor VIII inhibitors were noted in these previously treated patients.

Based upon above $t_{1/2}$ efficacy and safety results, it can be concluded that HemoRel-A®, the purified FVIII preparation marketed by Reliance Life Sciences Pvt. Ltd. is an efficacious and safe alternative for the bleed treatment for Hemophilia-A and is comparable to modern FVIII preparations. In comparison with literature, the half-life in PK analysis and majority of subjects showing excellent or good efficacy in bleeding events were seen as well matching with the data of EHL products.

**Orcid**

Savita Rangarajan [https://orcid.org/0000-0001-7367-133X](https://orcid.org/0000-0001-7367-133X)

Prasad Apsangikar [https://orcid.org/0000-0001-7111-5380](https://orcid.org/0000-0001-7111-5380)

**References**

Study of the Efficacy of Uptitrating Teneligliptin Dose from Standard Dose (20 mg) to High Dose (40 mg) in Patients with Type II Diabetes Mellitus

Vijay Panikar 1, Shashank Joshi 2, Mangesh Tiwaskar 3, Amit Bhondve 4, Nikhil Nasikkar 5, Sanhita Walawalkar 6, Ishita Sachdev 7, Krish Panikar 8, Khushbu Modhi 9, Pallavi Kulkarni 10, Rahul Medidar 11, Harshpreet Tuteja 12, Sana Mansoori 13

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ABSTRACT

Aim: To study the efficacy of uptitrating the dose of Teneligliptin from 20 to 40 mg in patients with type II diabetes mellitus.

Method: A retrospective, comparative analysis was undertaken in 853 type II diabetes mellitus patients (499 males and 354 females) who had follow-up records for more than 6 months. These patients were uncontrolled after use of at least three oral antidiabetic drugs (OADs) and Teneligliptin 20 mg was added as the fourth drug. Patients who remained uncontrolled with the addition of 20 mg of Teneligliptin at the end of 3 months were switched to receive 40 mg of Teneligliptin daily. Results were analyzed at 3 and 6 months to ascertain efficacy of high-dose (40 mg) Teneligliptin. All other OADs remained the same in both groups. In all patients, the fasting blood glucose, postprandial blood glucose, and hemoglobin A1c (HbA1c) were evaluated and compared.

Result: A total of 853 patients whose dose of Teneligliptin was increased from 20 to 40 mg were included in the study. At the end of 3 months after using Teneligliptin 40 mg, mean reduction in HbA1c was 0.5% (p-value 0.154). Similarly, mean reduction in fasting blood sugar (FBS) and postprandial blood sugar (PPBS) was 6.5 and 3.6 mg/dL, respectively (p-value 0.234 and 0.143). At the end of 6 months after using Teneligliptin 40 mg HbA1c showed no change but mean FBS and PPBS showed a modest reduction of 14.6 and 14 mg/dL, respectively (p-value < 0.001).

Conclusion: The results of our study show that there was no statistically significant improvement in glycemic parameters when dose of Teneligliptin was increased from 20 to 40 mg at 3 months. But at 6 months, the FBS and PPBS showed a modest reduction of 14.6 and 14 mg/dL, respectively (p-value < 0.001) but the HbA1c showed no change.

Introduction

Dipeptidyl peptidase-4 (DPP-4) inhibitors have recently emerged as a new class of antidiabetic drugs that show favorable results in improving glycemic control with minimal risk of hypoglycemia and weight gain. Teneligliptin has been reported to be a potent, long-lasting DPP-4 inhibitor and is licensed in Japan for administration at standard (20 mg/day) and high (40 mg/day) doses for glycemic control.

Teneligliptin is currently used in cases showing insufficient improvement in glycemic control even after diet control and exercise or a combination of diet control, exercise, and metformin, sulfonylurea- or thiazolidine-class drugs. In adults, Teneligliptin is orally administered at a dosage of 20 mg once daily, which can be increased up to 40 mg per day. Because the metabolites of this drug are eliminated via renal and hepatic excretion, no dose adjustment is necessary in patients with renal impairment. The safety profile of Teneligliptin is similar to those of other available DPP-4 inhibitors.

However, little is known about the efficacy of high-dose Teneligliptin (40 mg) compared to standard dose of Teneligliptin (20 mg).

Method

A retrospective, comparative analysis was undertaken in 853 type II diabetes mellitus patients (499 males and 354 females) who had follow-up records for more than 6 months. These patients were uncontrolled after use of at least three OADs and Teneligliptin 20 mg was added as the fourth drug. Patients who still remained uncontrolled with the addition of 20 mg of Teneligliptin at the end of 3 months and were switched to receive 40 mg of Teneligliptin daily were included in this study. Results were analyzed at 3 and 6 months to ascertain efficacy of high-dose (40 mg) Teneligliptin. All other OADs remained the same in both groups. In all patients, the fasting blood glucose, postprandial blood glucose, and hemoglobin A1c were evaluated and compared.

Exclusion Criterion

- Patients who have been previously on DPP-4i.
- Patients who were on insulin or previously were on insulin.

Statistical Analysis

Statistical testing was conducted with SPSS Statistics 23.0 (SPSS Inc., Chicago, Illinois, USA).
Efficacy of Upptitrating Teneligliptin Dose from Standard to High Dose

USA). Results for quantitative variables like age, height, weight, body mass index (BMI), and waist circumference are presented with mean ± standard deviation (SD). Parameters like fasting, postprandial blood sugars, and HbA1c were found to be normally distributed on applying Shapiro–Wilk test. Hence, comparison of parameters like fasting, postprandial blood sugars, and HbA1c between baseline (before changing Teneligliptin from 20 to 40 mg) and 3 and 6 months after changing Teneligliptin from 20 to 40 mg is done by using paired t-test. The p < 0.05 was considered significant.

RESULTS

- The mean age of females was 53.1 ± 10.2 and mean age of males was 52.6 ± 11.2 (Tables 1 and 2).
- The mean weight of the females was 68.33 ± 13.1 and mean weight of males was 75.19 ± 13.9.
- The mean height of females was 1.55 ± 0.06 and mean height of males was 1.67 ± 0.07.
- The mean BMI of females was 28.4 ± 4.9 and mean BMI of males was 26.7 ± 4.4.
- Mean fasting blood glucose when Teneligliptin 20 mg was increased to 40 mg was 156.5 ± 46.8 mg/dL.

Table 1: Basic demographic data of the study participants

<table>
<thead>
<tr>
<th>Gender</th>
<th>Female = 354</th>
<th>Male = 499</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>53.1 ± 10.2</td>
<td>52.6 ± 11.2</td>
</tr>
<tr>
<td>Height (m)</td>
<td>1.55 ± 0.06</td>
<td>1.67 ± 0.07</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>68.33 ± 13.1</td>
<td>75.19 ± 13.9</td>
</tr>
<tr>
<td>Waist (cm)</td>
<td>96.4 ± 10.4</td>
<td>96.65 ± 10.9</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>28.4 ± 4.9</td>
<td>26.7 ± 4.4</td>
</tr>
</tbody>
</table>

- Mean postprandial blood glucose when Teneligliptin 20 mg was increased to 40 mg was 201.5 ± 65.5 mg/dL.
- Mean HbA1c when Teneligliptin 20 mg was increased to 40 mg was 8.1 ± 1.5%.

Three months after starting Teneligliptin 40 mg mean FBS level was 150.1 ± 57.6 mg/dL with a mean difference of –6.5 mg/dL, mean PPBS level was 197.9 ± 70.1 mg/dL with a mean difference of –3.6 mg/dL and mean HbA1c level was 8.0 ± 1.4% with a mean difference level of –0.1. These differences were not statistically significant.

Six months after starting Teneligliptin 40 mg mean FBS level was 141.9 ± 47.5 mg/dL with a mean difference of –14.0 mg/dL, mean PPBS level was 187.5 ± 62.6 mg/dL with a mean difference of –14.6 mg/dL, and mean HbA1c level was 8.0 ± 1.6% (p-value 0.183) (Figures 1 and 2).

DISCUSSION

Teneligliptin has been reported to be a potent, long-lasting DPP-4 inhibitor and is licensed in Japan for administration at standard (20 mg/day) and high (40 mg/day) doses for glycemic control. In this study, we used fasting blood glucose levels, postprandial blood glucose, and HbA1c to assess whether high-dose Teneligliptin is superior to the standard dose in terms of glucose control and HbA1c reduction. The upper limit of HbA1c was not decided as poor glycemic control was only the criteria to be included here. As this study is carried out only to understand the efficacy of the uptitration of the dose of Teneligliptin, safety and tolerability of the drug are not in the purview of the study.

A study using Teneligliptin 10, 20, or 40 mg doses vs placebo showed that there was no statistically significant difference in the effects on HbA1c levels. In this randomized, double-blind, placebo-controlled, parallel-group study, patients (n = 324) were randomized to receive Teneligliptin 10, 20, or 40 mg, or placebo, once daily before breakfast for 12 weeks. The primary endpoint was the change in hemoglobin HbA1c from baseline to week 12. There were no significant differences in HbA1c among the three doses of Teneligliptin. The incidence of adverse events and adverse drug reactions was similar in each group. The incidence of hypoglycemia was not significantly different among the four groups.

The efficacy and safety when Teneligliptin dose is increased to 40 mg in patients with insufficient response to 20 mg are also available from one of the integrated analyses of the Japanese long-term treatment study as a review file by Japan Pharmaceuticals and Medical Devices Agency. Of 275 patients (275 of 290 patients) whose HbA1c data were available at 12 weeks after the dose increase, 30.9% (85 of 275 patients) showed a ≥0.3% decrease in HbA1c when switched to Teneligliptin 40 mg. Overall, HbA1c level decreased to <7.0% at 12 weeks after increasing the dose, in only 15.6% of patients.

Teneligliptin, a DPP-4 inhibitor, has been in use as an add-on, in patients with type II diabetes mellitus, with uncontrolled sugars with metformin, pioglitazone, and sulfonfonylurea. Few studies that have been undertaken to evaluate the efficacy of Teneligliptin with its standard dose (20 mg) and high dose (40 mg) have shown no significant increase in efficacy by uptitrating the dose to 40 mg. Our study further corroborates this finding as we found no statistical difference in improvement of HbA1c levels by increasing the dose of Teneligliptin from 20 to 40 mg.

Another study by Abe et al. used continuous glucose monitoring (CGM) to study the efficacy of high-dose Teneligliptin for the treatment of diabetic patients. Mean amplitude of glycemic excursions (MAGE), and mean, minimum, maximum, and SD of glucose concentrations were measured by CGM in 10 hospitalized individuals with type II diabetes mellitus. Compared with effects of standard-dose Teneligliptin, MAGE, SD, and maximum glucose concentrations were significantly reduced by high-dose Teneligliptin (p < 0.01) but there was no significant difference in mean glucose concentrations (p = 0.0314).
Further evaluation studies are needed for assessing long-term effects of Teneligliptin. It should be noted that the limitations of our study include the small number of cases and the short duration of the period of investigation. Thus, further randomized control studies including larger numbers of cases, with longer-term monitoring are required to see if there is a role for use of high-dose Teneligliptin (40 mg) in patients with type II diabetes.

**References**


**Conclusion**

The results of our study show that after 6 months, the difference in mean HbA1c, with the standard (20 mg) and high doses 40 mg is statistically not significant. Upptitrating the dose of Teneligliptin 20–40 mg may not be beneficial. This finding is similar to some studies which showed no significant increase in efficacy by upptitrating the dose to 40 mg.
Video Call-based Fitness Assessment shows Poor Fitness in People with Type II Diabetes: Findings from Diabefly Digital Therapeutics Program

Madhura Bhagat1, Anuradha Mandlekar2, Ritika Verma3, Tejal Lathia4, Snehal Tanna5, Amit Saraf6, Saifuddin Bandukwala7, Sonali Patange8, Piya Ballani Thakkar9, Arbinder Singh10

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Abstract

Objective: Exercise and physical activity are integral aspects for the effective management of diabetes. Unsupervised home exercise although very accessible is limited by poor adherence, risk of injury, and a higher dropout rate of participants. A fitness assessment by a qualified physiotherapist can help in understanding the baseline fitness of individuals and thus generating appropriate exercise prescriptions. The current study assesses the feasibility of video call-based fitness assessment for people with diabetes. The study also assesses the effect of current physical activity status and pain on performance in physical fitness tests.

Methods: One hundred participants with type II diabetes (T2D) underwent 6-minute walk test (6MWT), 1-minute push-up test, wall sit test, 1-minute sit-up test, and V-sit and reach test for measuring different components of physical fitness such as aerobic capacity, upper body strength, lower body strength, core strength, and flexibility, respectively. The performance in physical fitness of participants was analyzed after the video consult along with pain complaints and current exercise status.

Results: All the participants underwent the physical fitness test safely based on video call. Out of all the participants, a good range score was achieved by 52% in 6MWT, 17% in push-up test, 1% in wall sit test, 6% in sit-up test, and 9% in V-sit and reach test. Current physical activity status (aerobic exercise for minimum 20 minutes) did not show any association with performance in fitness tests (p = 0.89 for push-up test, p = 0.50 for wall sit test, p = 0.23 for sit-up test, and p = 0.10 for V-sit and reach test). Presence of upper body and lower body pain affected the performance in push-up test and wall sit test with 71.4% and 95.6% of participants achieving scores in poor to below-average range (p-value < 0.001).

Conclusion: The study showed the safety and feasibility of conducting video call-based assessment of physical fitness by physiotherapists. The study also highlighted the poor glycemic control, high cardiovascular risk, and poor level of physical fitness in people with diabetes in India. Insights based on physical fitness, current physical activity status, and pain can help in developing personalized exercise plans for people with diabetes.

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Introduction

Diabetes mellitus is a metabolic disease characterized by hyperglycemia resulting from defects in insulin secretion, insulin action, or both.1,2 Exercise has been known to increase insulin sensitivity and glucose tolerance, making it a safe, effective, and noninvasive treatment modality for T2D.3-5 Lifestyle modification interventions such as exercise have long been promoted as important in the management of T2D.3,4 Studies show that people with diabetes showed an accelerated decline in muscle strength and functional status. Exercise has also been shown to improve cardiovascular health, assist in weight management and also to maintain better glycemic control in people with diabetes.6

There is a huge burden of diabetes in India with 77 million people with diabetes in the year 2020.6 There are many barriers to delivering healthcare to such a large population, such as resource and time constraints, traveling hassles, cost-effectiveness, and noncompliance of patients. Digital therapeutics (DTx) platforms provide highly accessible and cost-effective evidence-based treatments which can help in better management of chronic conditions like diabetes.7 The lifestyle management of diabetes involves adequate diet, appropriate physical activity, and proper psychosocial care along with diabetes self-management education and support. The current work assesses the feasibility of video call-based fitness assessment for people with diabetes as a part of a mobile-based DTx program. The physiotherapy guidance along with diabetes education through the platform was designed to provide complete and holistic diabetes care.

Home-based exercise has been shown to improve glycemic control and quality of life in people with T2D.8 However, unsupervised home-based exercise is limited by low adherence and higher drop-out rates.9 Thus supervised exercise prescription after preliminary assessment of physical status might help in improving adherence as well as ensuring lower risk of injury. Pain influences an individual’s readiness to perform exercises.10 The analysis of a person’s current physical activity becomes necessary for prescribing a personalized exercise plan. The current study is aimed at the analysis of feasibility of online video call-based physical fitness assessment for people with T2D. The study analyzed the current status of exercise and musculoskeletal pain along with physical fitness. As per our knowledge, this is the first study in India aimed at the analysis of feasibility of video call-based physiotherapy consult in people with T2D.

1Physiotherapist; 2Head, Department of Physiotherapy, Fitterfly HealthTech Pvt Ltd; 3Lead, Department of Scientific Writing and Research, Fitterfly HealthTech Pvt Ltd; 4Consultant Endocrinologist and Diabetologist, Department of Diabetology, Apollo Hospitals, Navi Mumbai; 5Consultant Endocrinologist and Diabetologist, Department of Diabetology, Jupiter Hospital, Thane; 6Consultant, Department of Internal Medicine, Advance Diabetes Care Clinic; 7Consultant Diabetologist, Department of Diabetology, Sushrut Clinic; 8Consultant Endocrinologist and Diabetologist, Department of Diabetology, Bombay Hospital and Medical Research Centre, Mumbai; 9Chief Executive Officer, Office of CEO, Fitterfly HealthTech Pvt Ltd, Navi Mumbai, Maharashtra, India; *Corresponding Author

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**Methods**

**Study Design**

The study involved the preliminary assessment of physical activity status, physical fitness, and pain. The inclusion and exclusion criteria were.

**Inclusion Criteria**

- Clinically diagnosed diabetes mellitus type II,
- Age >20 years.

**Exclusion Criteria**

- Uncontrolled hypertension,
- Recent surgical history—cardiovascular disease, joint replacements, and abdominal surgeries,
- Vestibular and balance disorder,
- Neurological disorders,
- Acute musculoskeletal pain complaints interfering with assessment and intervention,
- Other contraindications if any as per the referring physician.

**Procedure of Assessment**

Participants were referred by medical practitioners and were enrolled in 90-day Diabefly DTx program (Fitterfly HealthTech©, India). All participants were provided with access to mobile application-based meal and physical activity tracking, educational content, nutritional assessment, and access to nutritionists, physiotherapists, psychologists, and remote health coaches. Individuals meeting the inclusion criteria underwent preparticipation screening using the Physical Activity Readiness Questionnaire to rule out participants with pain complaints that could potentially interfere with fitness assessment and exercise prescription.11,12 Participants underwent a physical fitness assessment on day 3 after enrolment into the program. Physical fitness assessment was done by qualified physiotherapists over a Google Meet call.

**Assessment Procedure Details**

**6-minute Walk Test**

The 6MWT was used as a measure of functional exercise performance in the participants. This test was done by measuring the distance covered by the participant in a duration of 6-minute normal-paced walk.11-13 Participants were instructed to walk continuously for 6 minutes at their comfortable walking speed and the pretest heart rate and step count were recorded. At the end of 6 minutes, heart rate and steps were recorded using a pulse oximeter and a step counter, respectively for all the participants.

The actual steps covered were recorded (pretest step count, if any, was subtracted from the post-test step count) and the distance covered by the participant was calculated in meters. The performance of the participants in this test was classified in the following score categories, based on the distance covered in meters: less than 300 m was rated as “poor”, 301–400 m was rated as “average”, 401–500 m was rated as “good”, and distance covered more than 500 m was rated as “excellent”.

**1-minute Push-up Test**

The 1-minute push-up test was used for the analysis of upper body strength. The aim of this test was to assess the upper body strength by recording how many push-ups (full push-ups in males and modified push-ups in females) the participant can perform in 1 minute. Pretest instructions were given to the participant regarding the test. A test (trial) movement was done by the participant to check the movement form. If the test form was correct, participants were allowed to proceed with the actual test. The starting position was on all four’s position—arms straight, elbows locked, body straight, hands placed slightly wider than shoulder width apart with fingers pointing forward, and both knees and feet on the floor (for females) and only feet on the floor (for males). From the starting position, on the command “START” the participants would initiate push-ups by bending the elbows and lowering the body until the shoulders drop below the level of the elbows and then returned to the starting position.14,15 They were instructed to continue doing so till they heard the “STOP” command from the physiotherapist. The number of push-ups performed in 1 minute was recorded by the physiotherapist. A scoring reference chart was used to score and categorize the participants’ performance into the following categories, based on age and gender-based normative data: score of –1 for “very poor” performance, 0 for “average” performance, 1 for “good” performance, and 12 for “excellent” performance.16

**1-minute Sit-up Test**

The 1-minute sit-up test was used for the analysis of core strength. The aim of this test was to assess the core muscle strength by recording how many sit-ups the participant can perform in 1 minute. A test (trial) movement was done by the participant to check the movement form. If the test form was correct, participants would be allowed to proceed with the actual test. The participants were told to lie on the back with knees bent and feet firmly placed on the floor. The arms were placed on the thighs proximally. On the command of “START” the participant initiated the sit-up (crunch) by raising the upper body while sliding the hands up to the knees, and then lowering the upper body until the shoulder blades touch the ground. This formed one complete sit-up.15 The number of sit-ups covered in 1 minute was recorded by the physiotherapist. A scoring reference chart was used to score and categorize the participants’ performance into the following categories, based on age and gender-based normative data: score of –1 for “very poor” performance, 2 for “poor” performance, 4 for “below average” performance, 6 for “average” performance, 8 for “above average” performance, 10 for “good” performance, and 12 for “excellent” performance.16

**V-sit and Reach Test**

V-sit and reach test was used for the analysis of flexibility in the participants. The participant was instructed to sit in a long sitting position. A cello tape was stuck at the heel level of the participant. A scale (ruler) was placed on this tape with 5 inches (considered as 0 for measurement) falling on the cello tape. The participant stretched one hand forward, superimposed his other hand over the first one, raised the hands overhead, and bent forward trying to reach the scale. Participants then measured where the tip of the middle finger touched the scale and it was recorded in inches. Three attempts...
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were made and the best performance was considered. During the test, the number 5 inches on the cello tape was marked as 0 inches for the purpose of measurement. Performance with less than 5 inches denoted negative flexibility while performance with greater than 5 inches denoted positive flexibility. A scoring reference chart was used to score and categorize the participant’s performance into the following categories, based on age and gender-based normative data: score of -1 for “very poor” performance, 0 for “poor” performance, 1 for “fair”, 2 for “average”, 4 for “good”, 6 for “excellent”, and 8 for “super” performance.16

**Total Score**
The total score was calculated as the summation of all the scores of the physical fitness tests including the push-up test, wall sit test, sit-up test, and V-sit and reach test. The sum of scores in all the physical strength assessment test performances was compared to the standard scoring reference table to score the performance of participants.16 The scores of the participant could have a minimum performance score of -4 and a maximum performance score of 44. An assessment report of performance was then shared with the participants and their primary physicians.

**Data Analysis**
The primary objective of the study was to determine the feasibility of video-based assessment of physical fitness of participants with T2D while the secondary objectives were as following:

- Analysis of preintervention physical activity status of the participants (termed as exercisers vs nonexercisers) and study its possible influence on their physical fitness performance.
- Analysis of prevalence of musculoskeletal pain complaints, their relationship with hemoglobin A1c (HbA1c), and their possible influence on physical fitness performance.

The data collected were statistically analyzed using SPSS (version 21). Descriptive statistics were used for describing the characteristics of study participants. Chi-square test and Fisher's exact test were conducted to examine the relationship between different categorical variables. Figure 1 depicts the summary of the participant recruitment and various analysis and assessment performed during the entire study.

**Results**
After excluding 42 participants that did not meet the inclusion criteria, 100 participants were included in the analysis. The average age of the participants was 43.75 ± 11.31 years with male to female ratio of 61:39. 

Table 1 summarizes the descriptive statistics of the study. The average body mass index (BMI), weight, and HbA1c were reported as 28.30 ± 9.48 kg/m², 78.04 ± 16.22 kg, 8.22 ± 2.22%, respectively. Body mass index was classified into five ranges involving normal (18–22.9 kg/m²), overweight (23–27.4 kg/m²), class I obesity (27.5–32.4 kg/m²), class II obesity (32.5–37.4 kg/m²), and class III obesity (>37.5 kg/m²). Out of all the participants, 12% (12/100) of the participants had a normal BMI, 35% (35/100) participants belonged to the overweight category, and 53% (53/100) of the participants were in the obese category (36/100 had grade I obesity, 12/100 had grade II obesity while 5/100 had grade III obesity). This data reflected a high prevalence of obesity in the participants. Waist–hip ratio (WHR) above 0.85 for female and 0.90 for male was used as a criterion for abdominal obesity.17

It was found that only 11% (11/100) of participants had a normal WHR while 89% (89/100) had abdominal obesity with an average WHR of 0.97 ± 0.09 for all the participants. About 68% (68/100) of the participants had a HbA1c value ≥7% while 32% (32/100) had HbA1c <7%.

Figure 2 shows the graphical representation of performance of participants in various physical fitness tests. Figure 2A shows the performance of participants in 6MWT, the average distance traveled by participants was 406.68 ± 100.17 m. Only 12% (12/100) of participants covered >500 m and scored in “excellent” category while 15% (15/100) of participants were in the category of “poor” performance (distance covered less than 300 m). About 52% (52/100) of participants were placed in “good” category covering 401–500 m while 21% (21/100) of participants were placed in “average” category covering 301–400 m.

Figure 2B shows the score achieved by the participants in 1-minute push-up test. About 62% (62/100) of participants showed very poor or poor strength, 21% (21/100) showed average strength, 17% (17/100) showed good strength while none of the participants showed excellent upper body strength. Figure 2C shows the score achieved by the participants in the wall sit test, 77% (77/100) of all participants showed very poor strength, 21% (21/100) showed below-average strength, while average and good strength was observed for 1% (1/100) of participants for both groups, but none of the participants reported excellent lower body strength.

Figure 2D shows the scores for the core strength test. It was found that 46% (46/100) of participants showed very poor to poor core strength, 22% (22/100) showed below-average strength, 9% (9/100) showed average strength, 14% (14/100) showed above-average strength, 6% (6/100) showed good strength while only 3% (3/100) showed excellent core strength. Figure 2E denotes the flexibility of the participants using the V-sit and reach test. About 82% participants (82/100) had flexibility scores ranging from poor to average, with only 7% (7/100) participants showing very poor score and 2% (2/100) showing excellent flexibility score. Figure 2F denotes the total fitness score of the participants. It was observed that 93% (93/100) of participants had very poor to poor fitness scores while only 6% (6/100) of participants had average fitness scores. Only 1% (1/100) of participant showed superlative performance in the fitness score falling in the good score category.

Figure 1: Summary of the study

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Mean ± standard deviation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>43.75 ± 11.31</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>78.04 ± 16.22</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>28.30 ± 9.48</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>8.22 ± 2.22</td>
</tr>
<tr>
<td>WHR</td>
<td>0.97 ± 0.09</td>
</tr>
</tbody>
</table>
The participant's performance was categorized into two subcategories within exercisers and nonexercisers. These subcategories were, namely, “poor to below-average performance” (obtained by combining the poor, very poor, and below-average score categories of each test, with scores ranging from –1 to 4 in the respective tests) and “average to excellent performance” (obtained by combining the average, above average, good, and excellent categories of each test, with scores ranging from 6 to 12 in the respective tests). There was no significant association between the exercise status and performance in physical fitness tests in the participants (p = 0.89 for push-up test, p = 0.50 for wall sit test, p = 0.23 for sit-up test, and p = 0.10 for V-sit and reach test, respectively). In both
categories, a relatively smaller proportion of participants had "average to excellent" performance scores.

Figure 3B denotes the incidence of musculoskeletal pain complaints and region-wise pain distribution in the participants. It was found that 57% (57/100) of participants had no musculoskeletal pain complaints while 43% (43/100) had musculoskeletal pain complaints. Out of all the participants, 23% (23/100) had lower body pain (hip/knee/ankle and foot joint involvement), 13% (13/100) had spine pain (cervical/lumbar involvement) while 7% (7/100) had upper body pain complaints (shoulder/elbow/wrist hand joint involvement). Figure 3C denotes the presence of pain complaints in exercisers and nonexercisers. About 56.1% (32/57) of the exercisers reported no musculoskeletal pain complaints while 43.8% (25/57) reported musculoskeletal pain complaints. Among the nonexerciser category, 51.1% (22/43) participants had pain while 48.8% (21/43) reported absence of pain. No significant association between the musculoskeletal pain complaints and the physical activity status of participants was observed ($p = 0.47$).

Figure 3A shows the performance in strength tests by exercisers vs nonexercisers. It was observed that 71.4% (5/7) of the participants with upper body musculoskeletal pain showed very poor to poor score in the push-up test which was used as an indicator of upper body strength, while only 28.6% (2/7) showed average to excellent score. About 95.6% (22/23) of the participants with lower body musculoskeletal pain complaints showed very poor to poor score in the wall sit test which was used as an indicator of lower body strength, while only 4.3% (1/23) showed average to excellent score ($p < 0.001$).

Participants with spinal pain complaints took sit-up test as an indicator of core strength showing that 46.1% (6/13) of the participants showed very poor to poor score while 53.8% (7/13) showed average to excellent core strength. The impact of spine and lower body pain complaints on flexibility was also assessed by the V-sit and reach test. It was found that 36.1% (13/36) of participants having spine and lower body musculoskeletal pain showed very poor to poor performance ($p = 0.033$).

Figure 4A shows the variation in pain complaints with respect to HbA1c values. In participants with HbA1c of $<$7%, 50% (16/32) of participants complained of musculoskeletal pains and 50% (16/32) reported no pain complaints. In participants with HbA1c $\geq$7%, 39.7% (27/68) reported musculoskeletal pain complaints, while 60.3% (41/68) reported absence of any pain. No significant association was observed between the HbA1c and the presence of pain complaints ($p = 0.33$).

Figure 4B denotes the performance in strength test performance of the participants who had musculoskeletal pain complaints. It was observed that 71.4% (5/7) of the participants with upper body musculoskeletal pain showed very poor to poor score in the push-up test which was used as an indicator of upper body strength, while only 28.6% (2/7) showed average to excellent score. About 95.6% (22/23) of the participants with lower body musculoskeletal pain complaints showed very poor to poor score in the wall sit test which was used as an indicator of lower body strength, while only 4.3% (1/23) showed average to excellent score ($p < 0.001$).

Participants with spinal pain complaints took sit-up test as an indicator of core strength showing that 46.1% (6/13) of the participants showed very poor to poor score while 53.8% (7/13) showed average to excellent core strength. The impact of spine and lower body pain complaints on flexibility was also assessed by the V-sit and reach test. It was found that 36.1% (13/36) of participants having spine and lower body musculoskeletal pain showed very poor to poor performance while 63.9% (23/36) of participants showed average to excellent performance in flexibility ($p < 0.001$).

**Discussion**

The study showed the feasibility of performing physical fitness tests via video call in presence of trained physiotherapists as a part of Diabefly DTx program. The study showed data from five physical tests which included 6MWT, 1-minute push-up test, wall sit test, 1-minute
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About 88% (88/100) of participants were in the overweight and obese category while 89% (89/100) of them had abdominal obesity. Abdominal obesity is a predictor of risk of cardiovascular diseases. These results highlighted the presence of obesity and higher risk of cardiovascular disease in the participants. The American Diabetes Association recommends HbA1c value ≤7% as glycemic target for adults with diabetes. About 68% of the participants had HbA1c value ≥7% while only 32% had HbA1c below 7%. Thus, the study showed a poor level of glycemic control in the study population.

Video call-based tests were conducted successfully on all the participants for analysis of physical fitness. The analysis of the physical fitness of people with diabetes showed that very few participants achieved scores in a “good” range for tests including 1-minute push-up test (17%), wall sit test (1%), 1-minute sit-up test (6%), and V-sit and reach test (9%). The study showed a poor level of physical fitness and highlighted the need for improving the exercise regimen in the participants. The study also tried to analyze the effect of current exercise status on the performance in physical fitness tests. The exercisers in the study followed a minimum of 20 minutes of aerobic exercise (only walking), while nonexercisers did not perform any form of aerobic exercise. The study showed that no significant association was observed between the current status of exercise and the performance in the physical tests. This might be due to the fact that all the exercisers were initially performing only aerobic form of exercise and hence were accustomed to the walking. This was also supported by the fact that only 15% of total participants scored poor in the 6MWT while most of the participants could not perform well during the strength test. Thus, it becomes important to use different modes of exercise like resistance training for physical fitness. Similar results have also been reported earlier where resistance training led to better glycemic control in people with diabetes as compared to only aerobic exercise.

Musculoskeletal pain affects the physical activity in participants and as a result the study also evaluated the musculoskeletal pain complaints in people with T2D. About 23% (23/100) had lower body pain, 13% (13/100) had spine pain, and 7% (7/100) had upper body pain complaints. No significant association was observed between the presence of pain complaints and the current status of exercise in participants (p = 0.47). The participants were undergoing only aerobic form of exercise for a minimum of 20 minutes which did not get affected in the presence of pain.

The study also showed that presence of upper body and lower body pain affected the performance in push-up test and wall sit test as 71.4% and 95.6% of participants showed poor to below-average score in the tests, respectively. Sit-up test performance was not adversely affected by spinal pain, this might be due to the fact that test performance was recorded during the first 1 minute only. Performance in V-sit and reach test was also not negatively affected by the presence of lower body and spinal pain. This might be due to the nature of test where the scoring was done based on one-time performance only.

Physical fitness, pain, and current physical activity were successfully assessed in the study with an aim to develop a personalized exercise prescription for all the participants. The video call-based analysis of physical fitness helps in understanding the different components of fitness in each individual. The understanding of current level of exercise and physical fitness will help in prescribing a personalized mode of exercise regimen for each individual comprising both aerobic and resistance exercises. Higher improvement in strength and functional ability was reported in studies with supervised home-based resistance training. Online video call-based supervised exercise training can help in maintaining better adherence and can help provide cultural-appropriate personalized exercise training for people with T2D. Fear of injury is one of the common reasons limiting the adherence to exercise in people with T2D. Preliminary assessment of pain is required to have a full overview of the performance in physical fitness tests and for prescribing further exercise activities.

**CONCLUSION**

The study is the first of its kind to assess the feasibility of video call-based assessment of physical fitness among people with T2D in India. The study showed poor overall fitness levels as well in individual fitness tests like 6MWT, 1-minute push-up test, wall sit test, 1-minute sit-up test, and V-sit and reach test for measuring different components of physical fitness such as aerobic capacity, upper body strength, lower body strength, core strength, and flexibility, respectively. Thus, we conclude that physical assessment can be performed safely and effectively in people with T2D and can be the starting point for prescribing a personalized exercise plan. This plan should also take into consideration...
the pain and current exercise status of each individual. Future studies will further establish the effectiveness of these personalized exercise plans to ensure improved exercise capacity, physical fitness, and better glycemic control in people with diabetes.

**References**


Monkeypox: What do we know so far? A short narrative review of literature

Paulami Deshmukh1, Agam Vora2, Mangesh Tiwaskar3, Shashank Joshi4

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Abstract

Monkeypox was a zoonotic infection, first detected in parts of northern Africa in the 1970s. Monkeypoxvirus, the causative agent of monkeypox, is a species of genus Orthopoxvirus and is closely related to long-eradicated smallpox caused by variola virus. Outbreaks in the West (in USA, UK, and Ireland) along with periodic re-emergence of the disease in parts of Africa have generated concern among global health bodies due to the existing deficiency of guidelines for management of the disease. Genetic variations and altered mechanisms favoring better survival of the virus have made early identification of the disease during screening difficult, particularly in resource-limited settings like rural areas of Africa. Through evidences gathered from experimental studies conducted after these outbreaks, the virus is known to be transmitted from several animal reservoirs along with human-to-human contact of blood, body fluids, or aerosol. Early diagnosis through immunoassays and polymerase chain reaction (PCR) tests, although not very specific, allows early treatment and subsequently better patient survival and recovery. Presence of lymphadenopathy along with fever, sore throat, and a vesiculopustular rash is diagnostic. The virus affects the gastrointestinal, hematological, ocular, and respiratory systems, in like manner producing afflictions of the specific system. Treatment, through experimental data, has been preferred to be symptomatic, with the aim to prevent superinfections. Antivirals like cidofovir and tecovirimat have been studied upon used with success in certain patients for postexposure prophylaxis.

Introduction

Monkeypox virus (MPXV) is a zoonotic disease found sporadically in the tropical rainforest of central and western Africa1 with a considerable degree of threat to human life. It has been an emerging cause of frequent outbreaks in different parts of Africa in the past few weeks amidst the pre-existent COVID-19 pandemic. The geographic extent and status of the affected regions fail to bring the disease and the relevant news into global sight.2 There exist two genetic clades of MPXV, one is a Central African or the Congo basin clade found in the Democratic Republic of Congo, Gabon, Cameroon, Congo, and Central African Republic with a high level of infectiousness (up to seven generations) and a case fatality rate of up to 11%. The other is the relatively low infectious clade of Western Africa traced in Sierra Leone, Nigeria, Cameroon, Liberia, and Côte d ’Ivoire with a case fatality rate of up to 6%.3 Transmission in humans can occur enterally through improperly cooked animal meat and parenterally through blood and body fluids secretion, mainly from the respiratory tract or skin lesions. A few distinctive symptoms of human MPXV may greatly aid in its early detection and containment.4 However, secondary transmission from imported cases of nosocomial transmission to a health care worker has been documented in the United Kingdom of Great Britain and Northern Ireland in 2018.5 Animal contact has also been a potential source of this disease.5 A study conducted in the late 1900s, proved that wild squirrels (species: Funisciurus anerythrus and Heliosciurus rufobrachium) played a significant role in steady transmission of the virus.7 Epidemiological reports from the US outbreak of MPXV in 2003, proved pet prairie dogs housed with rodents imported from Ghana (Gynomys species) to be a potent animal contact, primarily responsible for the same.8 Additionally, in Africa, Gambian poached rats, dormice, and different species of monkeys have also been documented as the other possible animal contacts for MPXV transmission.9 Genetics and Pathogenesis The genus Orthopoxvirus includes a number of viruses such as MPXV virus, vaccinia virus, variola virus, and cowpox virus. The genome of these viruses is ~200 kb long with highly conserved central regions coding for replication and assembly machinery and more variable terminal ends that contain genes involved in host range determination and pathogenesis.10 Among these, MPXV virus has a relatively large genome made of the material needed for viral replication in cell cytoplasm causing pathogenicity in the host.11 The evolution of Orthopoxvirus has been postulated to be a result of progressive gene loss, particularly at the terminal end of the genome,12 which, along with gene copy number variation better virus survival and fitness.13 Vaccinia virus homologs to genes found in the terminal ends of the MPXV genome are predominantly involved in immunomodulation, and most are either predicted or known to influence host range determination and pathogenicity.14 Additionally, MPXV virus bears four open reading frames in its inverted terminal repeats unlike other species of the same genus like variola virus.15,16 Genetic analysis and culture of virus with human cells and mouse cells separately showed the evasion of host innate immune system by virtue of MPXV bearing a suppressor of a full-length N-terminal domain on its E3 homolog, which allows full inhibition of protein kinase R (PKR) and allows replication in JC (a mitochondrial stain) indicator cells.10 The E3 protein is able to bind double-stranded RNA and sequester it away from known pattern recognition receptors (PKR, RIG-I, MDA-5, and OAS), thereby preventing their activation.17–19 Mice are spared from this mechanism due to the lack of a full-length E3 homolog which

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1MBBS Student, Smt. Kashibai Navale Medical College and General Hospital, Pune; 2Chest Physician, Vora Clinic; 3Consultant Physician and Diabetologist, Shilpa Medical Research Centre; 4Consultant Endocrinologist, Joshi Clinic and Lilavati Hospital and Research Centre, Mumbai, Maharashtra, India; 5Corresponding Author

limits the interferon response to the disease in them.\textsuperscript{20}

The histopathological analysis of skin lesions of MPXV showed similarity to other viral exanthems like cowpox, variola, varicella-zoster, and herpes simplex viruses along with ballooning degeneration of keratinocytes, prominent spongiosis, dermal edema, and acute inflammation. Some keratinocytes showing large numbers of mature virions and immature virions in the process of assembly have been seen within the cytoplasm of infected cells.\textsuperscript{21}

**Diagnosis**

A preliminary diagnosis can be made based on a set of clinical evaluation criteria; it, however, must be differentiated from cowpox and smallpox due to the relative similarity in their presentation (Table 1). A definitive diagnosis can be made based on laboratory evaluation only. The available diagnostic assays for MPXV include virus isolation and electron microscopy, PCR, serum immunoglobulin M, and serum immunoglobulin G enzyme-linked immunosorbent assay, immunofluorescent antibody assay, and histopathologic analysis. The nonspecific nature of these tests makes it difficult to differentiate MPXV infection from other poxviruses.\textsuperscript{22}

A recent pilot of the Tetracore Orthopox BioThreat Alert provided promising results using lesion specimens from acute Orthopoxvirus infections. This assay reliably detected vaccinia and MPXV viruses in preparations with $10^7$ plaque-forming units/mL, and identified correctly five of six tested clinical specimens.\textsuperscript{23}

**Clinical Features**

**Skin**

After a 10–14 days incubation period, prodromal illness with fever, malaise, and swollen lymph nodes is observed in most of the patients prior to the development of rash. The prodromal period generally lasts 1–3 days before the occurrence of the typical maculopapular rash, which starts on the trunk and spreads in a peripheral distribution to the palms and soles of the feet.

Lesions can be observed on mucous membranes, in the mouth and tongue, and on the genitalia. During the 1st week of the rash, the patient is considered to be infectious and should be isolated until all scabs separate and results of throat swab PCR are negative. The mean diameter of the skin lesions is 0.5–1 cm, and the clinical progress is very similar to that of ordinary smallpox lesions. During a 2–4 weeks period, lesions progress from macules to papules, vesicles, and pustules, followed by umbilication, scabbing, and desquamation.\textsuperscript{24}

The pathology of these lesions intensifies as pustules form, with progressive ulceration, necrosis and epithelial hyperplasia, and prominent edema on the margins of necrotic areas. Development of clefts in the interstitial spaces between cells has also been noted. Later, apical evolution of the lesion with predominant inflammation and necrosis of the superficial dermis and destruction of sebaceous glands and follicles is evident.\textsuperscript{25}

Among patients with very high rash burdens (>250 lesions), interleukin-10, an anti-inflammatory, was markedly elevated which normally appears after the peak of illness severity, roughly coincident with the beginning of weight gain and recovery in the course of the disease.\textsuperscript{27}

**Lymph Nodes**

Prior to and concomitant with rash development is the presence of maxillary, cervical, or inguinal lymphadenopathy (1–4 cm in diameter) in many patients. Enlarged lymph nodes are firm and tender. It is hypothesized that the presence of lymphadenopathy may be an indication that there is a more effective immune recognition and response to infection, favoring the diagnosis of MPXV since lymphadenopathy is not a prominent feature of other poxviruses (smallpox or variola virus).\textsuperscript{29}

**Eyes**

One of the most significant sequelae of MPXV infection is corneal scarring and concomitant loss of vision.\textsuperscript{30} In the previous outbreaks, stringent measures were taken to provide the affected individuals with ophthalmic lubrication, vitamin supplementation, and

### Table 1: Clinical features of different Orthopoxvirus species

<table>
<thead>
<tr>
<th>Variable</th>
<th>Monkeypox</th>
<th>Smallpox</th>
<th>Chickenpox</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incubation period, days</td>
<td>7–17</td>
<td>7–17</td>
<td>12–14</td>
</tr>
<tr>
<td>Prodrome period, days</td>
<td>1–4</td>
<td>2–4</td>
<td>0–2</td>
</tr>
<tr>
<td>Symptoms</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fever, severity</td>
<td>Moderate</td>
<td>Severe</td>
<td>Mild or none</td>
</tr>
<tr>
<td>Malaise, severity</td>
<td>Moderate</td>
<td>Moderate</td>
<td>Mild</td>
</tr>
<tr>
<td>Headache, severity</td>
<td>Moderate</td>
<td>Severe</td>
<td>Mild</td>
</tr>
<tr>
<td>Lymphadenopathy, severity</td>
<td>Moderate</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Lesions</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Depth (diameter in mm)</td>
<td>Superficial to deep (4–6)</td>
<td>Deep (4–6)</td>
<td>Superficial (2–4)</td>
</tr>
<tr>
<td>Distribution</td>
<td>Centrifugal (mainly)</td>
<td>Centrifugal</td>
<td>Centripetal</td>
</tr>
<tr>
<td>Evaluation</td>
<td>Homogeneous rash</td>
<td>Homogeneous rash</td>
<td>Homogeneous rash</td>
</tr>
<tr>
<td>Time to desquamation, days</td>
<td>14–21</td>
<td>14–21</td>
<td>6–14</td>
</tr>
<tr>
<td>Frequency of lesions on palms or soles of feet</td>
<td>Common</td>
<td>Common</td>
<td>Rare</td>
</tr>
</tbody>
</table>

Signs and symptoms of the diseases are not age-specific
antibiotics to prevent superimposed bacterial infections. Outbreaks of smallpox were successful in proving bacterial superinfection virus-induced corneal ulcerations to have been associated with catastrophic damage to the eye (perforation, anterior staphyloma, and phthisis bulbi). 31

Systemic Illness
Observations collected from patients infected with a West African genetic variant of MPXV during an outbreak in the United States, demonstrated that parenteral exposures tended to be associated with more profound systemic illness, a greater likelihood of the patients experiencing nausea and vomiting compared to the probability of febrile proctitis, due to the pathology in the former resulting from an early inoculation lesion. 32

One of the many studies conducted among nonhuman primates proved the development of ulcerative stomatitis and necrotizing lesions along the upper gastrointestinal tract among the studied animals. 33 This provided a basis for justifying the involvement of the gastrointestinal tract in the course of the disease.

Hypoalbuminemia and low hematocrit, suggestive of malnutrition, were observed in patients who were hospitalized with MPXV during the US outbreak in 2003. 34 These were most apparent in those who had relatively severe manifestations of infection (defined as three or more aberrant clinical chemistry values or duration of hospitalization more than 48 hours) along with predominant anorexia. The appearance of mouth and throat sores, nausea and vomiting, and cervical lymphadenopathy, which occurred early during the illness could be an important contributing factor to the patients’ decreased appetite. 35

Another feature of MPXV infection was found to be bronchopneumonia. Studies conducted among nonhuman primates across a range of infectious doses have shown to result in the development of focal necrosis of lung tissues, diffuse pulmonary consolidation, and fulminant bronchopneumonia. In several studies, the intratracheal deposition of virus-containing aerosols led to significant respiratory distress and death in a high proportion of animals. 36

Treatment
The available treatment at the moment includes cidofovir—a broad-spectrum antiviral drug that has activity against many DNA viruses, including MPXV. 37 Cidofovir and tecovirimat have also been used with success for the treatment of MPXV. Studies using a variety of animal species have shown that tecovirimat is effective in treating Orthopoxvirus-induced disease. Human clinical trials indicated the drug was safe and tolerable with only minor side effects. 38

A retrospective observational study conducted in the UK showed a decline in complications, days of hospitalization, and complete recovery of the documented seven cases in different parts of the nation over the past 3 years (2018–2021) with symptomatic illness management. 39 Vaccination with smallpox is effective in prevention and postexposure prophylaxis of MPXV. 40 However, in cases with contraindications to smallpox vaccines, the vaccinia virus immunoglobulin administered is equally effective as a means of postexposure prophylaxis. 41

CONCLUSION
The periodic occurrence and frequency of such outbreaks bring to light the need of epidemic awareness, research, and preparedness. Although the availability of literature is limited, we must improve upon research pertaining to the outcomes of conventional practices so as to devise specific, disease-modulating strategies to prevent transition to complications. Early detection and screening along with the available means of disease management can be helpful. Disparities in provision of healthcare facilities must be addressed in like manner, so as to permit better primordial prevention of the disease.

REFERENCES
Monkeypox: What do we know so far? A short narrative review of literature

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Post-transplant Diabetes Mellitus: What Physicians Need to Know
Praveen Kumar Etta*
Received: 02 March 2019; Accepted: 12 March 2022

ABSTRACT
Post-transplant diabetes mellitus (PTDM) is a common problem among solid organ transplant recipients contributing to morbidity and affecting patient as well as graft survival adversely. It can occur at any period following transplantation, but maximum incidence is observed in the first few months, with a second peak after a few years after transplantation. The pathogenesis is complex and poorly understood, however, it is associated with both dysfunctional beta-cells and insulin resistance. Both nonpharmacologic and antidiabetic therapies are important for adequate glycemic control. This point of view article provides a short review on PTDM in solid organ transplantation (SOT) recipients from a general physician’s perspective.

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Solid organ transplantation is currently the best choice of treatment for most patients suffering from end-stage organ failure. Successful organ transplantation offers enhanced quality and duration of life with lower morbidity and mortality. Innovations in SOT, advances in surgical techniques, progress in immunosuppressive regimens, and critical care have greatly improved both the patient and graft survival in last several decades. The discovery of calcineurin inhibitors (CNIs) represents a milestone event in the history of immunosuppression and it has revolutionized transplant medicine; further breakthrough in immunosuppressive regimens is the cornerstone for existing successful transplant program. The current 5-year graft survival is about 80% for kidney and heart transplants, and 70% for liver and lung transplants (UNOS-OPTN and SRTR registry data). Cardiovascular disease (CVD), infections, and drug toxicity play an important role in the long-term morbidity and mortality of this patient population. This risk is not only due to presence of underlying pre-existing comorbidities, but also results from adverse effects of the immunosuppressive drugs such as hypertension, dyslipidemia, and PTDM. The risk of PTDM after SOT varies from 10 to 40% during the first year. This risk depends on several factors including the type of transplanted organ (10–20% of kidney transplant recipients [KTRs] and 20–40% of patients with heart, liver, and lung transplants). Post-transplant diabetes mellitus is widely studied in KTRs, but the risk factors and pathophysiology seem to be similar in all kinds of SOT.

Post-transplant diabetes mellitus (previously termed, new-onset diabetes mellitus after transplantation [NODAT]) results in a remarkable proportion of SOT recipients and contributes to increased risk of CVD and infections, leading to significant mortality and morbidity. The pathogenesis is complex and poorly understood, however, it is associated with both dysfunctional beta-cells as well as reduced sensitivity to insulin. Consensus guidelines and proceedings from international consensus meeting on PTDM updated its recommendations in 2014, preferred to call it as PTDM rather than NODAT, as few patients could have undiagnosed diabetes prior to transplantation. New-onset diabetes mellitus after transplantation simply indicates exclusion of pretransplant diabetes and it is found that around 10% of KTRs have undetected diabetes prior to transplantation. Hence, PTDM represents timing of diagnosis in post-transplant period rather than time of occurrence of disease. The gold standard method to diagnose PTDM is the oral glucose tolerance test (OGTT). Post-transplant diabetes mellitus typically presents with postprandial hyperglycemia (impaired glucose tolerance [IGT]) rather than impaired fasting glucose (IFG). International consensus guidelines for PTDM recommend standard diagnostic criteria by American Diabetes Association (ADA) and World Health Organization (WHO) for the diagnosis of PTDM and these are almost same as to those used for type II diabetes mellitus (T2DM) in the general population with few exceptions (Table 1).

Following transplantation, there is increased turnover of red blood cells due to perioperative blood loss and regain of renal function in case of kidney transplantation with normal erythropoietin production. The immunosuppressant drugs can have a negative effect on red cell proliferation in the bone marrow. Hence the glycated hemoglobin (HbA1c) can be erratic and accurate interpretation is not possible in the first 2–3 months, and is not a recommended test to identify PTDM in early post-transplant period. After 3 months post-transplant, HbA1c is reliable and ADA cut-off can be followed to diagnose PTDM. As per ADA guidelines, “prediabetes” is diagnosed with OGTT if fasting plasma glucose is 100–125 mg/dL (IFG) or 2-hour plasma glucose is 140–199 mg/dL (IGT). American Diabetes Association and WHO criteria differ with respect to normal ranges of fasting plasma glucose. American Diabetes Association criteria are more sensitive in detecting transplant candidates at risk for PTDM as its threshold value is lower. Impaired fasting glucose is diagnosed if fasting plasma glucose is ≥100 mg/dL by the ADA and ≥110 mg/dL by the WHO. Oral glucose tolerance test is more sensitive for detecting prediabetes as IGT is more commonly seen than IFG.

The incidence of PTDM is higher in the first year, with a second peak after a few years following transplantation. Early peak is usually the result of metabolic adverse effects of immunosuppressive drugs, whereas late peak is due to post-transplant weight gain, obesity, metabolic syndrome, and insulin resistance. There is a great variability in the prevalence and incidence rates in the published literature. This is due to differences in the proposed diagnostic criteria, definitions used, organs transplanted, timing from transplantation, follow-up duration, population genetics, geographical differences, immunosuppressive drug regimens, and other risk factors. The prevalence of PTDM varied from 15 to 55% in the literature. It is identified that up to one-third of nondiabetic KTRs develop
Post-transplant Diabetes Mellitus: What Physicians Need to Know

Table 1: Diagnosis of PTDM

<table>
<thead>
<tr>
<th>Any of the following criteria should be satisfied for the diagnosis of PTDM at any time after transplantation</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Fasting plasma glucose ≥126 mg/dL (7.0 mmol/L)</td>
</tr>
<tr>
<td>• Two-hour plasma glucose ≥200 mg/dL (11.1 mmol/L) with OGTT after consuming 75 gm anhydrous glucose as per WHO recommendation</td>
</tr>
<tr>
<td>• Random plasma glucose ≥200 mg/dL (11.1 mmol/L) along with symptoms suggestive of diabetes mellitus</td>
</tr>
<tr>
<td>• Glycated hemoglobin of ≥6.5% (should not be used in first few months of transplantation)</td>
</tr>
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Table 2: Post-transplant diabetes mellitus and its risk factors

<table>
<thead>
<tr>
<th>Traditional risk factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Elderly age</td>
</tr>
<tr>
<td>• Hispanic, South Asian, and African American ethnicity</td>
</tr>
<tr>
<td>• Sedentary behavior</td>
</tr>
<tr>
<td>• Metabolic syndrome</td>
</tr>
<tr>
<td>• Obesity and overweight</td>
</tr>
<tr>
<td>• Family history of diabetes</td>
</tr>
<tr>
<td>• Genetic predisposition</td>
</tr>
<tr>
<td>• Gestational diabetes</td>
</tr>
<tr>
<td>• Nonalcoholic steatohepatitis</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Transplant specific risk factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Drugs—CNIs (especially tacrolimus), mTOR inhibitors, and glucocorticoids</td>
</tr>
<tr>
<td>• Native kidney disease—polycystic kidney disease and interstitial nephritis</td>
</tr>
<tr>
<td>• Type of solid organ transplanted</td>
</tr>
<tr>
<td>• Prediabetes prior to transplant</td>
</tr>
<tr>
<td>• HLA-mismatch transplant</td>
</tr>
<tr>
<td>• Cadaver donor</td>
</tr>
<tr>
<td>• Acute rejections</td>
</tr>
<tr>
<td>• HCV infection</td>
</tr>
<tr>
<td>• CMV infection</td>
</tr>
<tr>
<td>• Hypoglycemia</td>
</tr>
<tr>
<td>• Post-transplant weight gain</td>
</tr>
</tbody>
</table>

Impaired glucose metabolism by 6 months following transplantation. Currently, the prevalence of PTDM appears to be reducing, mainly due to use of lower doses of immunosuppressive drugs targeting lower trough levels to prevent drug toxicity.9 Transient hyperglycemia is highly prevalent in the early post-transplant period; it can be identified in ~90% of KTRs in the first few weeks. It can result from use of higher doses of immunosuppressive drugs, antirejection therapy, stress, infections, sepsis, and other critical conditions. While detecting transient post-transplantation hyperglycemia is crucial as it is a predisposing factor for consequent PTDM, universally labeling all of them as PTDM in the early post-transplant setting is not acceptable. The diagnosis of PTDM should be delayed until the recipient is clinically stable, with stable allograft function, and on lower doses of immunosuppression without acute infections. To avoid overdiagnosis, few authors proposed to define PTDM as a long-term (usually more than 3 months) need for antihyperglycemic therapy.

The common predisposing factors for the occurrence of PTDM are side effects of immunosuppression and their effect on glucose metabolism, infections especially due to certain viruses, and hypoglycemia, along with traditionally identified predisposing factors seen with T2DM (Table 2). Risk factors for PTDM should be analyzed during the pretransplant period to prevent or delay the development of PTDM. Some of these include older age, high-risk race or ethnic groups, obesity or metabolic syndrome, prediabetes prior to transplant, gestational diabetes, first degree relative with diabetes, nonalcoholic steatohepatitis, polycystic kidney disease, higher human leukocyte antigen (HLA)—mismatches, acute rejection episodes, cadaver donor, cytomegalovirus (CMV) and hepatitis C virus (HCV) infections, and use of immunosuppression.5 Induction with basiliximab may predispose patients to PTDM as concluded in a study from North India.10

Glucocorticoids induced PTDM seems to be dose-dependent. It is characterized mainly by insulin resistance and higher postprandial blood glucose levels. Although, it could be dose-dependent, there is no evidence that steroid withdrawal prevents or reduces PTDM incidence.11,12 Calcineurin inhibitors have toxic effect on islet cells of pancreas and alter insulin secretion pattern.13 Calcineurin inhibitors by causing hypomagnesemia, precipitate PTDM. Diabetes Incidence after Renal Transplantation: Neoral C Monitoring Versus Tacrolimus (DIRECT) study observed a greater risk of PTDM with tacrolimus than cyclosporine (CsA).14 In the Efficacy Limiting Toxicity Elimination (ELITE) study, low-dose tacrolimus (8.4%) was more diabetogenic at 1 year than standard-dose CsA (6%), low-dose CsA (4.2%), and low-dose sirolimus (6.6%).15 Various meta-analyses also concluded that tacrolimus is more diabetogenic than CsA.16,17 Mammalian target of rapamycin (mTOR) inhibitors such as sirolimus can also induce PTDM. Conversion from one of the CNIs (either tacrolimus or CsA) to sirolimus resulted in worsening of glycosorine and insulin resistance as shown in a study.18 Antimetabolites such as mycophenolate mofetil (MMF) and azathioprine seem to be nondiabetogenic and may not contribute to the pathogenesis of PTDM. The combination immunosuppressive drug regimens were assessed in some studies. One study found that the combination of CNI and sirolimus has a greater risk of PTDM than the combination of CNI and MMF.19 Some other drugs such as renin-angiotensin-aldosterone system (RAAS) blockers [angiotensin-converting enzyme inhibitor (ACEI) or angiotensin receptor blocker (ARB)], co-trimoxazole and statins may reduce the risk of PTDM.20,21

Hepatitis C virus infection was associated with almost fourfold higher risk of acquiring PTDM than those who were not infected in a meta-analysis among KTRs.22 The pathogenesis of HCV-induced PTDM seems to be multifactorial including abnormal glucose metabolism, insulin resistance, and beta-cell dysfunction. Anti-HCV treatment and sustained virological remission in pretransplant period may prevent the development of PTDM. A large North Indian retrospective study compared long-term outcomes of HCV-infected and noninfected KTRs and concluded greater risk of PTDM in the HCV-infected group (~40 vs 19%). In the same study, anti-HCV therapy was given to all infected recipients before transplantation.23 Hepatitis C virus-associated PTDM is usually noticed in liver transplant recipients, especially in cases with hepatic steatosis. Association of PTDM with CMV infection is unclear. There was a fourfold greater risk of PTDM in patients with asymptomatic CMV infection in a study.24

Prediabetes before transplantation can predispose to PTDM. A percentage of 35% of KTRs with PTDM had pretransplant IGT in one study.25 Risk adaptive approach and tailoring of immunosuppression seems to be the fundamental concept to delay and prevent the occurrence of PTDM, especially in those with greater risk for PTDM. Transient hyperglycemia is widely prevalent in early post-transplant period; though it can predispose the recipient to PTDM, it should not be considered as an expression of PTDM. The contribution of transient hyperglycemia to the risk of PTDM was assessed in the past. Around 29% of recipients with postoperative transient hyperglycemia progressed to develop PTDM within 1 year, in a study.26 In another similar study, 46.7% of recipients with early transient hyperglycemia developed PTDM. There was a fourfold higher risk of PTDM in patients with transient hyperglycemia.27

Post-transplant diabetes mellitus, due to its predisposition to infections and CVD, adversely affects graft and overall patient
Post-transplant Diabetes Mellitus: What Physicians Need to Know

Post-transplant diabetes mellitus (PTDM) is a common complication following solid organ transplantation (SOT) which affects 20-60% of patients in the early post-transplant period. It is a significant risk factor for increased mortality and morbidity due to complications such as cardiovascular disease (CVD) and renal allograft dysfunction.

Cardiovascular disease is the most common cause of death and poor patient survival in SOT recipients, and PTDM has a correlation with CVD mortality. There is also an increased risk of death-censored graft loss due to PTDM. Some of these complications include development of de novo diabetic nephropathy in the renal allograft, excessive risk for infections such as pneumonia, urinary tract infection, and viral infections including CMV.

Immunosuppressive drugs are used to prevent rejection after transplantation. Tacrolimus is the first-line drug, especially in patients with obesity and insulin resistance. It can precipitate lactic acidosis in high-risk subgroup of patients, especially in the presence of renal dysfunction. Majority of the reported cases of lactic acidosis have been identified in patients who were already on RAAS blockers (ACEi or ARB) in the presence of renal dysfunction. It can be initiated safely in patients with an estimated glomerular filtration rate (eGFR) up to 45 mL/min/1.73 m². It is not recommended to start metformin once eGFR is less than 45 mL/min/1.73 m² and is currently contraindicated if eGFR<30 mL/min/1.73 m², although data are emerging on its metabolic benefits even in patients with advanced CKD. Due to its safety concerns, it is necessary to monitor renal function closely while on metformin therapy. It can also aggravate gastrointestinal (GI) side effects of immunosuppressive drugs. Gliclazide, glipizide, and glimepiride are preferred among sulfonylureas in patients with renal dysfunction. Meglitinides, such as repaglinide, due to their short duration of action, may be preferred over sulfonylureas in the presence of low GFR as the latter drugs are associated with significant risk of hypoglycemia. However, there are no strong data supporting the use of repaglinide or nateglinide among SOT recipients, as the studies performed were short-term. But they were considered safe and efficacious. Dipeptidyl peptidase-4 inhibitors or glitazins inhibit DPP-4 enzyme which is responsible for degradation of endogenous incretins leading to restoration of insulin secretion and inhibition of glucagon release. They are weight neutral (do not induce weight gain), have glucose-dependent action with lesser risk for hypoglycemia, and are considered to be safe along with immunosuppressive drugs due to least interactions. They may be considered as the potential first-line OHAs to manage PTDM. The studies performed on the available glitazins such as sitagliptin and vildagliptin are of small sample size with short-term follow-up, however, they documented their safety and efficacy in SOT recipients. In T2DM, long-term safety data are available for sitagliptin but not for vildagliptin.33 Vildagliptin was considered as safe and effective in KTRs as concluded in a double-blind RCT.34 There is some drug interaction between sitagliptin and CNI drugs especially CsA with regard to prolongation of QT interval in the combination group. Linagliptin was found to be safe and effective for PTDM management as concluded in one Indian study. As it is nonrenally eliminated, it does not require dose adjustment in renal failure.35 Thiazolidinediones are considered as the last resort of therapy in SOT recipients with PTDM due to their side effect profile as these patients generally suffer from multiple
comorbidities. These drugs can worsen post-transplant mineral bone disease and bone loss, precipitate congestive heart failure, and lead to anemia, fluid overload, and weight gain. Drug interaction with CNIs is observed as they predispose to CNI toxicity. Alpha-glucosidase inhibitors such as acarbose and miglitol are not recommended if eGFR is <30 mL/min/1.73 m² and they can aggravate GI side effects of MMF.

Incretin mimetics [glucagon-like peptide 1 (GLP1) receptor agonists] such as exenatide, lixisenatide, and semaglutide, have not been evaluated for their safety in SOT recipients except for a few small studies. Physicians should be cautious against using GLP1 receptor agonists due to risk of GI tract side effects and precipitation of prerenal acute kidney injury in SOT recipients having GFR <30 mL/min/1.73 m². Recent clinical trials with GLP1 receptor agonists in nontransplant population showed their potential benefit on adverse cardiovascular as well as renal outcomes in high-risk CVD patients; the data in SOT recipients are still awaited. The data are emerging for the use of sodium-glucose cotransporter 2 (SGLT2) inhibitors in SOT recipients with PTDM. Important drugs include canagliflozin, dapagliflozin, empagliflozin, and etogliptin. They have been evaluated in large clinical trials in nontransplant population and found to significantly reduce the risk of major adverse cardiovascular and renal outcomes. They are now considered as first choice therapies for both cardiovascular and renal protection in patients with heart failure with reduced ejection fraction, diabetic kidney disease, and proteinuric nondiabetic kidney diseases, and this benefit was observed irrespective of presence of diabetes. Their efficacy and safety in patients with kidney and other SOT recipients are not known as these patients were excluded from large clinical trials. The only concern with these drugs is increased predisposition to genital, fungal and lower urinary tract infections, and this could be life-threatening in immunosuppressed SOT recipients. The antihyperglycemic effect of these drugs diminishes once GFR is <60 mL/min/1.73 m² and is practically nil at GFR <30 mL/min/1.73 m². In an RCT that included KTRs with PTDM who were randomized to either SGLT2 inhibitor or placebo found that empagliflozin is safe and efficacious for treatment of PTDM, and moderate weight loss was also observed in the treatment arm. A pilot study from India also concluded that canagliflozin use resulted in better glycemic control with lower HbA1c level, body weight, and blood pressure reduction. The requirement of other OHAs was also reduced, with no adverse effects including hypoglycemia in the treatment arm. There is an immense need for a large-scale intervention trials in SOT recipients with PTDM with these newer hypoglycemic agents, that is, GLP1 receptor agonists and SGLT2 inhibitors that have been proved to have pleiotropic benefits and lower major adverse cardiovascular and renal events in high-risk patients with T2DM.

Conclusions
Post-transplant diabetes mellitus is quite common, diagnosed in about 20–30% of SOT recipients by 1 year post-transplantation. It has an adverse effect on graft and patient survival, directly and indirectly. Calcineurin inhibitors (tacrolimus more than CsA), mTOR inhibitors (sirolimus), and glucocorticoids promote beta-cell dysfunction and insulin resistance, leading to PTDM. Management should focus on prevention, delaying the onset, early detection of PTDM, and adequate glycemic control. Pretransplant screening should include assessing the risk by identifying prediabetes and insulin resistance. Posttransplant surveillance should focus on identifying PTDM at early stages by regular monitoring of blood sugars. Both nonpharmacological strategies and antihyperglycemic agents should be used to achieve glycemic targets. Long-term PTDM can be managed similar to T2DM with individualized glycemic targets, cardiovascular risk reduction, and screening for complications. Tailoring of immunosuppressive regimen to achieve glycemic targets should be balanced and weighed against the risk of rejection with the primary aim of preserving graft function as a priority. Switching to CsA from tacrolimus can be considered in a few circumstances especially in patients with poor glycemic control in spite of targeting lower trough levels of tacrolimus. Insulin is the primary therapeutic option in first weeks after SOT. Along with insulin, OHAs can be added either as monotherapy or combination regimen. Commonly used OHAs include metformin, sulfonylureas, meglitinides, and DPP-4 inhibitors. Sodium-glucose cotransporter 2 inhibitors and GLP1 receptor agonists are emerging therapies with pleiotropic benefits with respect to lowering of major adverse cardiovascular and renal events in high-risk patients with T2DM; there is a robust need for clinical trials in SOT recipients. With the growing number and survival of SOT recipients, primary care physicians should be aware of PTDM to reduce the disease burden and its life-threatening complications.

References
Post-transplant Diabetes Mellitus: What Physicians Need to Know


A 40-year-old male driver from Karnataka, presented with complaints of progressive dyspnea and dry cough of 2 weeks duration. General and systemic examination was normal. Chest X-ray revealed bilateral hyperopaque deposits in all lung zones predominantly in the lower zone following pulmonary vascular distribution suggestive of heavy metal exposure (Fig. 1). On repeated questioning, he committed to taking two intramuscular injections from a traditional healer in his village 3 weeks ago for polyarthralgia. Toxicologic analysis revealed a high level of mercury in both urine and serum. A 24-hour urine levels of mercury was >1600 μg/L (normal < 20 μg/L) and serum level was >250 μg/L (Fig. 2). PET CT revealed multiple high attenuation lesions in the lungs, liver, stomach, pericardium, bowel wall, axial and appendicular skeleton, meninges, skin, and subcutis. The prominent uptake of tracer during PET in the region of the left gluteus maximus, the site of IM depot injection is shown in Figure 3. A diagnosis of mercury embolism was made and he was managed with chelation therapy with dimercaprol as per standard guidelines. At follow-up at 1 year, though the urinary mercury level did not change, he was healthy with none of the clinical features of chronic mercury poisoning.

By virtue of its ubiquitous presence in the environment, humankind is exposed to mercury routinely. This is further compounded by accidental industrial exposure and mercurial compounds in alternative medicines and voluntary use of mercury in performance-enhancing drugs. Route of exposure and type of mercurial compound decides the phenotype of the toxidrome in humans. Though no stochastic relationship has been established between mercury levels in body fluids or hair and level of exposure management of toxicity through early and prompt chelation based on the clinical phenotype can lead to a reversal of clinical manifestations in most cases.

References

Fig. 1: Chest radiography showing bilateral hyperopaque deposits in all lung zones predominantly in the lower zones following pulmonary vascular distribution

Fig. 2: Contrast enhanced CT scan for chest showing dense deposits in the lung and lymph nodes in the axillary and mediastinal regions

Fig. 3: Fluorodeoxyglucose (FDG)-Positron Emission Tomography (PET) showing prominent uptake of tracer in the region of left gluteus maximus, the site of intramuscular injection depot injection
A 36-year-old nonobese female presented to us with drug-resistant hypertension. She had no other atherosclerotic risk factors. There was no history of any drug intake, paroxysmal palpitations, headache, fatigue, stroke, weight gain, or weight loss. On examination her blood pressure was 190/110 mm Hg in all four limbs, no radio-femoral delay, no carotid or renal bruit, no arcus senilis, no xanthomas, and rest of systemic examination was normal.

His routine investigations which included complete blood count, erythrocyte sedimentation rate, liver function test, kidney function test, electrolytes, lipid profile, and blood glucose were normal. Electrocardiogram revealed left ventricular hypertrophy. The echocardiogram revealed left ventricular hypertrophy with left ventricular diastolic dysfunction. The renal ultrasound revealed small size right renal artery (7 × 3.5 cm) as compared to left renal artery (11 × 5 cm) with maintained corticomedullary differentiation and no parenchymal lesion. She underwent renal angiography through right femoral artery route by using JR diagnostic catheter. The right-sided renal artery showed beaded appearance and small-sized right kidney. The left side renal artery was normal. Based on angiographic findings, the final diagnosis of fibromuscular dysplasia (FMD) was made. The patient was planned for DTPA scan to look for the function of right renal artery followed by percutaneous transluminal renal angioplasty.

Fibromuscular dysplasia is a vascular disease affecting small- to medium-sized vessels. It is a noninflammatory, nonatherosclerotic condition occurring more frequently in younger individuals and women. The presence of FMD has been demonstrated in almost every vascular bed. Renal artery involvement is most common (60–75%), followed by the cervicocranial arteries (25–30%), visceral arteries (9%), and the arteries in the extremities (5%).

The diagnosis is most often made by the characteristic angiographic appearance. Although the pathologic specimen is diagnostic, it is rarely obtained. These are intimal fibroplasia, medial dysplasia, and adventitial fibroplasia. Medial FMD is further divided into medial fibroplasia, perimedial fibroplasia, and medial. Medial fibroplasia, a subtype of medial FMD, is the histological finding in 75–80% of all cases of fibrous dysplasia. Microscopically there are alternating areas of thinned media and thickened fibromuscular ridges containing collagen. Some areas of the internal elastic membrane are lost. A “string of beads” is used to describe its angiographic appearance, where the “bead” diameter is larger than the proximal vessel seen in arteries affected by medial and perimedial fibroplasias. Angiography demonstrates focal or tubular stenosis in arteries affected by intimal fibroplasia (Fig. 1).

Fibromuscular dysplasia is usually easy to differentiate from atherosclerosis. As a general rule, atherosclerosis occurs proximally and FMD (especially medial fibroplasia) occurs in the mid or distal portion of the blood vessel. Patients with atherosclerosis often have multiple atherosclerotic risk factors, whereas most individuals with FMD are younger and have fewer risk factors. Symptomatic patients can undergo percutaneous transluminal angioplasty.

Fig. 1: The “string of beads” appearance of the right renal artery involves the distal portion of the main renal artery, and the “beads” are larger than the normal diameter of the artery. The left side renal artery is normal. Note the size of right kidney is small as compared to left kidney.
Thomas Morgan (1866–1945) was born in Lexington, Kentucky. He received his B.S. degree from the State College of Kentucky in zoology in 1886 and then entered Johns Hopkins University for graduate work in biology. Morgan earned his Ph.D. in 1890 and became Associate Professor of Biology at Bryn Mawr College for Women until 1904, when he became Professor of Experimental Zoology at Columbia University, New York. He remained there until 1928. He was then appointed Professor of Biology and Director of the Kirschhoff Laboratories at the Caltech, Pasadena. Morgan applied experimental techniques to fundamental problems of embryology during this period.

When Morgan began his work on genetics, he was looking for less expensive material that he could breed in the very limited space at his command. He apparently began breeding the fruit fly (Drosophila) in 1908-1909. It was a small insect capable of breeding in large numbers with virtually no trouble. Its cells possessed only four pairs of chromosomes.

Initially, he was doubtful about the truth of Mandel’s views but study of Drosophila soon convinced him and he became a vigorous supporter of Gregor Mandel. He felt that Mandel’s “factors” might be the chromosomes, and proved him right by showing that units of heredity (genes) are carried in the chromosomes. He established sex linkage through the observation that the mutant “white eye” variety occurs exclusively in male fruit flies. Morgan also discovered the crossover (exchange of genes between chromosomes) and with his coworkers devised the first chromosome map. In 1911, he showed relative position of sex-linked genes; and by 1922, they had a map showing relative positions of over 2000 genes in the four chromosomes of Drosophila.
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**Zoster Sine Herpete and COVID Vaccine**

Delanthimar J Bhandary¹, Nilesh N Goyal²

¹Clinical Associate; ²Consultant, Department of Dermatology, Lilavati Hospital and Research Centre, Mumbai, Maharashtra, India

**Introduction**

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) virus responsible for COVID-19 pandemic, was first reported in China in 2019 and spread rapidly across all continents within a span of 1 year.

After the acute (first-time exposure) infection subsides, the varicella-zoster virus (VZV) remains dormant in the dorsal root ganglion, cranial nerve ganglion, and autonomic ganglia. Years later, during times of extreme stress or immunodeficiency, it gets reactivated as herpes zoster (HZ). Vesicular eruptions on the skin with an erythematous base along the dermatomal distribution accompanied by characteristic neuralgic pain are pathognomonic of HZ.

We describe two cases of neuropathic pain in a dermatomal distribution without the presence of skin lesions brought on immediately after COVID-19 vaccination. This has been described as zoster sine herpete (ZSH). But the occurrence of two cases in a cluster of this rare presentation of VZV reactivation brings us to wonder if the COVID-19 infection or vaccination is responsible.

**Case Description 1**

A 55-year-old lady presented to the dermatology outpatient department in our hospital with 3-day history of pain below the scapula on left side. It started suddenly without any preceding history of injury or lifting heavy weights or sleeping in unusual position. The pain was excessive in the area of left scapula and radiated to the front of chest in the inframammary region. The pain was completely absent on the right side of thorax. There was no associated fever or any skin lesions in the pain-affected areas. She is a known diabetic which was well controlled. She had received the first dose of Covishield (Serum Institute India, Pune, India) vaccine (Recombinant, replication-deficient chimpanzee adenovirus vector encoding the SARS-CoV-2 spike glycoprotein). Produced in genetically modified human embryonic kidney 293 cells) 10 days prior to onset of pain. Postvaccination she had mild fever for 3 days with body ache which resolved completely with antipyretics. She denied history of being affected by COVID-19 infection at any time prior.

On examination, there was a distinct increase in touch up to the point of describing it as pain sensation in the distribution of T4 and T5 dermatomes on left side of thorax when checked with finger touch. It was distinctly restricted to left half of the body. The area affected was from infrascapular area medial to spine all the way anteriorly up to midstch including the nipple and inframammary areas. No vesicles or erosions were seen in the pain-affected areas. No lymph nodes were palpable in the axillae or cervical regions. Movement of left upper limb was normal with no loss of power but she described the movements as pain-inducing. She was able to bend forward and backward with no difficulty. A chest X-ray in anteroposterior and lateral views showed no abnormality of body structures including spine.

She was started on oral Valaciclovir 1000 mg thrice daily for 5 days along with pregabalin 75 mg once daily. This helped her symptoms of pain significantly. After a week of above treatment, the pain intensity had reduced but she continued to get sharp bouts of shooting pain in the affected areas. Her pregabalin dose was doubled which helped her symptoms significantly. In view of her ongoing diabetes, it was decided to avoid treating her with oral steroids. She confirmed reduction in symptoms 6 weeks after initiation of treatment.

**Case Description 2**

A 22-year-old female presented to the dermatology department with sudden onset of severe pain on right side of chest radiating to the back along the rib cage. It was only on the right side of chest. There was no history of fall or lifting of heavy weights or exercise. The pain was very severe to the point that it affected her sleep. She described it as a deep boring type. It did not get worse on deep breathing or eating. She was a completely healthy individual with no known previous medical illnesses or any regular medications. Her immunization history revealed no vaccination for VZV but had received both doses of COVID-19 vaccination, the last dose being 3 months prior. She had been infected with COVID-19 virus 6 months prior which was treated with oral antivirals and antipyretics at home. She had not needed any hospitalization.

On examination, there was no burning sensation or increased touch sensation. Her movements of body and limbs were not restricted due to pain. The pain did not have any localizing point. It was restricted to the T3–T5 thoracic dermatomes on right side. The breasts was normal to examination with no skin lesions.

X-ray of chest and neck in anteroposterior and lateral views revealed no bony abnormality or any other soft tissue lesions. She found good relief with oral Pregabalin 75 mg and Tramadol 50 mg both given once daily. In view of her sudden onset of symptoms in unilateral distribution she was given a 5-day course of Valaciclovir 500 mg thrice daily. She found significant relief in symptoms within 2 weeks with return to college studies.

**Discussion**

Of late, we have been observing an unusually high number of HZ cases in our outpatient department practice as compared to pre-COVID times. This has been supplemented by a record of increased number of HZ ophthalmicus cases presenting to the ophthalmology department of our hospital since the onset of pandemic. Although preliminary studies suggested no association between HZ and COVID-19, mounting evidence to the contrary is getting published by the day. Researchers from Brazil conclude that there exists a correlation between HZ and COVID-19 after they observed an increase in HZ infection across the entire country. Similar observations made in Turkey and Egypt give credence to the hypothesis that HZ could be a marker of COVID-19 infection.

Herpes zoster reactivation is not only seen in COVID patients but also in those receiving mRNA and inactivated COVID-19 vaccine. It is thought to occur due to failure of immune system to control the VZV. T cell immune dysfunction is known to occur in patients with COVID-19. Reportedly, there is a decrease in the number of CD4⁺, CD8⁺, CD3⁺, and natural killer cells resulting in impaired antiviral response. It is observed that COVID-19 vaccination triggers the immune system and polarizes it to a vaccine-induced T cell response, thereby directing both the humoral and cellular immunity responses towards producing interferon-γ. This, temporarily though, reduces the T cell immunity against the VZV thereby causing HZ reactivation. Both our patients had received at least one dose of Covishield vaccine (Serum Institute India, Pune, India), a nonreplicating chimpanzee adenovirus vector encoding SARS-CoV-2 spike glycoprotein, few weeks prior to the time of diagnosis.

Zoster sine herpete is unique in that the vesicular eruptions are conspicuously absent, but the dermatomal pain and burning are reportedly severe in intensity as compared to pain in HZ. Such cases are likely to present to pain/orthopedic clinics. Timely diagnosis and initiation of treatment are of paramount importance as rare complications of ZSH such as vasculopathy, myelopathy,
Correspondence

and meningoencephalopathy could be fatal if missed or misdiagnosed. Considering the increased incidence of HZ during this pandemic, it is pertinent for physicians and specialists across clinical branches to be wary of these conditions.

Notwithstanding the fact that common risk factors exist for both HZ and COVID, few other factors could possibly have an impact on immune dysregulation and the resultant increase in the number of HZ cases encountered during these unprecedented times viz.,

• Bereavement and physical stress can impair immune function in the elderly.
• Loss of beneficial effects of natural sunlight due to prolonged indoor stay.
• Increased mental stress following lockdown.
• Uncustomary change in lifestyle for individuals and disruption of normal day-to-day activities.
• Widespread consumption of concoctions made from commonly available herbs and plants for preventive and prophylactic purposes; plant secondary metabolites are known to exert diverse range of pharmacological effects in mammalian systems.

CONCLUSION

There is a rise in occurrence of HZ infections with uncommon presentations like ZSH during the COVID-19 pandemic. Factors other than COVID-19 infection or vaccination can be attributed during the pandemic to this increased incidence of HZ infections.

REFERENCES


Cerebral Infarction and Homocysteine

Khichar Shubhakaran
Professor and Head, Department of Neurology, Dr. Sampurnanand Medical College, Jodhpur, Rajasthan, India

Sir,

I read an interesting article entitled “Co-relation of Cerebral Venous Sinus Thrombosis with Vitamin B<sub>12</sub> and Homocysteine Levels in a Tertiary Care Centre” by Harale et al. published in January 2019 issue of our esteemed journal JAPI (vol. 67, page no. 34–37). In a study of 50 patients including those of puerperium by the eminent authors noted that the commonest clinical presentation was headache (88%) followed by altered sensorium (56%), seizures (56%), and papilloedema (54%). In our study the clinical presentations were like that of idiopathic intracranial hypertension as the most common one, that is, in 20 (50%), followed by isolated seizures in 10 (25%), stroke-like presentation in eight (20%), and encephalopathy in two (5%) patients, which is more or less similar.

In the present study the authors found that hyperhomocysteinemia (HHC) was found in 35, comprising 70% cases, which is quite high and is statistically significant (p < 0.05) in comparison to the controls. We in a prospective study on cerebral venous sinus thrombosis in 40 male patients found, HHc as the most common etiology in 25% (10 patients) cases. This is less in comparison to the present study which could be due to patient population being of both genders and also including peripartum patients. Similarly in a recent study on arterial ischemic stroke found HHc to be quite significant (p < 0.001). Besides this in the patients of ischemic stroke the levels of vitamin B12 and folate were also significantly associated positively and negatively with lower and higher or normal levels of homocysteine, respectively, and there was a strong inverse correlation of plasma HCC with plasma folate concentration, while there was a weak association with serum vitamin B<sub>12</sub> or vitamin B<sub>6</sub> levels in the present study.

The authors found factor V Leiden mutation as the commonest hereditary prothrombotic state while antiphospholipid antibody (APLA) syndrome is the commonest acquired prothrombotic state, in contrary to our observation of protein C deficiency in two patients in comparison to one patient of factor V Leiden mutation, and protein S deficiency each, which could be because of differences in gender, geography, and arterial vs venous thrombosis. Furthermore, the APLA syndrome was found to be the commonest acquired prothrombotic state in the study contrary to no such finding in our study. We in our study found the various risk factors as hyperhomocysteinemia in seven (17.5%), alcoholism in seven (17.5%), polycythemia in two (5%), trauma in two (5%), dehydration in two (5%), and protein S deficiency in one (2.5%) patients.

A paragraph comprising “All patients with neuroimaging suggestive of thrombosis in venous sinuses with age >18 years. Patients of acute myocardial infarction, other patients of stroke who may have raised homocysteine levels. After taking a detailed clinical” the meaning of this is unclear or an erratum.

So the take-home message of this correspondence is that malnutrition in form of vitamin B<sub>12</sub>, folate, and B<sub>6</sub> be taken care of as a national program and there should be free test facilities for all these investigations.

REFERENCES


Myth or Fact: Diet in Jaundice

Rudrajit Paul1, Rathindranath Sarkar2
1Consultant Physician, Ruby General Hospital; Ex-professor and Head, Department of Medicine, Medical College Kolkata, Kolkata, West Bengal, India

Sir/Madam,

Diet in various diseases is a controversial issue and patients are often bewildered by the multitude of “advice” and “expert opinion” in circulation. Many of these are not based on scientific evidence and actually can harm the patient. Jaundice or liver disease is one such area where the composition of a proper diet is often debated.

COMMON PUBLIC KNOWLEDGE

Whenever someone has jaundice, the diet must be changed drastically. All oil in food must be eliminated and the patient must eat only boiled vegetables. The patient needs to consume a lot of sugar. Also, turmeric must be absent from cooked food.

SCIENTIFIC ARGUMENT

Diet in jaundice is a contentious issue and sadly, there are a lot of pseudosciences involved in it. The concept of turmeric elimination from food obviously came due to the yellow color of turmeric. But there is no scientific evidence of the relation between turmeric and worsening of liver disease. If anything, curcumin in turmeric reduces liver inflammation and upregulates antioxidant pathways.1

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Curcumin has also been shown to have protective effects against hepatotoxins. Thus, if anything, turmeric is a desirable addition to the diet in patients with jaundice.

The idea of eliminating fat from the diet in jaundice is also controversial. In obstructive jaundice, of course, fat should be minimized as bile flow is obstructed and hence, micelle formation is reduced. Most of the dietary fat is undigested in such cases and this causes steatorrhea or colonic discomfort. Moreover, some animal studies have shown that excess dietary fat can have direct hepatotoxic effect in biliary obstruction.

But in other cases, especially prehepatic jaundice, there is no justification of fat restriction in diet. Fat makes food palatable. Patients with liver disease have anorexia to start with. Further advice of bland fat-free diet makes eating even more repulsive. In patients with risk of pigment gallstones (like hemolytic anemia), a low-fat diet is recommended in order to reduce chances of gallstone formation. But it must be remembered that the relation between dietary fat and gallstones is still not conclusively established. Thus, reducing fat in diet may or may not help in prevention of gallstone formation.

Similarly, high sugar diet may also cause nausea and has not been shown to be beneficial unless the patient has episodes of hypoglycemia. Thus, there is no justification of adding excess sugar to a normal diet in jaundice.

But an internet search of English literature revealed that there is a surprising lack of proper scientific evidence on diet in hepatic diseases. In absence of scientific data, the void is filled with various pseudoscientific articles. A google search of “jaundice+diet” or “liver+diet” returns search results filled with information from questionable sources like health magazines, media houses of questionable authenticity, and self-declared health advisors. Proper randomized trials are necessary for answering this query.

According to the website of the British Liver Trust, a normal diet should be maintained in acute hepatitis, fasting should be avoided and high-energy diet may be needed if there is significant weight loss. Also, small frequent meals are preferred rather than one or two large meals.

**Conclusion**

There is no justification of omitting turmeric from diet. Low-fat diet is necessary in obstructive jaundice. But for other types, fat content does not affect recovery unless the patient is taking very high amounts of fat.

**References**


**Study of Diversity of Metformin Related Gastrointestinal Side Effects**

Shivabalłam Kathavarayan Ramu¹, Praveen², Ankith³, Kiran Yadav⁴

¹Senior Resident, ²–⁴Junior Resident, Mahatma Gandhi Medical College and Research Institute, Puducherry, Puducherry, India

Sir,

We read with great interest the article titled “Study of Diversity of Metformin Related Gastrointestinal Side Effects” written by Saluja et al. The authors have to be lauded for having studied about a quite common but clinically relevant scenario encountered by physicians almost in most of the outpatient departments. Although it was a very well analyzed and written article, we have a few queries and comments such as:

- The patients who were intolerable to the side effects of the drug metformin were changed to some other antidiabetic drug of different class. This was taken into account yes but what about changing the short-acting formulation of metformin into a sustained release formulation which would have subsided the symptoms soon without the need for changing to yet another completely different group of drugs.

Kim et al. showed that treatment with extended-release metformin was well tolerated, with 97.4% of patients completing 12 weeks of treatment. Only 3.3% of patients experienced one or more gastrointestinal (GI) side effects and only 0.7% of patients discontinued for this reason (primary endpoint). The incidence of GI side effects and related discontinuations appeared to be considerably lower during short-term extended-release therapy than during previous treatment (mean 2.71 years’ duration), most commonly with immediate-release metformin. A similar kind of stratification could have been used in the author’s study to have a clearer view on safety profile depending on the formulation used.

- Patients could have also been stratified based on the dosage of the drugs used which could have also provided a profile on the dose-related side effects on the GI system.

- p value or the confidence interval could have been obtained using analysis of variance test for the objectification of the findings to prove a statistically significant relation.

**Reference**


**Study of Adverse Events following COVID-19 Vaccination: A cross-sectional Survey in India**

Amey Kundawar¹, Chinmay O Guralwar², Smita Sontakke³

¹Medical Intern, King Edward Memorial Hospital and Seth Gordhandas Sunderdas Medical College, Mumbai; ²Medical Intern, Government Medical College and Hospital Nagpur; ³Associate Professor, Department of Pharmacology, Government Medical College and Hospital Nagpur, Nagpur, Maharashtra, India

Sir,

Coronavirus disease of 2019 (COVID-19), caused by the novel coronavirus strain severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has caused havoc across the world. Vaccines are probably the most important public health measure and most effective strategy to protect the population from COVID-19. Covishield (AstraZeneca’s vaccine manufactured by Serum Institute of India) and Covaxin (manufactured by Bharat Biotech Limited) have been granted emergency use authorization by the Central Drugs Standard Control Organization in India. There are a lot of published studies on the efficacy of these vaccines but little is known about adverse events following vaccination outside of clinical trial data. An Indian study evaluating symptoms following the first dose of the COVID-19 vaccine found that 65.9% of respondents reported at least one postvaccination symptom. No comparison between adverse events after
Covishield and Covaxin vaccine administration has been reported so far. Hence, this study was planned to determine the incidence of adverse events experienced by participants post-COVID-19 vaccination and compare adverse events in participants receiving Covishield and Covaxin. This was a cross-sectional, questionnaire-based study carried out in persons of either gender, above 18 years of age who had received at least one dose of any of the two COVID-19 vaccines (Covishield or Covaxin). Information was gathered using a self-designed, pretested, semi-structured questionnaire in the form of a Google Form which was shared via the internet to participants meeting the selection criteria.

Our study population consisted of 565 participants with a mean age of 36.66 ± 17.01 years. Covaxin vaccine was received by 128 (22.6%) participants while 437 (77.3%) participants had received Covishield vaccine. There were 309 (54.6%) females and 256 (45.4%) males. Forty-five (8%) of the participants were rural residents and 520 (92%) were urban residents. Out of the total sample of 565 participants, 76 (13.4%) participants had a history of infection with SARS-CoV-2 before vaccination and 354 (62.6%) participants experienced adverse events postvaccination. The number of participants who experienced adverse events after Covishield (299, 68.4%) were significantly higher when compared to those who experienced adverse events after Covaxin (55, 42.9%) (p = 0.0000001).

Table 1 shows that pain at the injection site was the most common adverse event. Although significantly more participants over the age of 50 reported experiencing pain at the injection site compared to the participants under the age of 50 (p = 0.001), majority of the adverse events including malaise (p < 0.001), fatigue (p < 0.001), fever (p = 0.005), and headache (p = 0.002) were experienced more by participants under the age of 50 and this difference was statistically significant.

Considering the type of vaccine, significantly more participants in the Covaxin group (94.5%) reported pain at the injection site compared to 77.6% in Covishield group (p = 0.009) while malaise (p = 0.005), fever (p < 0.001), body ache (p = 0.002) headache (p = 0.037), and insomnia (p = 0.016) were reported by significantly more number of participants receiving Covishield vaccine (Table 1).

Out of the participants who reported a history of infection with SARS-CoV-2 before vaccination 92.5% (49) experienced pain at the injection site compared to 77.6% in Covishield group (p = 0.005) while malaise (p = 0.005), fever (p < 0.001), body ache (p = 0.002) headache (p = 0.037), and insomnia (p = 0.016) were reported by significantly more number of participants receiving Covishield vaccine (Table 1).

In our study of 565 participants who received the first dose of either Covaxin or Covishield vaccine, 343 (60.7%) participants reported experiencing adverse events while 130 (23.2%) participants out of the 349 participants who had received the second dose of either of the vaccines reported experiencing adverse events and this difference was statistically significant (p = 0.0000001). Adverse events like malaise, fatigue, fever, body ache, headache, joint pain, and decreased appetite were experienced by statistically significantly more participants after the first dose of vaccine than after the second dose.

In both the groups onset of adverse events was between 1 and 24 hours after vaccination in majority of the participants (50.9% in Covaxin and 86.2% in Covishield).

Duration (mean ± standard deviation) of adverse events after Covishield (2.27 ± 3.92 days) was significantly more than that after Covaxin (2.07 ± 1.20 days) (p < 0.0000001). Day-to-day activities were affected in significantly more number of participants in the Covishield group (57.8%) compared to Covaxin (32.7%) (p = 0.0004).

Table 1: Adverse events stratified by age, vaccine type, and history of infection with SARS-CoV-2 before vaccination

<table>
<thead>
<tr>
<th>Adverse events</th>
<th>Number of participants (n = 354)</th>
<th>Age, n (%)</th>
<th>p-value</th>
<th>Vaccine, n (%)</th>
<th>p-value</th>
<th>Previously detected for COVID-19, n (%)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>&lt;50 (n = 294)</td>
<td>&gt;50 (n = 60)</td>
<td>Covaxin (n = 55)</td>
<td>Covishield (n = 299)</td>
<td>No (n = 300)</td>
<td>Yes (n = 54)</td>
</tr>
<tr>
<td>Pain at the injection site</td>
<td>248, (84.3)</td>
<td>59, (98.3)</td>
<td>&lt;0.001*</td>
<td>52, (94.5)</td>
<td>232, (77.6)</td>
<td>0.0098*</td>
<td>235, (78.3)</td>
</tr>
<tr>
<td>Redness/swelling/itching at the injection site</td>
<td>48, (16.3)</td>
<td>4, (6.6)</td>
<td>0.052</td>
<td>7, (12.7)</td>
<td>45, (15.0)</td>
<td>0.602</td>
<td>40, (13.3)</td>
</tr>
<tr>
<td>Malaise</td>
<td>157, (53.4)</td>
<td>16, (26.6)</td>
<td>&lt;0.001*</td>
<td>18, (32.7)</td>
<td>155, (51.8)</td>
<td>0.005*</td>
<td>138, (46.0)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>193, (65.6)</td>
<td>25, (41.6)</td>
<td>&lt;0.001*</td>
<td>32, (58.2)</td>
<td>186, (62.2)</td>
<td>0.419</td>
<td>180, (60.0)</td>
</tr>
<tr>
<td>Fever</td>
<td>192, (65.3)</td>
<td>28, (46.6)</td>
<td>0.005*</td>
<td>19, (34.5)</td>
<td>201, (67.2)</td>
<td>&lt;0.0018*</td>
<td>180, (60.0)</td>
</tr>
<tr>
<td>Body ache</td>
<td>170, (57.8)</td>
<td>29, (48.3)</td>
<td>0.154</td>
<td>21, (38.2)</td>
<td>178, (59.5)</td>
<td>0.0028*</td>
<td>164, (54.6)</td>
</tr>
<tr>
<td>Headache</td>
<td>125, (42.5)</td>
<td>13, (21.6)</td>
<td>0.002*</td>
<td>15, (27.3)</td>
<td>123, (41.1)</td>
<td>0.037*</td>
<td>113, (37.6)</td>
</tr>
<tr>
<td>Nausea/vomiting</td>
<td>26, (8.8)</td>
<td>1, (1.6)</td>
<td>0.055</td>
<td>3, (5.5)</td>
<td>24, (8.0)</td>
<td>0.479</td>
<td>20, (6.6)</td>
</tr>
<tr>
<td>Joint pain</td>
<td>50, (17.0)</td>
<td>8, (13.3)</td>
<td>0.469</td>
<td>5, (9.1)</td>
<td>53, (17.7)</td>
<td>0.097</td>
<td>45, (15.0)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>10, (3.4)</td>
<td>4, (6.6)</td>
<td>0.242</td>
<td>2, (3.6)</td>
<td>12, (4.0)</td>
<td>0.866</td>
<td>13, (4.3)</td>
</tr>
<tr>
<td>Runny nose</td>
<td>6, (2.0)</td>
<td>2, (3.3)</td>
<td>0.545</td>
<td>1, (1.8)</td>
<td>7, (2.3)</td>
<td>0.790</td>
<td>7, (2.3)</td>
</tr>
<tr>
<td>Cough</td>
<td>8, (2.7)</td>
<td>5, (8.3)</td>
<td>0.036*</td>
<td>0, (0)</td>
<td>13, (4.3)</td>
<td>0.110</td>
<td>11, (3.6)</td>
</tr>
<tr>
<td>Sore throat</td>
<td>12, (4.0)</td>
<td>5, (8.3)</td>
<td>0.165</td>
<td>1, (1.8)</td>
<td>16, (5.3)</td>
<td>0.247</td>
<td>14, (4.6)</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>9, (3.0)</td>
<td>1, (1.6)</td>
<td>0.547</td>
<td>1, (1.8)</td>
<td>9, (3.0)</td>
<td>0.605</td>
<td>9, (3.0)</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>42, (14.2)</td>
<td>5, (8.3)</td>
<td>0.209</td>
<td>3, (5.5)</td>
<td>44, (14.7)</td>
<td>0.055</td>
<td>38, (12.6)</td>
</tr>
<tr>
<td>Insomnia</td>
<td>26, (8.8)</td>
<td>2, (3.3)</td>
<td>0.149</td>
<td>0, (0)</td>
<td>28, (9.3)</td>
<td>0.016*</td>
<td>22, (7.3)</td>
</tr>
<tr>
<td>Allergic rash</td>
<td>5, (1.7)</td>
<td>1, (1.6)</td>
<td>0.980</td>
<td>2, (3.6)</td>
<td>4, (1.3)</td>
<td>0.239</td>
<td>5, (1.6)</td>
</tr>
<tr>
<td>Weakness in limbs</td>
<td>7, (2.3)</td>
<td>1, (1.6)</td>
<td>0.734</td>
<td>0, (0)</td>
<td>8, (2.6)</td>
<td>0.220</td>
<td>8, (2.6)</td>
</tr>
</tbody>
</table>

Figures in parentheses indicate percentage; *Figures in bold indicate significant p-value (<0.05) by Chi-square test.
To conclude, higher number of participants who received Covishield experienced adverse events compared to those who received Covaxin. Participants under the age of 50 experienced more adverse events. Adverse events such as malaise, fever, body ache, headache, and insomnia were reported more by participants receiving the Covishield vaccine. Pain at the injection site and malaise were reported by significantly more participants who reported a history of infection with SARS-CoV-2 before vaccination. A greater number of participants experienced adverse events after the first dose compared to the second dose of the vaccine.

**References**


Angiopoietin-like 3 Inhibition: New Kid on the Block?

Rakesh Agarwal
University of Adelaide/Adelaide Medical School and The Lyell McEwin Hospital Adelaide, Australia

Despite advances in the development of lipid-lowering therapies, the need of agents to achieve optimal baseline lipid levels remains unmet. Even after currently recommended medical therapy, substantial risk for cardiovascular disease persists. Recent approval of proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors has added to our armamentarium in the war against dyslipidemia, despite there being concerns about cost and lack of data demonstrating their use to reduce cardiovascular disease events.

Angiopoietin-like 3 (ANGPTL3), a secreted protein expressed in the liver increases plasma triglyceride (TG), low-density lipoprotein cholesterol (LDL-C), and high-density lipoprotein cholesterol (HDLC) levels. It regulates lipid metabolism by inhibiting the lipolysis of TG-rich lipoproteins. Recent evidence suggests inhibition of ANGPTL3 by antibodies (evinacumab) or antisense oligonucleotides (ASOs) could lead to significantly reduced levels of TG, LDL-C, non-HDL-C, very low-density lipoprotein cholesterol (VLDL-C), and apolipoprotein B levels. This translates into a reduced coronary artery disease risk, improved insulin sensitivity, and favorable effects in subject with genetic disorders like familial hypercholesterolemia.

The DiscovEHR study showed that heterozygous loss of function variants of ANGPTL3 had significantly lower levels of TG, HDL-C, and LDL-C compared to participants without these variants. Dyslipidemic mice treated with evinacumab, an ANGPTL3 inhibitor, had greater decrease in atherosclerotic lesion area and necrotic content than those treated with a control antibody. Evinacumab caused reductions in fasting TG levels up to 76% and LDL-C levels up to 23% in humans. This effect was dose-dependent.

Graham et al. evaluated ASOs targeting ANGPTL3 mRNA in a recent study. Treated mice showed reduced TG and LDL levels as well as reduced liver TG content and atherosclerosis progression. Insulin sensitivity also increased. Human volunteers receiving ASOs had dose-dependent reduction in TG levels (33.2–63.1%), LDL-C (1.3–32.9%), VLDL-C (27.9–60%), non-HDL-C (10–36.6%), apolipoprotein B (3.4–25.7%), and apolipoprotein C-II (18.9–58%). Favorable effects of evinacumab have also been demonstrated in patients with homozygous familial hypercholesterolemia with substantial reductions in LDL-C and TG levels. These effects were in addition to already achieved reduced baseline levels with aggressive lipid-lowering therapy.

**References**


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**Composition:** Each Olmesar 10/20/40 tablet contains Olmesartan 10/20/40mg. **Indication:** Hypertension. **Dosage:** Adult: 20 mg once daily when used individually, increase to 40 mg after 2 weeks of therapy if required. Children (age of 6 to 16 years): 10 mg once daily for patients who weigh 20 to < 35 kg or 20 mg once daily for patients who weigh ≥ 35 kg. Increase to a maximum of 20 mg for patients who weigh < 35 kg or 40 mg once daily for patients who weigh ≥ 35 kg after 2 weeks of therapy if required. **Contraindications:** Hypersensitivity to Olmesartan, co-administration with aliskiren in diabetic patients, 2nd and 3rd trimester of pregnancy, biliary obstruction. **Special Precautions:** Assess renal function, BP & volume status during initiation of therapy & dose escalation periodically thereafter. Use with caution in elderly. Children < 1 year of age must not receive Olmesartan for hypertension. In patients whose renal function may depend on activity of the renin-angiotensin-aldosterone system (e.g., patients with severe CHF), treatment may be associated with oliguria &/or progressive azotemia, rarely resulting in acute renal failure &/or death. Symptomatic hypotension may be anticipated after initiation of treatment in patients with an activated renin-angiotensin system, such as volume &/or salt-depleted patients. In patients with unilateral or bilateral renal artery stenosis, increases in serum creatinine or BUN may occur. **Adverse Drug Reactions:** most commonly observed adverse reaction is Hyperuricemia, Dizziness, Headache other ADRs may be: Rhinitis, Pharyngitis, Cough, Pain, Angioedema, Pruritus, Rash, Uricinca, Hyperkalemia, Hypotension & Muscle spasm. Full prescribing information is available on request.
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