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Sepsis definition has undergone quantum shift over the last 3 decades. From using host systemic inflammatory response syndrome (SIRS) to identify sepsis, we have now moved to define sepsis as a life-threatening organ dysfunction due to dysregulated host response to infection. More importantly predicting mortality in sepsis has been a challenge and continues to remain a challenge due to the heterogeneity of patients and also the various scoring systems used.

Through the various definitions and criteria used Sepsis-1 was developed using SIRS criteria. Four SIRS criteria were defined, namely tachycardia (heart rate >90 beats/min), tachypnea (respiratory rate >20 breaths/min), fever or hypothermia (temperature >38 or <36°C), and leucocytosis or leukopenia (white blood cells >12000/mm³ or <4000/mm³). Patients who met two or more of these criteria fulfilled the definition of SIRS and sepsis was defined as infection of suspected infection leading to SIRS. The SIRS concept had its validity challenged over the next decade because of onset of inflammation in absence of infection like pancreatitis, burns, and other disease processes. A 2001 task force led by Levy et al. identified this, however, due to lack of alternate evidence-based criteria, same definition was continued but they expanded the list of diagnostic criteria thus giving rise to Sepsis-2 criteria.

It was in 2016 Society of Critical Care Medicine and European Society of Intensive Care Medicine relooked at criteria to identify sepsis and compared SIRS to other methods like logistic organ dysfunction score (LODS) and sequential organ failure assessment (SOFA) score. The authors concluded that SOFA score was more predictive in assessing the severity of organ dysfunction in a septic patient. The predictive value for in hospital mortality of septic patients was more with SOFA (10%) as compared to SIRS. They also concluded that LODS and SOFA had similar prediction capacity, however, due to its ease of calculation SOFA was recommended. They further concluded that lack of complete variables of SOFA and complexity of method may result in late recognition of sepsis, hence a simplified method quick SOFA (qSOFA) was introduced for early and ease of identification. Quick SOFA consisted of three variables: hypotension—systolic blood pressure <100 mm Hg, altered mental status, and tachypnea—respiratory rate >22/min. A qSOFA of ≥2 predicted organ dysfunction.

The simplified definition came with its own criticism. William et al. very eloquently demonstrated the lack of sensitivity of qSOFA in identifying early sepsis, a stage in which the treatment is most effective. This qSOFA cannot be relied upon as a screening tool for patients presenting to hospital. However, it could still be useful in patients who are admitted to hospital with suspected sepsis. Moving from an inflammatory-based definition in Sepsis-1 and -2 to a more syndromic-based definition in Sepsis-3 we have certainly made the diagnostic criteria wide. The term organ dysfunction in new Sepsis-3 criteria still remains a difficult one to understand as many organs have more than one function and also the inappropriate host response how to measure that. With these lacunas in the definition its ability to predict mortality also becomes varied. In 2017 Raith et al. performed a retrospective analysis of 184,875 patients admitted to Australian and New Zealand intensive care units (ICUs) with primary infection-related diagnosis. They compared the increase in SOFA, SIRS, and qSOFA by two or more points, respectively, and looked at the patient’s outcomes. The study was conducted in 182 ICUs from 2000 to 2015. They concluded that SOFA had a greater accuracy in prognosticating mortality in admitted ICU adult patients as compared to SIRS or qSOFA. When compared between SIRS and qSOFA they found that SIRS was better in prediction of in hospital mortality.

In this edition, Bhattacharya et al. have attempted to compare ability of SIRS, SOFA, and qSOFA in predicting mortality in sepsis. To conduct a prospective study looking at predictability of SIRS, SOFA, and qSOFA in ICU patients is very challenging technically and logistically, due to the complexity of collecting data, presentation of patient directly to hospital, or been referred from a peripheral center and previous treatment received have all been shown to influence the sepsis outcomes. The authors must be commended for this. The authors have used the Sepsis-2 definition of severe sepsis and septic shock and correlated it to sepsis and septic shock by the Sepsis-3 definition. We are well aware of the limitation of comparison as on looks at the inflammatory syndrome and the Sepsis-3 looks at dysregulated response and organ dysfunction. This has resulted in a very complex interpretation of sepsis, severe sepsis, and septic shock patients. If we take the current Sepsis-3 definition then only 96 of the total 122 patients (78.6%) fulfill the Sepsis-3 criteria. This emphasized that identification of sepsis could have been done using the current definition only. One of the important study findings is the distribution of septic patients as per etiology of sepsis. Scrub typhus was 30.32% followed by pneumonia 25.41% and urinary tract infection 17.21%. The overall mortality was 61/122 (50%), which is a bit higher than most studies. However, the important point to note is scrub typhus patients forming more than 30% of total sample size. Scrub typhus is a tropical infection, while its prevalence in Indian subcontinent is well documented it is difficult to interpret or predict mortality in this group of patients as none of the criteria SIRS, SOFA, or qSOFA ever had such a large population of tropical infections in their validation studies. Hence the applicability of these scores in this population of patients is unique and probably requires further studies. Also, deep diving into the mortality data reveals 78% mortality in septic shock patients and 32% in severe sepsis patients. This is due to the two different definitions used to identify sepsis.

The ability of SIRS, SOFA, and qSOFA to predict mortality is well appreciated and comparable to some of the other studies in literature. The highest area under the receiver operating characteristic curve in predicting mortality is the SOFA score followed by the qSOFA and SIRS scores. The highest sensitivity was seen for SIRS score >2 (91.80%) with the highest specificity for a SOFA score on the second day after admission >12 (83.61%). They have very clearly demonstrated that predication of mortality by SOFA is most specific followed by qSOFA and SIRS is highly sensitive but specificity is very poor.
Where do we go from here is the big question? While studies have clearly shown SOFA to be superior and specific in predicting mortality, the complexity and several variable availability remain the limiting factor in measuring SOFA in every patient. With qSOFA we do have limited ability to diagnose sepsis in its early stage when the treatment is most effective. It is very clear that SIRS has lost steam due to its poor specificity. Also in a heterogeneous patient population like India where tropical diseases form a major chunk of admissions, how justified are we in using the sepsis definition, which was never tested against such group of patients.

I believe we in the subcontinent will have to conduct studies in our patient population, just like Bhattacharya et al. and come out with our very own sepsis definition and mortality prediction model. I am confident with the large pool of patients we have across the country, such a study would be a landmark in identification of sepsis and predicting mortality.

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**References**

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Comparison of Systemic Inflammatory Response Syndrome, Sequential Organ Failure Assessment, and Quick Sequential Organ Failure Assessment Scores to predict Mortality in Sepsis

Prasanta Kumar Bhattacharya1, Subrahmanya Murti V2, Md Jamil3, Bhupen Barman4, Patrick SR Marak5

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ABSTRACT

Objectives: Sepsis-3 criteria define sepsis as ≥2 points rise of Sequential Organ Failure Assessment (SOFA) score, either from zero or a known baseline. We compared the efficacies of quick Sequential Organ Failure Assessment (qSOFA), SOFA, and Systemic Inflammatory Response Syndrome (SIRS) scores to predict sepsis mortality.

Methods: Prospective, hospital-based study was undertaken to determine the efficacies of various sepsis-scoring systems to predict mortality in sepsis. The “Sepsis-2” criteria of “severe sepsis” and “septic shock” were used as selection criteria as they correspond to “sepsis” and “septic shock” of “Sepsis-3”. Statistical analysis was done by SPSS Statistics version-16. Mortality predictions were made using receiver operator characteristic curve testing.

Results: We included 122 sepsis patients diagnosed by “Sepsis-2” definition; 78.68% (n = 98) of whom met “Sepsis-3” criteria for sepsis. All-cause mortality was 50%. On univariate analysis, we found age over 60 years (odds ratio (OR) = 4.244, 95% confidence interval (CI) = 1.309–13.764, p = 0.016), invasive mechanical ventilation (OR = 7.0076, 95% CI = 3.053–16.0809, p < 0.0001), and presence of acute respiratory distress syndrome (ARDS) (OR = 2.757, 95% CI = 1.0091–7.535, p = 0.048) were significant predictors of mortality. The SOFA score yielded the best result with area under the curve (AUC) of “receiver operating characteristic” (ROC) curve of 0.868. On comparing AUCs between these scores difference between both SOFA and qSOFA was highly significant (p < 0.0001) compared to SIRS. However, such statistical difference was not found between AUCs of SOFA and qSOFA.

Conclusions: Both SOFA and qSOFA are superior prognostication tools compared to SIRS to predict sepsis mortality; SOFA being better than qSOFA.

Introduction

Sepsis, a severe form of organ dysfunction resulting from altered host response to sepsis, is an important healthcare problem, affecting millions of people globally.1 Being a medical emergency, initiation of therapy within half an hour of presentation to the healthcare facility is shown to positively influence the outcome.2 Besides, in the survivors, the long-term sequelae of sepsis have significant health care and social implications.3 So prompt and accurate diagnosis, triage, and treatment initiation of sepsis in the emergency room are very important.

In the last 3 decades the diagnostic criteria of sepsis have been revised many times due to lack of consensus in arriving at some definite diagnostic yardstick.4,5 The recent “Sepsis-3” guidelines include only two entities, namely “sepsis” and “septic shock” for its diagnosis, and the qSOFA score, comprising several clinical parameters, is to be used as an initial triage tool.3 However, there has been considerable debate as to which of these scores is superior, with various studies showing evidence in favor of either.6–19

In this background, this work was carried out to find out the efficacy of the qSOFA and SOFA scores as compared to the SIRS score alone in predicting mortality in sepsis.

Methods

This observational study was carried out in the internal medicine department of a teaching medical institute from January 2017 to June 2018. The definitions of “severe sepsis” and “septic shock” from the “Sepsis-2” guidelines1 were used as the background as they roughly correspond to “sepsis” and “septic shock” of the “Sepsis-3” guidelines.5

Definitions

Sepsis-2 definitions of “severe sepsis” and “septic shock” as per Dellinger et al.1 are:

Systemic Inflammatory Response Syndrome: presence of ≥2 of the following1:

• Fever (oral temperature >38°C) or hypothermia (<36°C);
• Respiratory rate >24/min;
• Heart rate >90/min;
• Leukocyte count <4000/µL or >12,000/µL, or presence of >10% band forms.

Severe sepsis: Presence of SIRS together with organ dysfunction or tissue hypoperfusion due to sepsis, including any of the following:

• Increased lactate level above normal;
• Oliguria with urine output <0.5 mL/kg/hr for >2 hours even after adequate fluid replacement;
• Acute lung injury:
  • PaO2/FiO2 <250 in absence of pneumonia as the source of infection;
  • PaO2/FiO2 <200 if pneumonia is the source of infection;
• Serum creatinine >2.0 mg/dL;
• Serum bilirubin >2 mg/dL;
• Thrombocytopenia (platelet count <100,000/µL);
• Coagulopathy (International Normalized Ratio > 1.5);
• Sepsis-induced hypotension:
  • Systolic blood pressure (SBP) <90 mm Hg;
  • Fall in SBP, either >40 mm Hg or <2 standard deviations below normal for age in the absence of other causes of hypotension;
  • Mean arterial pressure (MAP) <70 mm Hg;
• Sepsis-induced tissue hypoperfusion: infection-induced hypotension, elevated lactate, or oliguria.

Septic shock: Persistent hypotension due to sepsis in spite of adequate fluid replacement for at least 1 hour, or the requirement for vasopressors to maintain SBP ≥90 mmHg or MAP ≥70 mmHg.

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Sepsis-3 definition:
Sepsis: Life-threatening organ dysfunction due to abnormal host response to infection.

- Sepsis clinical criteria: Organ dysfunction ≥2 points increase in SOFA score;
- A bedside qSOFA (“HAT”) ≥2 can identify patients with suspected infection who are likely to have a prolonged intensive care unit (ICU) stay or in-hospital mortality, where “HAT” stands for:
  - Hypotension: SBP ≤100 mmHg;
  - Altered mental status: A Glasgow Coma Scale score < 15;
  - Tachypnoea: Respiratory rate greater than or equal to 22.

Septic shock: Subset of sepsis with underlying circulatory and cellular/metabolic abnormalities sufficiently severe to increase mortality significantly.

- Septic shock clinical criteria: Sepsis and presence of the following in spite of adequate volume replacement:
  - Persistent hypotension requiring vasopressors to maintain a MAP ≥65 mm Hg, and
  - Lactate ≥2 mmol/L.

### Inclusion Criteria

Patients aged 18 years and above, admitted to the internal medicine department with the diagnosis of “severe sepsis” and/or “septic shock” as defined by Dellinder et al.1 were included.

### Exclusion Criteria

Patients with pre-existing immune-compromised states like advanced malignancy, human immunodeficiency virus infection, and chronic kidney disease were excluded.

### Ethical Clearance

Ethical clearance was obtained from the Institutional Ethics Committee and written informed consent was taken from all the subjects included in the study.

On admission to the emergency room all patients with presumptive sepsis were identified based on SIRS score ≥2 or a qSOFA score ≥2. All such patients with presumptive sepsis were then subjected to routine laboratory investigations and standard of ICU care as per individual requirements of each case to reach a diagnosis of “severe sepsis” or “septic shock” as per “Sepsis-2” criteria.1 Further, all patients also underwent concomitant SOFA scoring on admission and thereafter daily to identify patients who satisfied the “Sepsis-3” criteria of “sepsis” and “septic shock”. Patients were followed up for the entire length of hospital stay, as regards ventilator requirement and its duration, and mortality.

### Statistical Analysis

Statistical analysis was done using the SPSS statistical software, version 16. Tables were made using Microsoft Word 2016. Mortality predictions were made using ROC curve testing. Categorical variables were analyzed by the Chi-square test.

### Results

Our study comprised 122 patients, with 73 (59.8%) males and a female: male ratio of 1:1.5. The mean and median ages of the study population were 42.91 ± 17.60 and 46 years, respectively. Forty-seven patients had “septic shock” and the remaining 75 had “severe sepsis” based on “Sepsis-2” criteria. Further, 49 out of 75 patients of “severe sepsis” (by “Sepsis-2” criteria) were also in “sepsis” (by “Sepsis-3” criteria); and all 47 patients of “septic shock” (“Sepsis-2” criteria) also fulfilled all the criteria for “septic shock” (“Sepsis-3” criteria). Further, 96 of the 122 (78.6%) patients were in “sepsis” or “septic shock” by “Sepsis-3” criteria.

Table 1 shows the etiologies and clinical characteristics in sepsis. The common etiologies for sepsis were scrub typhus (30.32%), pneumonia (25.41%), and urinary tract infections (17.21%) in order of frequency. The average hospital stay was higher in septic shock compared to sepsis (9.53 ± 2.62 vs 5.81 ± 1.85 days). The proportion of patients developing hypotension (100 vs 38.7%), those on vasopressor support (100 vs 46.6%), those receiving ventilator support (100 vs 37.3%) and hemodialysis treatment (38.3 vs 10.6%) was highest among septic shock patients compared to severe sepsis.

In-hospital death occurred in 61 of the 122 patients with sepsis, with an overall mortality of 50%. Among the 47 patients with septic shock, 37 expired leading to a mortality of 78.72%, while among the 75 patients with severe sepsis, 24 expired leading to a mortality of 32%. Thus, the mortality in “septic shock” was significantly higher than in “severe sepsis” (78.7 vs 32%, p < 0.05). On univariate analysis, age greater than 60 years (OR = 4.244, 95% CI = 1.309–13.764, p = 0.016), invasive mechanical ventilation (OR = 7.0076, 95% CI = 3.053–16.0809, p < 0.0001), and presence of ARDS (Berlin definition) (OR = 2.757, 95% CI = 1.0091–7.535, p = 0.048) could significantly predict mortality.

The median qSOFA and SIRS scores on admission were 2 and 3, respectively. The mean SOFA scores were 11.19 ± 2.89 on admission and 12.87 ± 3.27 on second day after admission. Table 2 shows the SIRS and qSOFA scores based on mortality. Table 3 shows the data from the ROC curves for all three scoring systems in predicting mortality. The highest AUC in predicting mortality is of SOFA score followed by qSOFA and SIRS scores. The highest sensitivity is seen for a SIRS score ≥2 (91.80%) with the highest specificity for a SOFA score on the second day after admission ≥12 (83.61%). On comparing the AUCs between scores the difference between both SOFA and qSOFA compared to SIRS is highly significant (p < 0.0001). However, the difference between AUCs of SOFA and qSOFA is not statistically significant (Table 3). This suggests that prediction of mortality by the SOFA score is the most specific, followed by the qSOFA score. The SIRS score, on the other hand, is highly sensitive for predicting mortality although its specificity is poor. The ROC curves for all scores are shown in Figure 1.

### Discussion

In present study we enrolled 122 patients with sepsis diagnosed as per the laid down criteria. The mean and median ages of the study population were 42.91 ± 17.60 and 46 years, respectively, with 85.24% patients below the age of 60. These are lower than that found in other studies, where the mean age ranged between 60 and 65 years.21-25 The higher incidence of younger patients in our study could be due to the etiology of sepsis in our study, with scrub typhus, which is found commonly in younger people, being the cause of sepsis in 30% of cases. Prevalence of scrub typhus is reported to be high in northeast India,26-29 where the current study has also been undertaken. The overall mortality in sepsis in our study was 50%. While the mortality was 32% in severe sepsis, it was significantly higher (78.72%) in septic shock (p < 0.05). Several studies23,30-33 have also found an overall high mortality in sepsis, ranging from 24 to 67%, with 40% mortality from severe sepsis. Our study follows the higher mortality trend as seen in other studies carried out in India (55–67%),23,30 which is much higher than in the industrialized countries.31-33 This difference could be due to several factors: first, protocol-based management of sepsis is not universally followed in India; second, delay in reaching healthcare setup compared to industrialized countries; third, higher proportion of sepsis due to tropical infection has different outcomes compared to bacterial sepsis.

In our study ARDS and ventilator use were associated with a significantly increased mortality (p < 0.05). While there have been reports that ARDS did not alter the outcome of patients with sepsis,34 several studies35-37 have concluded that ARDS worsens the prognosis. Eggimann et al. in their study showed that...
SIRS, although, there was no clear distinction between the two in predicting “ventilator and organ dysfunction free-days.” Boulos et al.,<sup>16</sup> however, did not observe any clear distinction between the qSOFA and SIRS in terms of mortality prediction. However, a meta-analysis of 38 studies comprising over 385,000 subjects concluded that the specificity and sensitivity of qSOFA were moderate and poor, respectively, for predicting in-hospital mortality.<sup>6</sup> Further, the sensitivity with the SIRS criteria was superior to that of qSOFA.<sup>6</sup> Another meta-analysis<sup>7</sup> SIRS-based Sepsis-2 criteria vs the SOFA/qSOFA-based Sepsis-3 criteria in predicting prognosis in sepsis. Khwannimit et al.<sup>14</sup> have found that the SOFA score predicted sepsis-related organ failure and mortality more accurately as compared to SIRS. The study further showed that although >2 SIRS criteria were common in sepsis patients admitted in ICU, it had a poor outcome prediction.<sup>14</sup> Finkelsztein et al.<sup>15</sup> observed that qSOFA score before ICU admission could more accurately predict mortality and “ICU-free” days as compared to SIRS, although, there was no clear distinction between the two in predicting “ventilator and organ dysfunction free-days.” Boulos et al.<sup>16</sup> however, did not observe any clear distinction between the qSOFA and SIRS in terms of mortality prediction. ARDS in sepsis did not alter outcome.<sup>34</sup> In contrast, Sharif et al. have shown that mortality of patients of sepsis with ARDS exceeded 70%.<sup>35</sup> A systematic review also indicated the poor prognosis of ARDS in sepsis.<sup>36</sup> Irrespective of presence of ARDS, ventilator use also was found to be an independent risk factor for mortality in sepsis.<sup>30</sup> A study by Mohamed et al. has shown that invasive mechanical ventilation was an independent predictor of mortality in severe sepsis.<sup>30</sup>

There has been considerable discussion among doctors worldwide about the SIRS-based Sepsis-2 criteria vs the SOFA/qSOFA-based Sepsis-3 criteria in predicting prognosis in sepsis. Khwannimit et al.<sup>14</sup> have found that the SOFA score predicted sepsis-related organ failure and mortality more accurately as compared to SIRS. The study further showed that although >2 SIRS criteria were common in sepsis patients admitted in ICU, it had a poor outcome prediction.<sup>14</sup> Finkelsztein et al.<sup>15</sup> observed that qSOFA score before ICU admission could more accurately predict mortality and “ICU-free” days as compared to SIRS, although, there was no clear distinction between the two in predicting “ventilator and organ dysfunction free-days.” Boulos et al.<sup>16</sup> however, did not observe any clear distinction between the qSOFA and SIRS in terms of mortality prediction. However, a meta-analysis of 38 studies comprising over 385,000 subjects concluded that the specificity and sensitivity of qSOFA were moderate and poor, respectively, for predicting in-hospital mortality.<sup>6</sup> Further, the sensitivity with the SIRS criteria was superior to that of qSOFA.<sup>6</sup> Another meta-analysis<sup>7</sup>

### Table 1: Showing clinical characteristics of the patients with sepsis

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Severe sepsis (n = 75)</th>
<th>Septic shock (n = 47)</th>
<th>Total (n = 122)</th>
<th>p-value (severe sepsis vs septic shock) where applicable</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male sex, n (%)</td>
<td>47 (62.7)</td>
<td>26 (55.3)</td>
<td>73 (59.8)</td>
<td>0.4522</td>
</tr>
<tr>
<td>Mean length of stay (±standard deviation)</td>
<td>5.81 (±1.85)</td>
<td>9.53 (±2.62)</td>
<td>7.24 (±2.83)</td>
<td></td>
</tr>
<tr>
<td>Hypotension (SBP ≤ 90 mm Hg), n (%)</td>
<td>29 (38.7)</td>
<td>47 (100)</td>
<td>76 (62.3)</td>
<td>&lt;0.00001</td>
</tr>
<tr>
<td>Treatment with vasopressor, n (%)</td>
<td>35 (46.6)</td>
<td>47 (100)</td>
<td>82 (67.2)</td>
<td>&lt;0.00001</td>
</tr>
<tr>
<td>Need for hemodialysis, n (%)</td>
<td>8 (10.6)</td>
<td>18 (38.3)</td>
<td>26 (21.3)</td>
<td>&lt;0.0005</td>
</tr>
<tr>
<td>Need for ventilator support, n (%)</td>
<td>28 (37.3)</td>
<td>47 (100)</td>
<td>75 (61.5)</td>
<td>&lt;0.00001</td>
</tr>
<tr>
<td>Source of infection, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Scrub typhus</td>
<td>18 (24)</td>
<td>19 (40.4)</td>
<td>37 (30.3)</td>
<td></td>
</tr>
<tr>
<td>Complicated malaria</td>
<td>2 (2.6)</td>
<td>1 (2.1)</td>
<td>3 (2.4)</td>
<td></td>
</tr>
<tr>
<td>Leptospirosis</td>
<td>1 (1.3)</td>
<td>0</td>
<td>1 (0.8)</td>
<td></td>
</tr>
<tr>
<td>Bacterial meningitis</td>
<td>5 (6.6)</td>
<td>6 (12.8)</td>
<td>11 (9.1)</td>
<td></td>
</tr>
<tr>
<td>Japanese encephalitis</td>
<td>2 (2.6)</td>
<td>0</td>
<td>2 (1.6)</td>
<td></td>
</tr>
<tr>
<td>Herpes simplex encephalitis</td>
<td>0</td>
<td>1 (2.1)</td>
<td>1 (0.8)</td>
<td></td>
</tr>
<tr>
<td>Enteric fever</td>
<td>2 (2.6)</td>
<td>0</td>
<td>2 (1.6)</td>
<td></td>
</tr>
<tr>
<td>Pneumonia</td>
<td>20 (26.6)</td>
<td>11 (23.4)</td>
<td>31 (25.4)</td>
<td></td>
</tr>
<tr>
<td>Bacterial endocarditis</td>
<td>2 (2.6)</td>
<td>0</td>
<td>2 (1.6)</td>
<td></td>
</tr>
<tr>
<td>Acute gastroenteritis</td>
<td>3 (4)</td>
<td>0</td>
<td>3 (2.4)</td>
<td></td>
</tr>
<tr>
<td>Urinary tract infections and pyelonephritis</td>
<td>12 (16)</td>
<td>9 (19.1)</td>
<td>21 (17.2)</td>
<td></td>
</tr>
<tr>
<td>No focus or etiology</td>
<td>8 (10.6)</td>
<td>0</td>
<td>8 (6.5)</td>
<td></td>
</tr>
</tbody>
</table>

### Table 2: Showing mortality by qSOFA and SIRS individual score

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Severe sepsis (n = 75)</th>
<th>Septic shock (n = 47)</th>
<th>Mortality by score</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total no. of patients</td>
<td>Nonsurvivors</td>
<td>Total no. of patients</td>
</tr>
<tr>
<td>qSOFA score</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>26</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>1</td>
<td>23</td>
<td>8</td>
<td>2</td>
</tr>
<tr>
<td>2</td>
<td>26</td>
<td>16</td>
<td>39</td>
</tr>
<tr>
<td>3</td>
<td>0</td>
<td>0</td>
<td>6</td>
</tr>
<tr>
<td>Total</td>
<td>75</td>
<td>24</td>
<td>47</td>
</tr>
<tr>
<td>SIRS score</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>23</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>27</td>
<td>12</td>
<td>21</td>
</tr>
<tr>
<td>4</td>
<td>25</td>
<td>7</td>
<td>26</td>
</tr>
<tr>
<td>Total</td>
<td>75</td>
<td>24</td>
<td>47</td>
</tr>
</tbody>
</table>
Scoring Systems in predicting Sepsis Outcome

Table 3: Receiver operator characteristic curve characteristics and comparisons for various scores in mortality prediction

<table>
<thead>
<tr>
<th>Score</th>
<th>Area under ROC curve</th>
<th>95% CI for AUC</th>
<th>p-value for AUC</th>
<th>Criterion</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SIRS</td>
<td>0.609</td>
<td>0.516–0.696</td>
<td>0.0226</td>
<td>&gt;2</td>
<td>91.80</td>
<td>29.51</td>
</tr>
<tr>
<td>qSOFA</td>
<td>0.817</td>
<td>0.737–0.881</td>
<td>&lt;0.0001</td>
<td>&gt;1</td>
<td>85.25</td>
<td>68.85</td>
</tr>
<tr>
<td>SOFA on admission</td>
<td>0.868</td>
<td>0.795–0.923</td>
<td>&lt;0.0001</td>
<td>&gt;10</td>
<td>78.69</td>
<td>78.69</td>
</tr>
<tr>
<td>SOFA on day 2</td>
<td>0.899</td>
<td>0.831–0.946</td>
<td>&lt;0.0001</td>
<td>&gt;12</td>
<td>81.97</td>
<td>83.61</td>
</tr>
</tbody>
</table>

AUC comparisons

<table>
<thead>
<tr>
<th>Score</th>
<th>Difference between AUC</th>
<th>Standard error</th>
<th>95% CI for difference</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>qSOFA vs SIRS</td>
<td>0.209</td>
<td>0.0543</td>
<td>0.102–0.315</td>
<td>p = 0.0001</td>
</tr>
<tr>
<td>SOFA on admission vs SIRS</td>
<td>0.260</td>
<td>0.0586</td>
<td>0.145–0.375</td>
<td>p &lt; 0.0001</td>
</tr>
<tr>
<td>SOFA on day 2 vs SIRS</td>
<td>0.291</td>
<td>0.0576</td>
<td>0.178–0.403</td>
<td>p &lt; 0.0001</td>
</tr>
<tr>
<td>SOFA on admission vs qSOFA</td>
<td>0.0512</td>
<td>0.0473</td>
<td>–0.0415 to 0.144</td>
<td>p = 0.2788</td>
</tr>
<tr>
<td>SOFA on day 2 vs qSOFA</td>
<td>0.0818</td>
<td>0.0442</td>
<td>–0.00477 to 0.168</td>
<td>p = 0.0640</td>
</tr>
<tr>
<td>SOFA on day 2 vs SOFA on admission</td>
<td>0.0306</td>
<td>0.0127</td>
<td>0.00566–0.0556</td>
<td>p = 0.0162</td>
</tr>
</tbody>
</table>

Figs 1A to D: Showing ROC curve and AUC for the various scores in predicting mortality. (A) ROC curve for SIRS score showing AUC of 0.609 with sensitivity of 91.80% and specificity of 29.51% and p-value for AUC 0.0226; (B) ROC curve for qSOFA score showing AUC of 0.817 with sensitivity of 85.25% and specificity of 68.85% and p-value for AUC <0.0001; (C) ROC curve for SOFA score at the time of admission showing AUC of 0.868 with sensitivity of 78.69% and specificity of 78.69% and p-value for AUC <0.0001; (D) ROC curve for SOFA score 2 days after admission showing AUC of 0.899 with sensitivity of 81.97% and specificity of 83.61% and p-value for AUC <0.0001

Suggested that while SIRS was a better tool than qSOFA in diagnosing sepsis, qSOFA was superior to SIRS in the prediction of in-hospital mortality. It further suggested that perhaps both criteria used together could provide a better model. Other studies have also found the qSOFA a poor predictive marker in sepsis-related mortality. The study by the ANZICS Australian Group in over 180,000 patients found that a ≥2 rise in the SOFA score could predict sepsis-related mortality better than qSOFA and SIRS, thereby suggesting the limited role of SIRS and qSOFA in the prediction of ICU mortality. All these studies suggest that none of the criteria is perfect and the
search for ideal sepsis definitions and criteria continues.

**Conclusion**

In our study both SOFA and qSOFA scores could predict sepsis-related mortality better than SIRS, with SOFA being superior to qSOFA. Further, since qSOFA has been shown to be superior to SIRS for predicting mortality, it is a better triage tool than SIRS.

**References**

Relation between Serum Ferritin Level and the Risk of Acute Myocardial Infarction

Mahender Kumar Medisetty1, Kiran Runwal2, Deepak S Phalgune3*

Received: 15 March 2019; Revised: 29 March 2022; Accepted: 13 April 2022

Abstract
Background: An association between increased incidence of acute myocardial infarction (AMI) and elevated levels of stored iron concentration was recently reported. The data in India regarding association between AMI and levels of serum ferritin are lacking.
Objectives: To study the association between serum ferritin level and risk of AMI.
Materials and Methods: The present case-control study was conducted from May 2016 to October 2017 on 64 patients aged ≥30 years of either sex who were diagnosed with AMI (group I) and 60 controls (group II). Patients who attended outpatient department of hospital for minor illnesses, routine health checkups, and persons accompanying patients were selected randomly as controls. The controls had no signs of AMI or coronary heart disease (CHD) on clinical examination and had normal electrocardiogram (ECG). Quantitative measurement of serum ferritin was done in all subjects. The Chi-square or Fisher’s exact test and unpaired t-test were used to compare the categorical and quantitative variables, respectively. The independent association of serum ferritin with AMI was tested using multivariate logistic regression analysis.
Results: The mean serum ferritin level was significantly higher in group I (203.5 µg/L) as compared to group II (111.8 µg/L). In group I, 82.9% patients had serum ferritin ≥150 µg/L as compared to group II (15.0%) with p-value = 0.001. Multivariate analysis showed history of smoking, body mass index (BMI) >25 kg/m², serum ferritin levels ≥200 µg/L, and high-density lipoprotein (HDL) cholesterol level <35mg/dL were independent and significant determinants of AMI.
Conclusions: There was an association between elevated serum ferritin levels with AMI.

Introduction
The incidence of coronary artery disease (CAD) and AMI is alarmingly increasing in India. There is a growing trend in proportionate cardiovascular disease mortality. It was reported that 20.6%, 21.4%, 24.3%, 27.5%, and 29.0% deaths occurred in 1990, 1995, 2000, 2005, and 2013, respectively.1 There is an increasing awareness regarding the factors responsible for atherothrombotic vascular diseases in the last few decades. Elevated levels of homocysteine, fibrinogen, atherogenic lipoprotein, elevated triglyceride (TG), and number of genetic polymorphism are some of the novel and emerging factors. There is also a robust proof that the occurrence of degenerative diseases such as CAD is due to oxidative free radicals.1,2 The peroxidation of low-density lipoprotein (LDL) is escalated by oxidative free radicals. Its uptake is increased by macrophages leading to amplified foam cell formation and atherosclerosis.3,4

Recently a detrimental biological consequence of unwarranted iron in the human body is proposed. Overloading of iron particularly in myocardial tissue is proposed to be a strong risk factor for ischemic heart disease (IHD) and AMI.5 As early as 1981, a relation between tissue iron stores and the risk of IHD was hypothesized to elucidate the gender difference in IHD.6 A reduction of heart function on some genetic related factors was observed with the deposition of cardiac iron.7 The deposited iron can damage the myocardium. Iron can be accrued in the cells as hemosiderin, ferritin, and free iron (labile cellular iron). This can lead to formation of free radicals which are the most harmful.5,9

The best clinical measure of body iron stores is serum ferritin concentration. The serum ferritin concentration is directly proportional to intracellular ferritin concentration.10 A raised level of stored iron concentration is linked to the increased incidence of AMI.11 Some studies have reported that higher iron stores in the body were connected with an augmented risk of CHD, mortality, or AMI.12 On the contrary, some researchers did not find this association.13,14

The huge biological and measurement variability in methods used in measuring the body iron stores might have caused the observed discrepancy. This may also have resulted, to some extent, the study outcomes. Whether AMI is caused by increased serum ferritin levels is still questioned. Hence, an attempt was made in the present research to study the association between serum ferritin level and risk of AMI.

Materials and Methods
Sixty-four patients aged ≥30 years of either sex who were admitted between May 2016 and October 2017 in a tertiary care hospital, Pune, India were included as cases in this case-control study. The study commenced after an approval from the scientific advisory committee and institutional ethics committee. A written informed consent was obtained from all the patients.

Inclusion Criteria
Acute myocardial infarction having chest pain of <12 hours duration, ECG criteria described as per “third universal definition of myocardial infarction”,15 increased cardiac markers (cTn with at least one value above the 99-percentile upper reference limit), new-onset left bundle-branch block, imaging evidence of new loss of viable myocardium or new regional wall motion abnormality.

Exclusion Criteria
Patients with high ferritin levels like hemochromatosis, liver disease, tuberculosis, chronic inflammatory diseases, those on iron therapy, those who received recent blood transfusion, and those having past history of AMI or CHD.

Sixty controls were selected randomly from subjects attending outpatient department of hospital for minor ailments or routine medical checkups, subjects accompanying patients without having any evidence of AMI/CHD on clinical examination, and having normal ECG. The controls were matched with known confounding variables such as age, sex,1

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Relation between Serum Ferritin Level and the Risk of AMI

In the present study, the mean serum ferritin was considerably higher in patients with AMI as compared to controls. The percentage of patients whose serum ferritin >150 µg/L was considerably higher in group I (82.9 %) as compared to group II (15.0%) (p-value = 0.001). The mean BMI was considerably higher in group I as compared to group II. As evident from Table 2, the mean TC, HDL cholesterol, LDL cholesterol, Tgs, and serum ferritin were considerably higher in group I as compared to group II. The mean serum ferritin levels were 160.0 ± 50.2 µg/L and 158.7 ± 67.9 µg/L in DM and non-DM patients, respectively (p-value > 0.05). The mean serum ferritin levels were significantly higher in the group of smokers (181.0 ± 69.0 µg/L) as compared to the group of nonsmokers (150.9 ± 58.7 µg/L).

The mean hemoglobin levels were comparable between the two groups. The mean serum ferritin was 203.5 µg/L and 111.8 µg/L in group I and group II, respectively (p-value = 0.001). The percentage of patients who had serum ferritin ≥150 µg/L was considerably higher in group I (82.9 %) as compared to group II (15.0%) (p-value = 0.001). The mean BMI was considerably higher in group I as compared to group II. As evident from Table 2, the mean TC, HDL cholesterol, LDL cholesterol, Tgs, and serum ferritin were considerably higher in group I as compared to group II. The mean serum ferritin levels were 160.0 ± 50.2 µg/L and 158.7 ± 67.9 µg/L in DM and non-DM patients, respectively (p-value > 0.05). The mean serum ferritin levels were significantly higher in the group of smokers (181.0 ± 69.0 µg/L) as compared to the group of nonsmokers (150.9 ± 58.7 µg/L).

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<table>
<thead>
<tr>
<th>Demographic characteristic</th>
<th>Group I (N = 64)</th>
<th>Group II (N = 60)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age (years) ± SD</td>
<td>53.7 ± 9.2</td>
<td>51.3 ± 10.8</td>
<td>0.186</td>
</tr>
<tr>
<td>Gender (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>47 (73.4)</td>
<td>45 (75.0)</td>
<td>0.842</td>
</tr>
<tr>
<td>Female</td>
<td>17 (26.6)</td>
<td>15 (25.0)</td>
<td></td>
</tr>
<tr>
<td>Habits (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nil</td>
<td>30 (46.9)</td>
<td>46 (76.7)</td>
<td>0.001</td>
</tr>
<tr>
<td>Smoking</td>
<td>15 (23.4)</td>
<td>4 (6.7)</td>
<td></td>
</tr>
<tr>
<td>Alcohol consumption</td>
<td>12 (18.8)</td>
<td>2 (3.3)</td>
<td></td>
</tr>
<tr>
<td>Both</td>
<td>7 (10.9)</td>
<td>8 (13.3)</td>
<td></td>
</tr>
<tr>
<td>Comorbidity (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nil</td>
<td>30 (46.9)</td>
<td>37 (61.7)</td>
<td>0.050</td>
</tr>
<tr>
<td>Hypertension</td>
<td>10 (15.6)</td>
<td>10 (16.7)</td>
<td></td>
</tr>
<tr>
<td>DM</td>
<td>10 (15.6)</td>
<td>10 (16.7)</td>
<td></td>
</tr>
<tr>
<td>Both</td>
<td>14 (21.9)</td>
<td>3 (5.0)</td>
<td></td>
</tr>
<tr>
<td>BMI (kg/m²) ± SD</td>
<td>24.1 ± 2.3</td>
<td>22.3 ± 2.3</td>
<td>0.001</td>
</tr>
</tbody>
</table>
advocates that these cells activated by steroids during stress could be a source of the increased serum ferritin level causing AMI.  

Kiechel et al. reported that in smokers, the effects of iron stores on atherogenesis were more obvious, and had synergistic effects between serum ferritin and serum cholesterol or LDL cholesterol. In carotid artery atherosclerosis, the elevated serum ferritin was observed as a strong indicator which was assessed sonographically. The risk of IHD is increased in patients with high serum ferritin, the risk further increases in the presence of other risk factors that raise the formation of free radicals, thus hastening atherogenesis via stimulation of LDL oxidation. The high-sensitive C-reactive protein may be increased by inflammatory reaction that is caused by the oxidation of LDL-cholesterol by serum ferritin. Despite some identified genetic and pathophysiological mechanisms for the role of serum iron and ferritin levels to predict occurrence of AMI, the underlying mechanism remained to be explained.

Diabetes mellitus is an acknowledged modifiable risk factor for AMI. Numerous studies stated an association between DM and levels of serum ferritin, in which serum ferritin was considerably higher in DM patients as compared to patients who were non-diabetic. It was proposed that the mechanism for DM is due to a reduced extraction of hepatic with increasing iron stores leading to peripheral hyperinsulinemia. In the present study, the mean serum ferritin levels were comparable between DM and non-DM patients.

Previous studies reported that cigarette smoke mediated iron deployment from ferritin and it represents specific pro-oxidant mechanism related to smoking. In the present study, the mean serum ferritin levels of group of smokers were significantly higher than group of nonsmokers. In the present study, the mean values of TC, TG, and LDL cholesterol were considerably higher in cases as compared to controls (p-value < 0.05) whereas mean HDL cholesterol was considerably lower in cases as compared to controls (p-value < 0.05). Multivariate logistic regression analysis showed low HDL as the independent risk factor for developing AMI.

The American Heart Association and the American College of Cardiology have described that overweight and obesity are the major modifiable risk factor for cardiovascular morbidity and mortality. Alam et al. reported that people with high BMI had elevated levels of serum ferritin notwithstanding low levels of iron. The possible explanation given was that the occurrence of increased adipose tissue may cause inflammatory conditions that may lead to increase in the levels of serum ferritin. A case-control study reported that serum ferritin and BMI had an additive interaction on the risk of CAD. In the present study, raised ferritin levels were observed in overweight and obese individuals as classified by South Asian criteria of BMI.

### Limitations

The serum ferritin is an acute-phase reactant and may be high in inflammatory conditions. The present study was case-control, hence it has its own limitations in assessment of the causal relationship of risk factors with AMI. The potential confounding factors such as sedentary lifestyle, underlying subclinical inflammation that may affect ferritin level in acute phase, and fibrinogen levels were

### Table 2: Comparison of laboratory parameters between the two groups

<table>
<thead>
<tr>
<th>Laboratory characteristic</th>
<th>Group I (N = 64)</th>
<th>Group II (N = 60)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hb (gm%) ± SD</td>
<td>13.6 ± 0.8</td>
<td>13.5 ± 0.7</td>
<td>0.483</td>
</tr>
<tr>
<td>Mean TC (mg/dL) ± SD</td>
<td>205.7 ± 22.9</td>
<td>168.6 ± 20.0</td>
<td>0.001</td>
</tr>
<tr>
<td>Mean TGs (mg/dL) ± SD</td>
<td>165.0 ± 46.2</td>
<td>128.2 ± 31.3</td>
<td>0.001</td>
</tr>
<tr>
<td>Mean HDL cholesterol (mg/dL) ± SD</td>
<td>40.0 ± 5.9</td>
<td>48.6 ± 5.7</td>
<td>0.001</td>
</tr>
<tr>
<td>Mean LDL cholesterol (mg/dL) ± SD</td>
<td>134.1 ± 23.9</td>
<td>94.6 ± 22.1</td>
<td>0.001</td>
</tr>
<tr>
<td>Mean serum ferritin (µg/L) ± SD</td>
<td>203.5 ± 50.7</td>
<td>111.8 ± 33.1</td>
<td>0.001</td>
</tr>
<tr>
<td>Serum ferritin (µg/L)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;50</td>
<td>0 (0.0)</td>
<td>1 (1.7)</td>
<td>0.001</td>
</tr>
<tr>
<td>50 &lt; 100</td>
<td>1 (1.6)</td>
<td>24 (40.0)</td>
<td></td>
</tr>
<tr>
<td>100 &lt; 150</td>
<td>10 (15.6)</td>
<td>26 (43.3)</td>
<td></td>
</tr>
<tr>
<td>150 &lt; 200</td>
<td>17 (26.6)</td>
<td>9 (15)</td>
<td></td>
</tr>
<tr>
<td>≥200</td>
<td>36 (56.3)</td>
<td>0 (0.0)</td>
<td></td>
</tr>
</tbody>
</table>

### Table 3: Multivariate logistic regression analysis showing the independent association of risk factors with AMI

<table>
<thead>
<tr>
<th>Risk factors</th>
<th>OR</th>
<th>95% CI for OR</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age group (years)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;50 years</td>
<td>1.00</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>≤50 years</td>
<td>1.95</td>
<td>0.86–2.15</td>
<td>0.213</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>1.00</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Male</td>
<td>1.49</td>
<td>0.37–1.79</td>
<td>0.314</td>
</tr>
<tr>
<td>H/O smoking</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Absent</td>
<td>1.00</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Present</td>
<td>2.69</td>
<td>1.63–3.78</td>
<td>0.018</td>
</tr>
<tr>
<td>Alcohol consumption</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Absent</td>
<td>1.00</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Present</td>
<td>1.03</td>
<td>0.74–1.73</td>
<td>0.211</td>
</tr>
<tr>
<td>Hypertension</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Absent</td>
<td>1.00</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Present</td>
<td>1.23</td>
<td>0.92–2.14</td>
<td>0.152</td>
</tr>
<tr>
<td>DM</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Absent</td>
<td>1.00</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Present</td>
<td>1.22</td>
<td>0.85–2.01</td>
<td>0.162</td>
</tr>
<tr>
<td>BMI</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤25 kg/m²</td>
<td>1.00</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>&gt;25 kg/m²</td>
<td>3.84</td>
<td>2.02–5.89</td>
<td>0.005</td>
</tr>
<tr>
<td>Serum ferritin</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤200 µg/L</td>
<td>1.00</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>&gt;200 µg/L</td>
<td>5.58</td>
<td>3.61–9.79</td>
<td>0.001</td>
</tr>
<tr>
<td>TC</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;200 mg/dL</td>
<td>1.00</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>≥200 mg/dL</td>
<td>1.34</td>
<td>0.94–2.03</td>
<td>0.102</td>
</tr>
<tr>
<td>HDL cholesterol</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥35 mg/dL</td>
<td>1.00</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>&lt;35 mg/dL</td>
<td>2.76</td>
<td>1.83–4.74</td>
<td>0.008</td>
</tr>
<tr>
<td>LDL cholesterol</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;130 mg/dL</td>
<td>1.00</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>≥130 mg/dL</td>
<td>1.66</td>
<td>0.97–2.34</td>
<td>0.095</td>
</tr>
<tr>
<td>TGs</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;150 mg/dL</td>
<td>1.00</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>≥150 mg/dL</td>
<td>1.03</td>
<td>0.83–1.76</td>
<td>0.113</td>
</tr>
</tbody>
</table>
not taken into consideration. The study was conducted in a single center and limited patient population of 124, hence it is recommended to conduct the multicentric prospective studies with a large sample size to validate the research findings.

**Conclusions**

The mean serum ferritin level was considerably elevated in AMI patients as compared to controls. The percentage of patients whose serum ferritin ≥150 µg/L was considerably elevated in AMI patients as compared to controls. Multivariate analysis showed history of smoking, BMI >25 kg/m², serum ferritin ≥150 µg/L was considerably elevated in AMI patients as compared to controls. The mean serum ferritin level was considerably elevated in AMI patients as compared to controls. The percentage of patients whose serum ferritin ≥150 µg/L was considerably elevated in AMI patients as compared to controls.

**References**

A clinico-epidemiological Study of acute Self-poisoning by different Types of herbicidal Substances used in agricultural Fields: A Study from Patients admitted in a Tertiary Care Hospital in West Bengal

Tuhin Subhra Sarkar¹, Gouranga Santra²*

Received: 21 January 2021; Revised: 31 March 2022; Accepted: 13 April 2022

ABSTRACT

Introduction: Herbicides are the chemical compounds used to control the growth of unwanted plants or to eliminate them. The common poisonous herbicides available in India are paraquat, glyphosate, pretilachlor, etc. Ingestion of herbicides with suicidal intention is common in rural India and West Bengal but very scanty literature is available.

Methodology: We conducted a unicentric, hospital-based, noninterventional, cross-sectional study comprising 50 consecutive patients to estimate the morbidity, case fatality, and clinical features of acute suicidal poisoning of different herbicides used in agricultural fields. Data were collected from history, clinical features, and laboratory findings. Proper statistical method was used for data analysis.

Results: Most of the study population were from 26 to 40 years age group (48%), followed by 13–25 years age group (34%). Paraquat was ingested by 64%, followed by pretilachlor (20%) and glyphosate (16%). Common symptoms were vomiting (60%), abdominal pain (40%), throat discomfort (26%), oral ulcer (24%), decreased urination (50%), and respiratory distress (30%). In laboratory investigation, 64% patients had deranged liver enzymes, 58% patients had acute kidney injury, and 30% patients had alveolar damage. A total of 62% patients were discharged after recovery and 38% patients died. Case fatality rate of paraquat was 56.2%, glyphosate was 12.5%, and pretilachlor was nil (0%).

Conclusion: Herbicides like paraquat and glyphosate are associated with high morbidity and case fatality. Paraquat has the highest case fatality rate. Pre-emergent herbicide pretilachlor is relatively safe.

INTRODUCTION

Herbicides are chemical substances used to kill plants specifically.¹ They work by imitating the plant hormones. Herbicides are commonly found as liquids or powders. The common poisonous ingredients found in herbicides which are available in India are paraquat, glyphosate, pretilachlor, pendimethalin, etc. They are sprayed onto the leaves of the plants or unwanted grasses. Herbicides may be of broad-spectrum or selective. Contact herbicides affect part of a plant that they touch, while systemic herbicides are drawn up through the roots of a plant or absorbed through its leaves and stems and kill the entire plant. Although many modern herbicides are less toxic than their predecessors, they are still poisons.

Herbicide poisoning may be acute or chronic and poisoning occurs following skin or eye contact, inhalation of spray droplets or vapors, or swallowing of the product. Ingestion of herbicides could be accidental, or intentional to bring self-harm with suicidal intention. In the absence of specific clinical features and diagnostic tests, the diagnosis is completely based upon a reliable clinical history.

A surprisingly few number of studies have been done on herbicide toxicity to human health throughout the world. Herbicides tend to get less publicity and less criticism than insecticides. Awareness about herbicidal poisoning is less among physicians. Herbicide poisoning is also a neglected field by researchers. More attention is given to insecticide poisoning, especially organophosphorus poisoning. Because of the unawareness and inability of the physicians to differentiate herbicides from more commonly used compounds like anticholinergic pesticides they are managed inappropriately and inadequately.

Because of widespread availability, ingestion of herbicides with suicidal intention is common in rural India. But reports of herbicide poisoning with suicidal intention are scarce in the Indian literature. It is an important cause of morbidity and high mortality, but little data are available regarding morbidity, mortality, and clinical features of herbicide poisoning in rural India. With the background of paucity of data and unawareness of physicians, we planned to conduct a study to enrich the literature regarding acute herbicide poisoning in humans and to create awareness among physicians. Herbicides are used in home gardens, farms, fields, ponds, etc. In rural West Bengal, herbicides are mainly used for agricultural purposes. So for the study, we included self-poisoning by herbicides in agricultural fields only.

The Aim of the Study

Aims of this study were to find out the case fatality rate and clinical features of different types of herbicidal poisoning in patients admitted in the Department of Medicine in Midnapore Medical College.

Objectives of the Study

Case fatality rate of different types of herbicidal poisoning.

Clinical features of different types of herbicidal poisoning.

METHODOLOGY

This is a unicentric, hospital-based, noninterventional, cross-sectional study. It was conducted in the Department of General Medicine of a tertiary care hospital in West Bengal over a period of 1 year. Fifty consecutive patients having alleged history of self-induced herbicidal poisoning admitted...
in emergency wards in the Department of General Medicine, Midnapore Medical College and Hospital were selected for the study. Patients irrespective of age and sex who were willing to participate in the study were included in the study. Patients who were not willing to participate in the study, who had ingested more than one poison, and who were referred out or left against medical advice from this hospital were excluded from this study.

Detailed history was taken about patients’ age, sex, occupation, name, and amount of poison ingested. Then clinical evaluations of the patients were done. We performed blood investigations like complete blood count, liver function test, and urea and creatinine levels. Chest X-ray, electrocardiogram, and other relevant investigations were done according to the cases.

We conducted the study in accordance with ethical standards of responsible committee on human experimentation and with Helsinki Declaration of 1975, as revised in 2010. Institutional ethical committee permission was taken prior to the study. Informed written consent was taken from the patients or family members for inclusion in the study.

**Statistical Analysis**

Data collected during the study were entered in Microsoft Excel spreadsheet and analyzed statistically using IBM SPSS version 23.0. Categorical data were expressed as a number (percentage) and continuous data were expressed as a mean ± standard deviation (SD).

**Results**

Fifty patients with different herbicides poisoning were recruited for the study. Table 1 shows the distribution of basic characteristics of the study population. We found that most of the study population were from 26 to 40 years age group (48%), followed by 13–25 years age group (34%), and it was followed by > 40 years age group (18%). We also found that male (68%) patients were more than females (32%) and male:female ratio was 2:1. Most of the study population were farmers (34%), followed by students (26%), and then followed by homemakers (24%) and small businessmen (16%). The mean age of study population was 31.7 ± 12.6 years (mean ± SD).

<table>
<thead>
<tr>
<th>Age group (years)</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>13–25</td>
<td>17 (34%)</td>
</tr>
<tr>
<td>26–40</td>
<td>24 (48%)</td>
</tr>
<tr>
<td>&gt;40</td>
<td>9 (18%)</td>
</tr>
</tbody>
</table>

The mean age of study population (mean ± SD): 31.7 ± 12.6.

Table 2: Distribution of study population according to ingested herbicide poisons, symptoms, and laboratory investigations (N = 50)

<table>
<thead>
<tr>
<th>Name of the herbicide ingested</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glyphosate</td>
<td>8 (16%)</td>
</tr>
<tr>
<td>Paraquat</td>
<td>32 (64%)</td>
</tr>
<tr>
<td>Pretilachlor</td>
<td>10 (20%)</td>
</tr>
</tbody>
</table>

Distribution of study population according to ingested herbicides and their clinical features is shown in Table 2. We found that most of the study population ingested paraquat (64%), followed by pretilachlor (20%), and it was followed by glyphosate (16%). We also found that patients who ingested herbicides had symptoms of vomiting (60%), abdominal pain (40%), throat discomfort (26%), oral ulcer (24%), decreased urination (50%), and respiratory distress (30%); and 10% patients were asymptomatic. Some of the patients had more than one symptom. On laboratory investigation, we found that 64% patients had deranged liver enzymes in liver function test, 58% patients had laboratory values suggestive of acute kidney injury, and 30% patients had chest X-ray features suggestive of alveolar damage. As per outcome data, 62% patients were discharged from hospital after recovery and 38% patients died. The mean amount of ingestion of herbicide was 32.5 ± 28.7 mL (mean ± SD). The mean duration of hospital stay was 7.5 ± 5.3 days (mean ± SD).

Distribution of the study patients according to ingested poisons and symptoms of respective poisonings are shown in Table 3.

Table 3: Distribution of study population according to poison ingested and symptoms (multiple responses)

<table>
<thead>
<tr>
<th>Name of poison</th>
<th>Symptoms</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glyphosate (N = 8)</td>
<td>Abdominal pain</td>
<td>2 (25%)</td>
</tr>
<tr>
<td></td>
<td>Vomiting</td>
<td>8 (100%)</td>
</tr>
<tr>
<td></td>
<td>Throat discomfort</td>
<td>3 (37.5%)</td>
</tr>
<tr>
<td>Paraquat (N = 32)</td>
<td>Oral ulcer</td>
<td>2 (25%)</td>
</tr>
<tr>
<td></td>
<td>Decreased urination</td>
<td>1 (12.5%)</td>
</tr>
<tr>
<td></td>
<td>Respiratory distress</td>
<td>1 (12.5%)</td>
</tr>
<tr>
<td>Pretilachlor (N = 10)</td>
<td>Abdominal pain</td>
<td>18 (56.2%)</td>
</tr>
<tr>
<td></td>
<td>Vomiting</td>
<td>19 (59.4%)</td>
</tr>
<tr>
<td></td>
<td>Throat discomfort</td>
<td>7 (21.9%)</td>
</tr>
<tr>
<td></td>
<td>Oral ulcer</td>
<td>9 (28.1%)</td>
</tr>
<tr>
<td></td>
<td>Decreased urination</td>
<td>23 (71.9%)</td>
</tr>
<tr>
<td></td>
<td>Respiratory distress</td>
<td>14 (43.8%)</td>
</tr>
</tbody>
</table>

Mean duration of hospital stay (mean ± SD): 7.5 ± 5.3 days; mean amount of herbicide poison ingested (mean ± SD): 32.5 ± 28.7 mL; PA, Posteroanterior.
A Study of acute Self-poisoning by herbicidal Substances

ulcers, and 10% had decreased urination; and 50% of preti lachlor ingested patients were asymptomatic.

Distribution of study population according to type and amount of ingested poisons and their outcomes is shown in Table 4. No person died among 10 patients who had ingested pretilachlor and only one person died among eight patients who had ingested glyphosate in amount of 200 mL. We found that case fatality rates were 12.5% and 56.2% in glyphosate and paraquat, respectively. We also found that persons (n = 7) who had ingested paraquat (24.00% w/w) ≤15 mL had no death. Patients (n = 10) who had ingested >30 mL had 100% case fatality and the patients (n = 15) who ingested paraquat 16–30 mL had case fatality rate of 53.3%.

**Discussion**

Pesticides include insecticides like organophosphorus, herbicides (weed killers), fungicides, rodenticides, etc. Suicidal poisoning with pesticides is prevalent, especially with insecticides and rodenticides. Herbicide poisoning is also not rare, but awareness among physicians is relatively poor. Among acute pesticidal poisoning, majority of deaths are from self-poisoning due to paraquat, organophosphorus, and aluminum phosphate.2 Herbicides are the chemical compounds used to control the growth of unwanted plants or to eliminate them. There is very little literature about morbidity, mortality, and differentiating clinical features among different types of herbicidal poisoning. Only few studies are found related to glyphosate and paraquat poisoning and some case reports are available on paraquat, pendimethalin, chlorophenoxyn, and glyphosate poisoning.

In our study, herbicides used for suicidal poisoning included paraquat, glyphosate, and pretilachlor. Most patients ingested paraquat (64%), followed by pretilachlor and then glyphosate. Males outnumbered females (2:1) and patients were mainly in third or fourth decades of their life with mean age 31.7 ± 12.6 years. Although case fatalities were mainly limited to paraquat, all types of herbicides were associated with morbidities and different signs and symptoms.

Different small studies or case reports revealed that signs and symptoms of herbicide poisoning vary with chemicals and from one individual to another.3–11 Clinical features range from mild symptoms like skin and mucosal irritation, nausea, vomiting, dysphagia, throat pain, stomach pain, diarrhea to severe life-threatening symptoms like hypotension, liver and kidney damage, coma or convulsions and death.3–11 Similar signs and symptoms were found in our study. Clinical features in our study ranged from mild/moderate to severe symptoms like nausea, vomiting, throat and abdominal pain to dyspnea and oliguria, though five (10%) patients were asymptomatic. Liver enzymes were elevated in more than half of patients. Case fatalities were due to respiratory and renal failures.

In a study from Karnataka of South India by Cherukuri et al. regarding demography, mortality, and presenting features of different types of herbicidal poisoning, 60 cases attending a tertiary care hospital were evaluated.7 The study included 36 male and 24 female patients (male:female ratio 3:2). Mean age of the study population was 25.38 ± 19.136 years. Most of the cases (95%) were self-poisoning (suicidal). Most patients ingested paraquat (78%) and 22% patients ingested glyphosate. The findings included vomiting (68.3%), oral ulcers (31.7%), throat discomfort (26.7%), abdominal pain (23.3%), and dyspnea (10.0%). Findings are quite similar to our study. Clinical characteristics of herbicide poisoning found in our study were vomiting (60%), oral ulcers (24%), throat discomfort (26%), abdominal pain (40%), dyspnea (30.0%), and decreased urination (50%). Ten percent (10%) were asymptomatic.

A study was conducted in Srilanka by Roberts et al. only on glyphosate in two different hospitals.8 A total of 601 patients were identified who ingested a concentrated formulation (36% w/v glyphosate). About 27.6% were asymptomatic, 63.7% had features of minor poisoning, and 5.5% of patients had features of moderate to severe poisoning. Gastrointestinal symptoms, respiratory distress, hypotension, altered level of consciousness, and oliguria were observed in fatal cases. Gastrointestinal symptoms like nausea, vomiting, diarrhea, dehydration, and abdominal pain were seen both in minor and severe symptomatic cases.8 In our study, patients who had ingested glyphosate had quite similar features like the Sri Lankan study including gastrointestinal symptoms, oliguria, and respiratory distress. Gastrointestinal symptoms were most common in both studies.

In a study at Ludhiana, India, Sandhu et al. evaluated 17 paraquat poisoning cases.9 The common symptoms were vomiting (100%) followed by oral ulceration or dysphagia (53%), dyspnea (41%), and loose stool (24%). Acute renal failure was seen in 76.5% cases. A total of 41% cases recovered from poisoning. Case fatality was seen in 35%, while 24% left against medical advice. In our study among patients who have ingested paraquat, vomiting (59.4%), dysphagia, and oral ulcers (28.1%) were less common in comparison to Ludhiana study. Geographic location, environmental factors, and genetic predisposition may be responsible for varied clinical features.

Different previous studies revealed that in pesticide poisoning the case fatality rate is between 18 and 23% with the highest fatality rates in paraquat poisoning.3–15 In outcome analysis from our study, 62% of herbicide poisoning cases recovered and 38% of cases expired. Paraquat had higher case fatality (56.2%) than glyphosate (12.5%). No case fatality was seen with pretilachlor (case fatality rate 0%), though half of them had mild/moderate symptoms. In our study, overall case fatality rate (38%) is lower than Cherukuri et al.’s study where case fatality rate was 61.7%.7 Case fatality rate of glyphosate is 12.5% in our study but the large Sri Lankan study revealed a case fatality rate of 3.2%.8

Amount of different substances consumed influences prognosis. In our study, persons who ingested paraquat (24.00% w/w) >30 mL had 100% case fatality and nil (0%) in patients who had ingested ≤15 mL, and 53.3% case fatality was seen in patients who had ingested between 16 and 30 mL. Newer herbicides are relatively safe but case fatality still occurs. A study from Sri Lanka with newer agent bispyribac revealed a case fatality ratio of 1.81%.10 It can cause nausea,
vomiting, epigastric pain, hypotension, altered sensorium, convulsion, and cardiac arrest.\textsuperscript{10} In our study also no case fatality was seen with pretilachlor, a preemerget selective herbicide; though half of them had mild/moderate symptoms.

Limitation of study: Our study is a small one and was done in a single center. It would be better if we had done the study in multiple centers for longer duration. Due to lack of facility plasma levels of herbicides were not estimated in our study.

CONCLUSION

Herbicides are important causes of morbidity and mortality in acute self-poisoning. Among the herbicides, paraquat has the highest case fatality rate. The most common symptoms are abdominal pain, vomiting, throat discomfort, oral ulcer, decreased urination, and respiratory distress. Most important laboratory findings are deranged liver enzymes, laboratory features suggestive of renal failure, and chest X-ray features suggestive of alveolar damage.

FUTURE SUGGESTIONS

Government level: Government should take necessary steps to ban very toxic herbicides like paraquat.

Individual level: Restriction of use of paraquat and glyphosate. Replacement of such toxic herbicides by relatively less toxic newer one.

REFERENCES

Pure Vitamin E in its Natural Form

For Defense against Free Radicals
D-alpha Tocopherol

Natvie®
Natural Vitamin E (d-alpha Tocopherol) Capsules

200 IU
400 IU

For Defense against Free Radicals in Chronic conditions

Tocotrienol

Natvie® Gold
Natural Vitamin E (Tocotrienol – 100 mg) Capsules

FRANCO INDIAN PHARMACEUTICALS PVT. LTD.
122, Dr. T. M. Malse Road, Mumbai 400 011
Introduction

Hypertension in adults of age 18 years and older is defined as SBP of 140 mm Hg or greater and/or DBP of 90 mm Hg or greater or any level of BP in patients taking antihypertensive medication. Hypertension and CVD remain one of the leading causes of morbidity and mortality in dialysis patients. Identification and treatment of hypertension is a persistent challenge that nephrologists face when managing patients on hemodialysis.²

Blood pressure control is of paramount importance in reducing morbidity and mortality in this high-risk population, although there is no consensus on target BP.² It has previously been shown that 2-week routine BP recordings in the dialysis unit when averaged can give a qualitative estimate of presence or absence of hypertension.⁴ However, the thresholds for these qualitative estimates were such that the individual BP recordings were not helpful in determining any trend in sensitivity or specificity.⁵,⁶ Thus, substantial uncertainty exists in making an accurate diagnosis of hypertension in hemodialysis patients.

Ambulatory BP recording is currently considered as gold standard in estimating the BP among patients on dialysis. However, this facility is not easily available, especially in rural health setup and it is not economical as well, apart from being a cumbersome procedure. Therefore, there is a need for an easier and more convenient method to monitor the BP in patients on hemodialysis. Further, ABPM can only be used as a one-time measure to evaluate BP which is not adequate, especially for patients on hemodialysis. Some studies have demonstrated that home BP recordings may be promising in making a more accurate diagnosis of hypertension in hemodialysis patients.⁵ However, the studies indicated further evaluation in making a home-based BP measurement a reliable alternative to ABPM. Also, these studies did not explore whether home BP recordings can improve the prediction of hypertension as assessed by ABPM.⁶,⁷ There is paucity on research studies that compare home-based BP monitoring with ambulatory BP recordings as a method of monitoring BP in patients on hemodialysis. Hence, our study was planned to examine the hypothesis that out-of-dialysis unit BP measurement in the form of home-based BP monitoring can be an economical, reliable, and convenient Tool over ambulatory Blood Pressure monitoring in Patients on Dialysis.

Materials and methods: This was a prospective observational study carried out in the Department of Medicine in a tertiary care hospital. The total duration of the study was 24 months. Fifty-two CKD patients on hemodialysis fulfilling the eligibility criteria were taken up for the study after informed consent. Blood pressure was measured using a standardized BP measuring equipment at home, thrice a day for 3 days in the interdialysis period. Also, all these patients were subjected to 24 hours of ABPM in the interdialysis period. Home-based BP monitoring records are then compared with the one-time ABPM records.

Conclusion: Our study shows that there is no difference between BP readings as observed by ABPM and home-based BP monitoring. Also, home-based BP monitoring can detect hypertension as effectively as ABPM among patients on hemodialysis, thereby making home-based BP monitoring a safe and reliable method of BP measurement in clinical practice.
Home BP monitoring: An economical, reliable, and convenient Tool

Measurement of BP is as efficacious and accurate as ABPM in evaluating hypertension among patients on hemodialysis.

Materials and Methods

Place of Study
The study was conducted in the Department of Medicine in a tertiary care hospital in Mumbai from Jun 2017 to May 2019.

Study Design
A prospective, randomized, observational study.

Sampling Technique and Sample Size
A consecutive type of nonprobability sampling was followed for selection of study subjects. A total of 52 consecutive patients fulfilling the eligibility criteria were taken up for the study after informed consent.

Inclusion Criteria
- Age above 18 years.
- Diagnosed case of CKD on maintenance hemodialysis.
- Completed a minimum period of 1 month on maintenance hemodialysis.

Exclusion Criteria
- Age less than 18 years.
- Chronic kidney disease patients who have not completed a period of 1 month on maintenance hemodialysis.
- Hemodynamically unstable patients.

Methodology
Blood pressure was measured using standardized BP measuring equipment at home, thrice a day for 3 days in the interdialysis period. Also, all these patients were subjected to 24 hours of ABPM in the interdialysis period. Ambulatory BP monitoring was done using ABPM apparatus—an oscillometric method-based recording device which was secured to the patient’s thorax with a belt provided and tethered around the neck. The first manual recording after the press of start button initiated automatic recordings every 30 minutes during daytime (from 7 am to 10 pm), and every 60 minutes at night (from 10 pm to 7 am). For all patients, ABPM was done for 24 hours in interdialysis period. The apparatus was detached from the patient after 24 hours, and reconnected to the computer for retrieving data. Home-based BP monitoring records are then compared with the one-time ABPM records.

Statistical Methods of Analysis
Data were statistically described in terms of mean (± standard deviation), frequencies (number of cases), and percentages when appropriate. Data were tested first for normal distribution by Kolmogorov–Smirnov test. Comparison of quantitative variables between the study groups was done using Student’s t-test for independent samples if normally distributed. Mann–Whitney U test was used for non-normally distributed quantitative data. For comparing categorical data, Chi-square test was performed. Exact test was used instead when the expected frequency is less than 5. Pearson’s correlation coefficient was computed to evaluate the correlation between quantitative variables. A probability value (p-value) less than 0.05 was considered statistically significant. All statistical calculations were done using computer programs Microsoft Excel 2007 (Microsoft Corporation, NY, USA) and SPSS (Statistical Package for the Social Science; SPSS Inc., Chicago, Illinois, USA) version 21.

Duration of Study
Two years, from June 2017 to May 2019.

Blinding
Unblinded study.

Ethical Issues
Ethical clearance was obtained from institutional ethical committee.

Result
A total of 52 consecutive patients on hemodialysis, fulfilling the eligibility criteria were taken up for the study after informed consent. Blood pressure was measured using a standardized BP measuring equipment at home, thrice a day for 3 days in the interdialysis period. Also, all these patients were subjected to 24 hours of ABPM in the interdialysis period. Home-based BP monitoring records are then compared with the one-time ABPM records.

Discussion
In patients with CKD, the diagnosis and management of hypertension rest almost entirely on BP measurements. Various studies have demonstrated that ABPM is superior to clinic-recorded BP in predicting cardiovascular events in patients with hypertension. The superior ability to risk stratify by ABPM has been confirmed in the general population, treated hypertensive patients, untreated hypertensive patients, refractory hypertension, and isolated systolic hypertension in the elderly. However, ABPM is not easily available, especially in rural health setup and it is not economical as well. Though ABPM is proven to be superior to clinic BP measurements, there are studies that demonstrated that home BP recordings may be promising in making a more accurate diagnosis of hypertension in hemodialysis patients. Since the evidence is not robust, still home-based BP measurements are not routinely used to diagnose or predict cardiovascular events in hemodialysis patients. Our study is aimed at establishing the fact that home-based BP measurements are as accurate, if not better than ABPM and can be safely used to diagnose and predict cardiovascular events in patients on hemodialysis.

In our present study, the mean age of the study subjects was 49.56 years with over half of them above 50 years of age (Table 1). Slight male predominance was observed in the study subjects with 55.8% males to 44.2% females. Similar observations were also made by Rahman et al. and Andersen et al. where the mean age of subjects on dialysis was 63.34 and 67.0 years, respectively with male predominance (64 and 96.1%) thereby confirming that our study population did not differ significantly from the representative general population.

In our study, the mean awake, asleep, and average ABPM readings of SBP were 141.69, 139.39, and 141.23 mm Hg, respectively. Mean awake, asleep, and average ABPM readings of DBP were 81.33, 80.04, and 80.67 mm Hg (Table 2). These results are corresponding to the studies conducted by Tonbul et al. and Farmer et al. Similarly, the mean SBP and DBP recorded on home-based measurements were 143.6 and 82.69 mm Hg, respectively, and similar observations were also made by Agarwal, Andersen et al., and Ye et al. The results confirm that there is not much of variation in BP as measured by ABPM and home-based BP measurements among different study population and hence the results of our study can be extrapolated to the target population. Also, our present study shows that there is no statistically significant difference between mean BP readings as observed by ABPM and home-based BP measurements among different study population and hence the results of our study can be extrapolated to the target population. Also, our present study shows that there is no statistically significant difference between mean BP readings as observed by ABPM and home-based monitoring (p = 0.493 for SBP and p = 0.329 for DBP) (Table 2). This supports our hypothesis that home-based monitoring is equally efficient and can replace ABPM.

Table 1: Distribution of subjects based on age group

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>No. of patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;30</td>
<td>4 (7.7%)</td>
</tr>
<tr>
<td>31–40</td>
<td>12 (23.1%)</td>
</tr>
<tr>
<td>41–50</td>
<td>6 (11.5%)</td>
</tr>
<tr>
<td>51–60</td>
<td>16 (30.8%)</td>
</tr>
<tr>
<td>&gt;60</td>
<td>14 (26.9%)</td>
</tr>
<tr>
<td>Total</td>
<td>52 (100%)</td>
</tr>
</tbody>
</table>
We also observed that all subjects showing mean SBP ≥140 mm Hg as per ABPM, also had home-based readings of above 140 mm Hg while 23 out of 27 patients (85.2%) with mean SBP <140 mm Hg as per ABPM had similar observation by home-based monitoring (Table 3). Overall a good measure of agreement was seen between the two methods (kappa 0.847; p<0.01). Similarly, all subjects showing mean DBP ≥90 mm Hg as per ABPM had home-based readings of above 90 mm Hg, while 42 out of 44 patients (95.5%) with mean DBP <90 mm Hg as per ABPM had similar observation by home-based monitoring (Table 3). Again, an overall good measure of agreement was seen between the two methods (kappa 0.866; p<0.01). Studies by Agarwal et al. also showed a similar good measure of agreement.13 They observed that standard deviation of the difference with ABPM was least for home BP. They concluded that home BP monitoring appears to be a better alternative than clinical measurements in dialysis. Our study too reiterates the fact that home-based BP could be an effective replacement to ABPM.

In a study of 32 peritoneal dialysis patients by Wang et al., the relationship between home BP monitoring and 24-hour ABPM was evaluated.14 Home BP was taken as the 10-day average of three BP readings obtained in the morning. There was a high correlation between home BP and 24-hour ABPM values (r = 0.54–0.71). In our present study too, an excellent correlation was observed between the home-based and ambulatory BP measurements (r = 0.93; p<0.01). These data suggest that home BP monitoring may add value to the diagnosis of hypertension in peritoneal dialysis patients. Similar results were also reported in children with CKD and people with type 2 diabetes mellitus.15,16

Ability to detect hypertension is an important measure of the diagnostic method adopted. Hence, in our study, we adopted the novel idea of knowing the ability of home-based BP measurement to detect hypertension among patients on hemodialysis. While 25 out of 52 (48.1%) subjects showed a systolic hypertensive record on ABPM, 29 out of 52 (55.8%) were detected to have systolic hypertensive record by home-based BP (Table 4). Similarly, while 8 out of 52 (15.4%) subjects showed a diastolic hypertensive record on ABPM, 9 out of 52 (19.2%) had a similar outcome by home-based BP (Table 4). The ability to detect hypertension by home-based BP measurement is the novelty of our study. Our study showed that home-based BP records can reliably detect hypertension when compared to the ABPM.

### Table 2: Mean SBP and DBP as measured by home-based and ambulatory BP measurement

<table>
<thead>
<tr>
<th>Variables</th>
<th>Group</th>
<th>Mean (mm Hg)</th>
<th>SE</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>SBP</td>
<td>Ambulatory BP</td>
<td>141.23</td>
<td>2.46</td>
<td>0.493</td>
</tr>
<tr>
<td></td>
<td>Home-based BP</td>
<td>143.60</td>
<td>2.49</td>
<td></td>
</tr>
<tr>
<td>DBP</td>
<td>Ambulatory BP</td>
<td>80.67</td>
<td>1.45</td>
<td>0.329</td>
</tr>
<tr>
<td></td>
<td>Home-based BP</td>
<td>82.69</td>
<td>1.43</td>
<td></td>
</tr>
</tbody>
</table>

### Table 3: Comparison of SBP and DBP as measured at home to ambulatory BP measurements

<table>
<thead>
<tr>
<th>Home-based BP</th>
<th>Ambulatory BP</th>
</tr>
</thead>
<tbody>
<tr>
<td>SBP ≥140/DBP ≥90 (number)</td>
<td>SBP &lt;140/DBP &lt;90 (number)</td>
</tr>
<tr>
<td>23/42</td>
<td>0/0</td>
</tr>
<tr>
<td>Kappa p-value</td>
<td>0.847</td>
</tr>
<tr>
<td>p-value</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

### Table 4: Distribution of hypertensive and nonhypertensive records as measured by ambulatory and home-based BP measurements

<table>
<thead>
<tr>
<th>SBP (mm Hg)</th>
<th>Ambulatory BP, n (%)</th>
<th>Home-based BP, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥140</td>
<td>25 (48.1)</td>
<td>29 (55.8)</td>
</tr>
<tr>
<td>&lt;140</td>
<td>27 (51.9)</td>
<td>23 (44.2)</td>
</tr>
<tr>
<td>DBP (mm Hg)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥90</td>
<td>08 (15.4)</td>
<td>10 (19.2)</td>
</tr>
<tr>
<td>&lt;90</td>
<td>44 (84.6)</td>
<td>42 (80.8)</td>
</tr>
</tbody>
</table>

### CONCLUSION

Home-based BP monitoring is a simple, easily available, and inexpensive tool that correlates well with ABPM, the present gold standard. Our study shows that there is no significant difference between BP readings as observed by ABPM and home-based BP monitoring. Also, home-based BP monitoring can detect hypertension as effectively as ABPM among patients on hemodialysis. Hence, home-based BP monitoring can replace ABPM, especially in patients of hemodialysis. Also, measuring home BP may lead to more active participation in health care by patients and enhance their quality of life.

### REFERENCES

Plasma Renin-guided Therapy in Patients of Primary Hypertension on Antihypertensives: A Prospective Cohort Study

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ABSTRACT

Background: Most guidelines for hypertension overlook the underlying pathophysiologic basis in deciding antihypertensives. Based on renin levels, hypertension may be classified as high-renin hypertension (HRH), low-renin hypertension (LRH), and normal-renin hypertension (NRH). The study examined the renin levels in a hypertensive population and assessed the effect of renin-guided antihypertensive management on blood pressure (BP) control.

Materials and methods: This study was a single-center prospective cohort study. Subjects with primary hypertension (aged 20–60 years) on antihypertensives were included in the study. Initial BP was recorded and subsequently, all antihypertensives were discontinued. After 2 weeks, second BP was recorded and plasma renin assay (PRA) sample was collected. All patients were restarted on their previous antihypertensives and further modification of medication was performed based on their PRA. Anti V drugs, such as diuretics and calcium channel blockers (CCBs) were used in LRH while beta-blockers and antirenin drugs (Anti R drugs) were used in HRH.

Results: The study included 918 patients with hypertension and 896 cases were finally analyzed. Of these patients, 287 (32.03%) had LRH (<0.51 ng/mL/hr), 412 (45.98%) had HRH (>2.64 ng/mL/hr), while 197 (21.99%) had NRH (0.51–2.64 ng/mL/hr). Renin-guided management caused significant BP reduction. In controlled BP group, the systolic BP (SBP)/diastolic BP (DBP) before and after renin-guided management caused significant BP reduction. In controlled BP group, the systolic BP (SBP)/diastolic BP (DBP) before and after renin-guided management caused significant BP reduction.

Conclusions: Renin-guided therapy is useful for improving BP control in both controlled and uncontrolled hypertensive patients and in reducing the number of antihypertensive drugs.

BACKGROUND

Hypertension is a common public health problem worldwide affecting approximately 25.3% of Indian population.¹ The Eighth Joint National Committee (JNC 8) guidelines recommend initiating treatment of hypertension with one of the four agents—angiotensin-converting enzyme inhibitor (ACEI), angiotensin receptor blocker (ARB), CCB, or thiazide-type diuretic, with a target BP of less than 140/90 mm Hg.² However, most national and international guidelines overlook the underlying pathophysiologic basis for deciding the antihypertensive therapy. The selection of the initial drug and any add-on drug is arbitrary, and therefore, is akin to the principle that "one size fits all."³ Therefore, in significant number of patients, BP is inadequately controlled which predisposes them to end-organ damage and vascular complications.⁴ Moreover, the use of a pathophysiologically “improper” antihypertensive drug may lead to a lesser BP reduction, and can induce a paradoxical pressor response that contributes to increase in the prevalence of resistant hypertension.⁵,⁶

The primary determinants of BP are vascular tone and circulating volume.⁷ Vascular tone (the “resistance” or “R-factor”) is mainly related to renin-angiotensin II system (RAS) dependent vasoconstriction and, therefore, to renin activity. Circulating volume (the “volume” or “V-factor”) may increase due to excessive sodium intake or primary aldosteronism, leading to renin suppression.⁷ The interaction between “R-factor” and “V-factor” maintains the BP in the normal range.⁶ Based on renin levels, hypertension may be classified as HRH, LRH, and NRH.⁸ High-renin hypertension is associated with increase of peripheral resistance and is likely to respond to Anti R drugs, whereas LRH may represent primary sodium-volume overload and is likely to respond to diuretics and CCB (Anti V drugs).⁹

Renin-guided therapy, to guide the use of antihypertensive drugs, evolved in the early 1970s,¹⁰,¹¹ and was tried for the management of hypertension, particularly poorly controlled hypertension.¹²,¹³ However, this concept has not gained much acceptance as past studies have reported ambivalent results with renin-guided therapy.¹⁴,¹⁵ A major reason has been the cost and difficulty in conducting the test and complicated patient preparation for sampling.⁶ However, with the advent of plasma-based commercially available tests, sample collection has been rendered easier.¹² Only a few studies on renin-guided hypertension therapy in Asian population have been reported. The present study was designed to examine the pattern of PRA levels of a group of multiethnic hypertensive population on medication and modify the antihypertensive therapy based on their PRA levels to assess the effect on control of BP.

MATERIALS AND METHODS

Study Design

This study was a single-center open-label prospective cohort study.

Study Population

Adult cases of primary hypertension in the age group of 20–60 years on follow-up in a tertiary care hospital in Mumbai were considered for the study. The study included cases with primary hypertension on antihypertensive medication, who agreed on discontinuation of ongoing medication for 2 weeks prior to PRA assessment. Patients...
with features of secondary hypertension, poorly controlled diabetes, chronic kidney disease stages 3–5, liver disease, congestive heart failure, renovascular hypertension, patients on oral contraceptive pills (OCPs) or nonsteroidal anti-inflammatory drugs (NSAIDs), any life-threatening illness, Cushing’s syndrome, genetic causes of hypertension, any active disease process requiring new medications, mental illness or personality disorder that might interfere with adherence to study protocol, were excluded from the study. Patients having a BP of >180/120 mm Hg on discontinuation of antihypertensives during the 2 weeks in the run-up to PRA assessment were also excluded, and advised to resume medication to prevent any possible adverse outcomes.

**Baseline Assessment**

A history and physical examination were performed for all subjects at the initial visit. A complete biochemistry, hemogram, metabolic panel, lipid profile, thyroid hormone level, electrocardiogram, and urinalysis with 24-hour urine protein were obtained at the time of the initial visit. Blood pressure was recorded at baseline. Those already on medication were advised to report after 2 weeks of abstinence from medication with close monitoring of BP at home. Thereafter, all the abovementioned tests were performed on them. Blood pressure was recorded at the initial visit after abstinence and thereafter, at each visit. Any symptoms or problems encountered were recorded.

**Measurement of BP**

In the hospital, BP was recorded using a digital sphygmomanometer (HEM-712 CLC; Omron Healthcare, Vernon Hill, Illinois) with appropriately sized arm cuff, after 5 minutes of rest in a quiet room, in sitting position. The mean of three readings was obtained and considered as the final SBP and DBP. All subjects were trained to measure BP at home or nearby suitable place with the use of any standard manual or digital sphygmomanometer. The patients recorded their BP twice daily in the week prior to each visit.

**Measurement of PRA**

Plasma renin assay was performed using plasma renin activity kits (RIAZEN, R-EX-125, Zentech Company). After lying in supine position for at least 15 minutes, 2 mL of blood was withdrawn from the patient in a fasting state and collected in chilled ethylenediaminetetraacetic acid vacu-container. Plasma was immediately frozen to avoid inadvertent conversion of pro-renin to active renin. The PRA value given in the renin kit, 0.51–2.64 ng/mL/hr was considered as the baseline normal PRA for the study.

**Protocol**

The study group of hypertensive subjects included diagnosed and followed-up cases fulfilling the mentioned inclusion or exclusion criteria. Informed consent from all the patients was taken. Appropriate clearance from the institutional ethical committee was obtained. Initial BP was recorded and patients were advised to discontinue all antihypertensives from the first day. Patients were advised to check their BP daily. In case of any symptoms, adverse events, or high BP (SBP ≥ 180 and DBP ≥ 120 mm Hg), patients were advised to resume their previous antihypertensives. These patients were excluded from the study.

After 2 weeks, second BP was recorded in the clinic and PRA sample was collected as per the study protocol. All patients were restarted on the same medication that they were using 2 weeks back. After 2 weeks, once the PRA levels were available, patients were recalled to the hospital for further action.

**Categorization of Hypertensives as per PRA**

- **Low-renin hypertension** was defined as hypertension with PRA <0.51 ng/mL/hr.
- **High-renin hypertension** was defined as hypertension with PRA >2.64 ng/mL/hr.
- **Normal-renin hypertension** was defined as hypertension with PRA 0.51–2.64 ng/mL/hr.

**Management based on PRA**

Patients were categorized as HRH, NRH, or LRH. The choice of antihypertensive is given in Table 1. If a patient was only on a single drug of one class (LRH or HRH) he/she was allowed to continue the same medication. In case a patient was on two drugs, one of R and the other of V class, treatment was adjusted as per PRA values, and if previously on three or more drugs, only one drug was initiated based on PRA value. Provision for fourth medicine, if required, was left to the individual judgment of the physician. Anti V drugs, such as diuretics (hydrochlorothiazide and indapamide) and CCBs (amlodipine) were used in LRH. In HRH, beta-blockers (atenolol and metoprolol), ACEI (ramipril and enalapril), or ARB (losartan and telmisartan) were used.

All medication was given once a day dose to start with. Care was taken to introduce minimal changes in existing medications as far as possible. No specific preference was given to any drug in each class and standard antihypertensive prescribing practice was followed. Medication was initiated from minimum therapeutic dose and was gradually increased till optimal response. Second drug was introduced only after maximum mentioned dose of first drug was exhibited. If BP was >140/90 mm Hg, relative efficacy of either drug in controlling BP was analyzed. All routine lifestyle recommendations were continued. Patients were recalled every 2 weeks until BP was controlled or until the clinician was satisfied that appropriate therapeutic adjustments had been made. When hypertension control was optimum on two occasions, follow-up was performed on monthly basis.

**Outcomes**

Primary outcome was defined as achieving BP <140/90 mm Hg with a single drug, while secondary outcome was defined as achieving BP <140/90 mm Hg with two or more drugs.

**Statistical Analysis**

The expected sample size was calculated to be 394, with an expected incidence of 10% (of uncontrolled hypertension), confidence interval of 0.95, power of 0.8, and assumed relative risk of 2. Statistical analysis of the data was performed using appropriate statistical packages (SPSS version 18). Frequency, percentage, and paired t-test were used for comparison. P-value less than 0.05 was considered statistically significant. Data were reported as mean ± standard deviation (SD). Changes in BP from initial and subsequent control were tested using the Student’s t-test for paired observations.

**Results**

In total, 1,142 patients with essential hypertension who visited the hospital from November 2015 to July 2017 were enrolled in the study, of which 188 cases were excluded (as given in Flowchart 1). Subsequently, 918 cases which were initially included in the study, underwent baseline assessment and BP measurements, and their antihypertensive medications were discontinued. Thirty-six cases had to be excluded further as 16 cases had to resume their medication and 20 cases withdrew from the study citing unwillingness to discontinue medication or visit hospital frequently. Renin levels were assessed in 918 subjects and subsequent modification of antihypertensives was possible in 896 subjects as 22 were lost to follow-up. The consort diagram of the study is shown in Flowchart 1.

**Baseline Characteristics**

Majority were males [531 (59.26%)] and were in the age group of 50–60 years [431 (48.10%)].
Of the total subjects, 813 (90.73%) had controlled BP while 83 (9.27%) had uncontrolled BP, despite medication. In the controlled BP group, 234 (28.78%) were on single drug, 381 (46.86%) on two drugs, 84 (10.43%) on three drugs, and 114 (14.02%) were on four or more drugs. The initial SBP and DBP (mean ± SD) (mm Hg) were 131 ± 26.22 and 82 ± 16.35, respectively, which increased to 166 ± 34.42 and 98 ± 19.33, after discontinuation of antihypertensives for 2 weeks.

The most commonly used antihypertensives used were diuretics in 529 (65.06%) cases, followed by CCB and beta-blockers used in approximately 50% of the population. In patients on four drugs or patients with uncontrolled BP, more than 90% were already on the above four groups of drugs.

**Plasma Renin Assay Measurements**

The estimation of PRA showed that 287 patients (32.03%) had low PRA levels (<0.51 ng/mL/hr), 412 (45.98%) had high PRA levels (>2.64 ng/mL/hr), while 197 (21.99%) had PRA in the normal range (0.51–2.64 ng/mL/hr). Among the patients on a single drug, 118 (50.42%) had low PRA and 116 (49.57%) had high PRA, while majority of the subjects on two or three drugs had high PRA, as given in Table 2. In uncontrolled BP group, all patients had normal PRA levels.

**Blood Pressure Control after Renin-guided Management**

The antihypertensives of the subjects were modified as per the protocol given in Table 1. Compared to the initial therapy, there was a significant reduction in BP after renin-guided management. In subjects

<table>
<thead>
<tr>
<th>Present type of drug</th>
<th>Status of BP</th>
<th>Modification advised</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low-renin hypertension (LRH)</td>
<td>If BP controlled</td>
<td>Same V drugs</td>
</tr>
<tr>
<td>≥1 V drug, no R drug</td>
<td>If BP &gt;140/90</td>
<td>Increase dose or add V drugs</td>
</tr>
<tr>
<td>≥1 R drug, no V drug</td>
<td>Initial step</td>
<td>Stop R drugs, add V drugs</td>
</tr>
<tr>
<td>≥1 R drug + ≥1 V drug</td>
<td>If BP &gt;140/90</td>
<td>Increase dose or add V drugs</td>
</tr>
</tbody>
</table>

Normal-renin hypertension (NRH) | If still BP >140/90 | Increase dose V/R drugs, additional V/R agent |

<table>
<thead>
<tr>
<th>Present type of drug</th>
<th>Status of BP</th>
<th>Modification advised</th>
</tr>
</thead>
<tbody>
<tr>
<td>High-renin hypertension (HRH)</td>
<td>If BP &gt;140/90</td>
<td>Increase dose or add R drugs</td>
</tr>
<tr>
<td>≥1 R drug, no V drug</td>
<td>Initial step</td>
<td>Stop V drugs, add R drugs</td>
</tr>
<tr>
<td>≥1 V drug, no R drug</td>
<td>If BP controlled</td>
<td>Same R drugs</td>
</tr>
<tr>
<td>≥1 R drug + ≥1 V drug</td>
<td>If still BP &gt;140/90</td>
<td>Increase dose V/R drugs, additional V/R agent</td>
</tr>
</tbody>
</table>

Anti V drugs include diuretics (hydrochlorothiazide and indapamide), CCBs (amlodipine); Anti R drugs include beta-blockers (atenolol and metoprolol), ACEI (ramipril and enalapril), or ARBs (losartan and telmisartan).
with controlled BP, the SBP before and after modification was 133.83 ± 3.36 and 123.87 ± 10.59, respectively (p-value < 0.05), while the corresponding DBP was 84.77 ± 3.12 and 84.05 ± 1.84, respectively (p-value < 0.00). The change in both SBP and DBP was statistically significant in the three- and four-drug group, as shown in Table 3. In subjects with uncontrolled BP, the SBP before and after modification was 152.17 ± 2.95 and 138 ± 1.23, respectively (p-value < 0.05), while the corresponding DBP was 90.36 ± 5.02 and 87.78 ± 0.84, respectively (p-value < 0.05).

The adequacy of BP control was compared before and after renin-guided antihypertensive therapy. In the initial stage, 234 patients (26.12%) were on single drug, 381 (42.52%) on two drugs, eight (9.38%) with controlled BP, the SBP before and after modification was 152.17 ± 2.95 and 138 ± 1.23, respectively (p-value < 0.05), while the corresponding DBP was 90.36 ± 5.02 and 87.78 ± 0.84, respectively (p-value < 0.05).

The adequacy of BP control was compared before and after renin-guided antihypertensive therapy. The SBP before and after modification was 152.17 ± 2.95 and 138 ± 1.23, respectively (p-value < 0.05), while the corresponding DBP was 90.36 ± 5.02 and 87.78 ± 0.84, respectively (p-value < 0.05).

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used by patients who were initially on two or four drugs.

**High-renin hypertension is seen in renovascular hypertension, pheochromocytoma, reninomas, or drugs such as ACEI/ARBs, diuretics, and OCPs.** Low-renin hypertension is seen in several secondary conditions like chronic kidney disease, Cushing’s syndrome, genetic monogenic causes, primary aldosteronism, drugs such as beta-blockers, or other sympatholytic agents like clonidine, alpha-methyl dopa, and NSAIDs. Most studies in the past have shown that HRH with nonsuppressed renin values is observed in approximately 70% of patients, while LRH is noted in 30% of cases.6,8,9

The renin-guided treatment algorithm is based on the vasoconstriction volume analytical model,7 which supports the view that there are two reciprocating long-term supports of BP levels.12 Laragh and Sealey first developed the renin-guided approach to choose antihypertensives and refined their observations over the years.9 Anti V drugs are natriuretic drugs which reduce sodium-related circulating volume and include CCBs, thiazides, loop diuretics, and mineralocorticoid receptor antagonists. Anti R drugs are antirenin/angiotensin II drugs which reduce renin/angiotensin II-related vasoconstriction and include ACEI/ARBs, beta-blockers, and alpha-2 adrenergic receptor antagonists.16 It, therefore, becomes logical to treat LRH patients (PRA < 0.65 ng/mL/hr) primarily with a natriuretic “V” drug and to discontinue “R” drugs in the absence of compelling indications. Similarly, HRH patients (PRA ≥ 0.65 ng/mL/hr) may be treated with an antirenin “R” medication, while subtracting any “V” drugs.13

Renin-guided management has been used in the past. Turner et al. showed that the renin levels and pretreatment BP were the main parameters which can predict systolic and diastolic response to both atenolol and hydrochlorothiazide, and observed an association between in-treatment renin levels and response to add-on therapy.17 The study also showed that hypertensive patients with higher renin, either at baseline or during treatment, responded most favorably to atenolol, an anti-R drug, while those with lower renin responded better to hydrochlorothiazide (anti-V drug).17 In a randomized controlled trial (RCT), Dickerson et al. reported superior efficacy of beta-blockers and ACEI in a population of young white patients with high renin, wherein PRA levels were also associated with BP response to ACE.18 Schwartz et al. observed that renin profiling was superior to the “age-race rule” in predicting BP response to a therapy with candesartan or hydrochlorothiazide.19

However, an RCT by Weir and Saunders observed a lack of correlation between BP reduction and pretreatment renin levels in a cohort of predominantly low-renin African-American hypertensive patients treated with trandolapril.20 Another study in older adult (>70 years old) hypertensive patients, failed to recognize an association between renin levels and BP response to valsartan and/or hydrochlorothiazide.21

To date, studies conducted on renin-guided treatment demonstrate conflicting conclusions regarding the predictive role of renin profiling, which may be likely due to the use of concomitant medications, such as NSAIDs or OCPs which may interfere with renin levels and RAS, and due to differential activity of tissue-specific RAS and systemic RAS in a patient, in whom the tissue-specific RAS cannot be adequately measured.

Renin profiling may be used successfully in the management of refractory hypertension.22 Egan et al. randomized 77 uncontrolled hypertension cases to renin-guided therapy and standard clinical therapy, and found that BP control was better in the former group (74 vs 59%, p = 0.17), and SBP fall was more in the former group (29.1 vs 19.2 mm Hg, p = 0.03).13 Eide et al. found that as many as 67% of their drug-resistant hypertensive patients had low PRA which was successfully managed with a diuretic, amiloride (Anti V drug).16 In PATHWAY-2 study of resistant hypertension, renin levels were estimated in 269 cases and it was found that most patients had low renin due to salt retaining state, which was successfully treated with spironolactone.23 In a hypertensive patient on multiple drugs, there always exists a possibility that few drugs are less effective and may be replaced with different class of drugs which may be more effective.24 Renin-guided therapy offers a possible option to add or titrate drugs based on renin levels. In this study, with renin-guided therapy, the proportion of patients taking polypharmacy (two, three, or four) drugs reduced and more patients could be maintained on a single drug. Minimizing medication burden is important in hypertension management as it reduces pill burden, reduces costs, prevents undue side effects, minimizes drug interactions, and ensures better adherence.25 The cost of renin estimation and its economic burden is a major concern in renin-guided hypertension management. However, a cost-effectiveness study performed by Smith and Campbell suggested that a renin-guided strategy may be more cost-effective in the longer run, particularly for patients with uncontrolled BP.25

The strengths of this study are the size of the study population, ethnic diversity of the population representing the general population, and a large number of PRA measurements using a sensitive assay method. The present study has a few drawbacks. Firstly, PRA levels may be affected by drugs and other conditions. Though these conditions were excluded, there is a likelihood that a few unknown factors could have affected the assay. Second, the adherence to medication and BP measurements at home could not be closely monitored which may lead to variation in BP control. Third, few patients were excluded from the study due to resumption of medication within 2 weeks of discontinuation of antihypertensives and could have led to variation in results.

Renin-guided therapy is a practical and objective method for improving BP control in both controlled and uncontrolled hypertensive patients, and in reducing the number of antihypertensive drugs. This renin-guided algorithm can be used in most clinical settings by a wide range of health care providers for addressing the public health burden of hypertension. Reliable commercially available plasma renin assays are becoming widely available and cheaper, and in the future, renin testing may be more accessible and easy. Further RCTs are recommended to study the effectiveness of renin test-guided treatment in a larger study population, different clinical settings, and patient subgroups.

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Plasma Renin-guided Therapy in Patients of Primary Hypertension

Histological Spectrum of Clinical Kidney Disease in Type 2 Diabetes Mellitus Patients with special Reference to nonalbuminuric Diabetic Nephropathy: A Kidney Biopsy-based Study

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ABSTRACT

Background: Diabetic nephropathy (DN) is an important and catastrophic complication of diabetes mellitus (DM). Kidney disease has heterogeneity in histology in diabetes patients and includes both diabetic kidney disease (DKD) (albuminuric or nonalbuminuric) and nondiabetic kidney disease (N DKD) either in isolation or in coexistence with DN. Diabetic nephropathy is hard to overturn. While ND KD is treatable and reversible.

Materials and methods: We enrolled a total of 50 type 2 diabetes mellitus (T2DM) patients with clinical kidney disease, of both genders and age >18 years, who underwent kidney biopsy from October 2016 to October 2018. Patients with proteinuria <30 mg per day were excluded from the study. The indications of the renal biopsy were nephrotic syndrome (NS), active urinary sediment, rapid decline in renal function, asymptomatic proteinuria, and hematuria.

Result: A total of 50 (males: 42 and females: eight) patients with T2DM who underwent kidney biopsy were enrolled. The clinical presentation was: NS 26 (52%), chronic kidney disease (CKD) 11 (22%), asymptomatic proteinuria and hematuria six (12%), acute kidney injury (AKI) four (8%), and acute nephritic syndrome (ANS) three (6%). Diabetic retinopathy (DR) was noted in 19 (38%) cases. Kidney biopsy revealed isolated DN, isolated ND KD, and ND KD superimposed on DN in 26 (52%), 14 (28%), and 10 (20%) cases, respectively. Idiopathic membranous nephropathy (MN) and amyloidosis (2) were the most common forms of ND KD, whereas diffuse proliferative glomerulonephritis (DPGN) was the main form of ND KD superimposed on DN. Diabetic nephropathy was observed in 15 (79%) cases in presence of DR and also in 11 (35.5%) cases even in absence of DR. Of eight patients with microalbuminuria four (50%) cases have biopsy-proven DN.

Conclusion: About 48% of patients had ND KD either in isolation or in coexistence with DN. Diabetic nephropathy was found in absence of DR and in patients with a low level of proteinuria. The level of proteinuria and presence of DR does not help to distinguish DN vs ND KD. Hence, renal biopsy may be useful in selected T2DM patients with clinical kidney disease to diagnose ND KD.

INTRODUCTION

Diabetes mellitus is an important problem globally. The incidence of T2DM is rapidly rising and accounts for 90% of all cases. Type 2 diabetes mellitus leads to damage to multiple organs, out of which DN is a life-threatening complication. Diabetic nephropathy is not the only renal manifestation of DM. The range of kidney diseases in DM includes both DKD (albuminuric and nonalbuminuric) and ND KD. Recently, a new entity called nonalbuminuric DKD has been described in diabetes patients and is characterized by normoalbuminuria or microalbuminuria with low glomerular filtration rate (GFR). In a patient with long-standing diabetes (both type 1 and type 2) initial GFR loss may occur in the absence of albuminuria and this is more frequent in T2DM. Approximately one-fourth of type 1 diabetes mellitus (T1DM) or T2DM have been found to have nonalbuminuric or microalbuminuric CKD. Nondiabetic kidney disease may occur either in isolation or in coexistence with DN. The prevalence and spectrum of ND KD in DM are extremely variable. Although the common cause of CKD in diabetes is DKD, the diagnosis of ND KD is a must because various ND KD is often plausibly treatable, reversible, and has a good prognosis. Hence, renal biopsy is the gold standard and should be considered in type 2 diabetes patients where the renal manifestation is atypical and with clinical suspicion of ND KD. At present, data on the prevalence and range of ND KD in patients with T2DM are limited from our country.

A Kidney Biopsy-based Study


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ANA, anti-dsDNA antibody, PR3 ANCA, MPO ANCA, and anti-GBM Ab), hepatitis B surface antigen, hepatitis C virus, and HIV were performed in all patients. On basis of 24-hour urinary protein excretion, levels of proteinuria were categorized into microalbuminuria (30–300 mg/day), subnephrotic proteinuria (300–3500 mg/day), and nephrotic range proteinuria (>3500 mg/day). Serum protein electrophoresis was done in the selected case as and when required.

We performed renal biopsy in patients who had been referred to or attended nephrology outpatient department with clinical evidence of kidney disease and met the indications of renal biopsy. The indications of the renal biopsy were: NS, active urinary sediments, rapid decline in renal function, and asymptomatic proteinuria and hematuria. The renal biopsy sample was preserved in a 10% buffered aqueous formaldehyde solution for light microscopy. The sample was studied under light microscopy using hematoxylin and eosin stain, periodic acid-Schiff stain, acid fuchsin orange G, and periodic acid silver methenamine stain. Methyl violet and congo red staining were done on suspicion of amyloidosis on light microscopy (extracellular organized deposits in glomeruli). Electron microscopy and immunofluorescence studies were done. Based on renal histopathology, kidney diseases were categorized into isolated DN, isolated NDKD, and NDKD superimposed on DN (mixed lesion).

**Result**

Of 50 patients (males: 42 and females: eight), male to female ratio was 5.2:1. The mean age of the subject was 52 ± 9.8 years with a range of 26–70 years. The average 24-hour urinary protein of 47 patients was 4.37 gm. Three patients had anuria. The clinical presentation in these patients was: NS 26 (52%), CKD 11 (22%), asymptomatic proteinuria and hematuria six (12%), AKI four (8%), and ANS three (6%) (Table 1). Diabetic retinopathy was observed in 19 (38%) cases and 31 (62%) cases had no evidence of DR. The most common indication of kidney biopsy was NS in 26 (52%) patients. Kidney biopsy revealed isolated DN, isolated NDKD, and NDKD superimposed on DN in 26 (52%), 14 (28%), and 10 (20%) cases, respectively. Idiopathic MN (4) and amyloidosis (2) were the most common cause of isolated NDKD (Table 2). Categories of NDKD in the mixed lesion were DPGN (6), followed by thrombotic microangiopathy (TMA) (2), pauci-immune glomerulonephritis (GN), and vasculitis in one each (Table 2). Of 11 diabetes patients with CKD; six (54.4%) had isolated DN, isolated NDKD in four (36.3%), and one patient had a mixed lesion. Of six diabetic patients with asymptomatic urinary abnormalities, isolated DN was observed in four (66.6%) cases. Isolated NDKD and NDKD superimposed on DN were noted in one patient. Nondiabetic kidney disease superimposed on DN was the most common lesion in patients with AKI in three (75%) and ANS in three (100%) (Table 3, Fig. 1). Of eight cases with microalbuminuria, four (50%) had DN (isolated DN three and mixed lesion one) and remaining four (50%) patients had isolated NDKD. Similarly, in nine cases with subnephrotic proteinuria, isolated DN, isolated NDKD, and NDKD superimposed on DN were observed in four (44.4%), two (22.2%), and three (33.3%) cases, respectively. In 30 cases with nephrotic range proteinuria, 19 (63.3%) patients had isolated DN, eight (26.7%) had NDKD, and the remaining three (10%) cases showed NDKD superimposed on DN (Table 4).

We noted isolated DN in 10 (43.5%) patients with diabetes of <5 years; while in the remaining cases isolated NDKD and NDKD superimposed on DN were observed in nine (39.1%) and four (17.4%) cases, respectively. We observed isolated DN as a predominant lesion in eight (66.7%) patients with diabetes of >10 years. However, we even noted NDKD either alone or superimposed on DN in the remaining four (33.3%) cases with diabetes of >10 years. A majority (79%) of patients with DR had isolated DN. However, NDKD either alone or in mixed form was observed in four (21%) patients in presence of DR. We noted biopsy-proven isolated DN in 11 (35.5%) patients in absence of DR. Twenty patients without DR had isolated NDKD in 12 (38.7%) and NDKD superimposed on DN in eight (25.8%). Thus, DN was the predominant lesion in presence of DR (79%), while a majority (64.5%) of patients had NDKD either alone or in mixed form in the absence of DR (Table 5).

**Discussion**

Although T2DM patients often encounter DKD, they may have other kidney diseases, which are histologically unrelated to diabetes and are called NDKD. Interestingly, the prevalence of NDKD in T2DM patients is widely variable and it depends on demographic features and criteria used for the selection of the population being studied. Gender distribution was male to female ratio 5.2:1, which is similar to other studies. Gender distribution was male to female ratio 5.2:1, which is similar to other studies. The average 24-hour urinary protein excretions was 4.37 g in our patients. Our observation of 24-hour urine protein excretions was 4.37 g in our patients. Our observation of 24-hour urinary protein excretions was similar to other studies. In our patients, NS was

### Table 1: Renal manifestation of T2DM patients (n = 50)

<table>
<thead>
<tr>
<th>Sl. no.</th>
<th>Clinical syndrome</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>NS</td>
<td>26 (52)</td>
</tr>
<tr>
<td>2.</td>
<td>CKD</td>
<td>11 (22)</td>
</tr>
<tr>
<td>3.</td>
<td>Asymptomatic proteinuria and hematuria</td>
<td>6 (12)</td>
</tr>
<tr>
<td>4.</td>
<td>AKI</td>
<td>4 (8)</td>
</tr>
<tr>
<td>5.</td>
<td>ANS</td>
<td>3 (6)</td>
</tr>
</tbody>
</table>

### Table 2: Spectrum of NDKD in type 2 diabetes patients (n = 24)

<table>
<thead>
<tr>
<th>Type of isolated NDKD</th>
<th>n (number)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MN</td>
<td>4</td>
</tr>
<tr>
<td>Amyloidosis</td>
<td>2</td>
</tr>
<tr>
<td>Membranoproliferative GN</td>
<td>1</td>
</tr>
<tr>
<td>Lupus nephritis (LN)</td>
<td>1</td>
</tr>
<tr>
<td>DPGN</td>
<td>1</td>
</tr>
<tr>
<td>Mesangiproliferative GN</td>
<td>1</td>
</tr>
<tr>
<td>Hypertensive nephropathy</td>
<td>1</td>
</tr>
<tr>
<td>Xanthogranulomatous pyelonephritis</td>
<td>1</td>
</tr>
<tr>
<td>Chronic tubulo-interstitial nephritis</td>
<td>1</td>
</tr>
<tr>
<td>TMA</td>
<td>1</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Type of superimposed NDKD</th>
<th>n (number)</th>
</tr>
</thead>
<tbody>
<tr>
<td>DN + DPGN</td>
<td>6</td>
</tr>
<tr>
<td>DN + TMA</td>
<td>2</td>
</tr>
<tr>
<td>DN + pauci-immune GN</td>
<td>2</td>
</tr>
<tr>
<td>DN + vasculitis</td>
<td>2</td>
</tr>
</tbody>
</table>

### Table 3: Type of nephropathy in patients with various renal syndrome (n = 50)

<table>
<thead>
<tr>
<th>Clinical renal syndrome</th>
<th>DN n (%)</th>
<th>NDKD n (%)</th>
<th>DN + NDKD n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NS (n = 26)</td>
<td>16 (61.5)</td>
<td>8 (30.7)</td>
<td>2 (7.6)</td>
</tr>
<tr>
<td>CKD (n = 11)</td>
<td>6 (54.4)</td>
<td>4 (36.6)</td>
<td>1 (9)</td>
</tr>
<tr>
<td>Asymptomatic proteinuria and hematuria (n = 6)</td>
<td>4 (66.6)</td>
<td>1 (16.6)</td>
<td>1 (16.6)</td>
</tr>
<tr>
<td>AKI (n = 4)</td>
<td>Nil</td>
<td>1 (25)</td>
<td>3 (75)</td>
</tr>
<tr>
<td>ANS (n = 3)</td>
<td>Nil</td>
<td>Nil</td>
<td>3 (100)</td>
</tr>
</tbody>
</table>

Histological Spectrum of Clinical Kidney Disease in T2DM Patients
the most common presentation noted in 26 (52%) patients. Nephrotic syndrome was present in 60.9% of cases in a previous study from the same center. In another study chronic renal failure was the most common clinical presentation (47%) followed by ANS (18.7%) and NS (15.6%) in diabetic patients with NDKD. However, in other studies also most frequent clinical presentations of diabetic patients with NDKD were NS, rapidly progressive renal failure, and AKI. Our observation with regards to clinical presentation is corresponding with the majority of the published studies. The decision for renal biopsy in proteinuric T2DM patients has not been defined and a decision is usually individualized. A systemic analysis of 48 studies, including 4,876 diabetic patients indicates that in diabetes patients with clinical suspicion of DN, the prevalence of NDKD is indeed very high (up to 82.9%) of the overall diagnosis. Hence, kidney biopsy should be considered for diagnostic purposes in diabetic patients with atypical clinical presentations and on suspicion of NDKD.

On kidney biopsy, we observed isolated DN in 26 (52%), isolated NDKD in 14 (28%), and NDKD superimposed on DN in 10 (20%) cases. The author had reported that the prevalence of isolated DN ranged from 56.3 to 87.6% in patients with T2DM in his previous study. In other studies, the reported prevalence of isolated DN in patients with T2DM were ranging from 27.5% to 61.5%. In a meta-analysis of 48 studies, it is revealed that the prevalence of DN was extremely variable, ranging from 6.5 to 94%. The reported frequency of NDKD either alone or superimposed on DN is widely variable from 13 to 53% of the total kidney biopsies. The wide variation in the frequency of NDRD in various studies is due to a policy of renal biopsy criteria, and regional and/or racial variations of the different study population.

In isolated NDKD categories, our observation revealed that idiopathic MN four (28.5%) and amyloidosis two (14.3%) were the most common cause of NDKD. Diffuse proliferative glomerulonephritis was the most common [six (60%)] NDKD in mixed lesions. In an earlier study from the same center, the author reported MN as the most common NDKD in 12.9% of proteinuric type 2 diabetic patients. The prevalence of MN in patients with T2DM is variable and ranges from 11.9 to 30%. However, in other studies IgA nephropathy, focal segmental glomerulosclerosis, and minimal change disease were the common NDKD. Hence, variation in prevalence and type of NDKD in diabetes is considerably high. On basis of our observation, it is clear that type 2 diabetes patients presenting with NS or CKD, or asymptomatic proteinuria had isolated DN in approximately two-thirds of cases and isolated NDKD or NDKD superimposed on DN in the remaining one-third cases. We performed kidney biopsy on the patients with T2DM who presented with AKI when renal failure was unexplained and there is clinical suspicion of NDKD characterized by proteinuria >30 mg/day or active urinary sediments. We noted that NDKD either in isolation or in coexistence with DN was the main (up to 100%) cause of rapid deterioration of renal function in type 2 diabetes patients presenting with AKI or ANS. In the four patients with AKI, the presumed diagnosis was NDKD and renal biopsy showed the presence of DPGN in all patients (one isolated NDKD and three superimposed NDKD). Diabetic kidney disease is characterized by slowly progressive renal failure. A rapid decline in renal function over days or weeks is not a feature of DKD and should trigger a search for NDKD.

We observed that isolated DN was more common (66.7%) in patients with diabetes of >10 years than the patients with diabetes of <5 years (43.5%). We noted NDKD either alone or superimposed on DN was more common than DN (56.5 vs 43.5%) in patients with diabetes of <5 years. However, the prevalence of NDKD either alone or superimposed on DN was lower (33.3%) in patients with diabetes of >10 years. Similarly in a previous study author had reported that NDKD was more common than DN (12.9 vs 3.2%)
in patients with diabetes of <5 years and DN was more common than NDKD (32.2 vs 6.5%) in patients with diabetes of >10 years. Thus, our observation supports the result of other studies, indicating that a longer duration of diabetes is associated with a greater likelihood of DN and a shorter duration of diabetes is associated with a greater likelihood of NDKD.

It is widely accepted that the first clinical pointer of DN is increased urinary albumin excretion. However, growing evidence has suggested that a significant number of T2DM patients have low GFR without significant albuminuria and are known as nonalbuminuric DKD. Biopsy studies in diabetic patients with normoalbuminuria and low eGFR revealed histological features of advanced diabetic glomerular lesion than in patients with preserved eGFR. We observed, that of eight cases with microalbuminuria, four (50%) had DN (isolated three and mixed one) and the other four (50%) had isolated NDKD. Although the prevalence of DKD increases with an increase in the degree of proteinuria, the reverse is not true and biopsy-proven DKD can occur in a patient with normo or microalbuminuria. These data do not support the classical model of progression of DKD. Thus, our observation revealed that the level of proteinuria does not help to distinguish between DN and NDKD, and proteinuria is a bad predictor of the type of nephropathy in T2DM patients.

Diabetic retinopathy is found in almost all T1DM with DN, while only 50–60% of cases with T2DM and DN have DR. We observed DR was present in 19 (38%) patients; whereas it was absent in 31 (62%) patients with T2DM. Biopsy proved DN was noted in 11 (35.5%) patients in absence of DR. The author observed that four patients (25%) with biopsy-proven DN did not have evidence of DR in the previous study. Our observation supports the other published studies. Thus, the absence of DR cannot rule out DN because various studies had demonstrated that a high proportion (50–70%) of cases with DN do not have DR.

We noted NDKD either in isolation or in coexistence with DN in four (21%) patients in the presence of DR. Other studies also reported that 31% of patients with NDKD had background DR. Recently one meta-analysis revealed that the sensitivity and specificity of DR in predicting DN were only 65% (95% CI 0.62–0.68) and 75% (95% CI 0.73–0.78), respectively. Thus, DR is a poor/bad predictor of the type of nephropathy in diabetes patients. Hence, the presence of DR may support the diagnosis of DKD but does not exclude NDKD.

**CONCLUSION**

The incidence of NDKD either alone or superimposed on DN was high (48%). Four out of eight (50%) patients with microalbuminuria had biopsy-proven DN. The presence of DR and degree of proteinuria is a poor/bad predictor of DN. Early diagnosis of NDKD in T2DM with help of kidney biopsy is justified; because NDKD is a treatable/curable form of kidney disease with a good prognosis.

**ACKNOWLEDGMENT**

This study was presented at the 49th Annual Conference of the Indian Society of Nephrology (ISNCON 2018, December 20th–23rd) Bhubneshwar, Odisha, India.

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Sodium-glucose Cotransporter-2 Inhibitors in Primary and Secondary Prevention of Cardiovascular and Renal Outcomes in Patients with Type 2 Diabetes Mellitus: A Meta-analysis

Rajiv Kovil1, Manoj Chawla2, Tejas Shah3, Abhay Sahoo4, Brij Makkar5, Jothydev Kesavadev6, Krishna Seshadri7, Mangesh Tiwaskar8, Rajesh Rajput9, Sanjeev Phatak10, Sujoy Majumdar11, Sunil Gupta12

Received: 27 May 2021; Revised: 09 December 2021; Accepted: 08 April 2022

ABSTRACT

Background: The available evidence was systematically reviewed to evaluate the effects of sodium-glucose cotransporter 2 (SGLT2) inhibitors (SGLT2is) on cardiovascular (CV) and renal outcomes in people with type 2 diabetes mellitus (T2DM) and atherosclerotic cardiovascular disease (ASCVD) or multiple risk factors (MRF), with or without heart failure (HF), and per estimated glomerular filtration rate (eGFR) rate at baseline.

Methods: We comprehensively searched three electronic databases to retrieve publications up to 30th November 2019, which were screened for inclusion. The data extracted for the outcomes according to baseline ASCVD, HF, and eGFR levels were meta-analyzed using fixed effects model.

Results: Of the 735 screened citations, 15 primary and secondary publications from five CV or renal outcome trials were included. SGLT2is reduced the risk of CV death or hospitalization for HF (HHF), HHF alone, and composite renal-specific outcome, irrespective of ASCVD and HF at baseline. The three-point major adverse cardiovascular events (3P-MACE) risk was reduced by 14% (p < 0.001) in patients with ASCVD and by 10% (p = 0.018) in those without baseline HF compared with their counterparts. SGLT2is significantly reduced the risk of MACE (18%) in patients with mild kidney dysfunction (eGFR within the range of 60–<90 mL/min/1.73 m² and <60 mL/min/1.73 m²).

Conclusion: SGLT2is are effective for both secondary and primary prevention of composite CV outcomes, and secondary prevention of MACE. The upcoming evidence may strengthen the primary prevention benefits of SGLT2is.

INTRODUCTION

Cardiovascular disease (CVD) is a major cause of death in individuals with T2DM, affecting 32.2% of individuals globally. Moreover, CVD increases the medical costs of T2DM substantially. Thus, primary prevention of CVD, HF, and renal complications is vital to alleviate the overall burden of T2DM.

In 2008, the United States Food and Drug Administration recommended conduct of cardiovascular outcome trials (CVOTs) to demonstrate that the new glucose-lowering agents will not result in an unacceptable increase in CV risk. Various systematic reviews and meta-analyses (SRMA) found SGLT2is to be beneficial in reducing MACE in patients with established ASCVD; some have reported SGLT2is to reduce HHF and progression of renal disease irrespective of pre-existing ASCVD or a history of HF. Nevertheless, the evidence on benefit of SGLT2is delaying CV/HF/renal complications in patients without history of CVD, HF, and normal kidney function is still emerging.

The current SRMA was aimed to evaluate the effects of SGLT2is on cardiovascular outcomes in people with T2DM and established ASCVD or MRF, with or without HF, and per eGFR categories at baseline.

METHODS

This SRMA was performed as per the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) group. High-quality randomized clinical trials (RCTs) with a sample size of ≥1,000 patients were included after systematic literature search and screening for eligibility (Table 1). Data on the study characteristics and efficacy parameters were extracted from the eligible CVOTs and their secondary articles. The Cochrane Handbook for Systematic Interventions Reviews process was applied to assess risk of bias.

Statistical Analysis

R Package Metafor version 2.1-0 was used to perform all statistical analyses. All reported p values and confidence intervals (Cls) are two-sided and no adjustments for multiple testing were made. Within each outcome measure, for each baseline subgroup strata, the hazard ratios (HRs) with 95% CI for the effect of SGLT2is were estimated between the treatments across different risk categories (established ASCVD vs MRF, history of HF vs without history of HF, and baseline eGFR status) and pooled across trials using fixed effects model. Heterogeneity between studies was evaluated using Cochrane’s Q-statistic and the Higgins and Thompson’s I² applying random effects model. Heterogeneity was termed as low, moderate, or high for the I² of around 25, 50, and 75%, respectively. The fixed effects model provided the comparison between the SGLT2i arm and the placebo arm. The difference between the treatment effects across studies is depicted by p for interaction values. Additionally, treatment

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**Table 1:** Search algorithm and selection criteria

<table>
<thead>
<tr>
<th>Database</th>
<th>Search string</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pubmed</td>
<td>(“type 2 diabetes mellitus” OR “T2DM”) AND (“sodium glucose cotransport 2 inhibitor” OR “sodium glucose cotransporter-2” OR “SGLT2”) AND (“stroke” OR “cardiovascular death” OR “myocardial infarction” OR “heart failure” OR “albuminuria” OR “death”)</td>
</tr>
<tr>
<td>Embase</td>
<td>‘sodium glucose cotransporter-2 inhibitor’/exp/mj AND (‘non insulin dependent diabetes mellitus’/exp OR ‘t2dm’/ab,ti OR ‘type 2 diabetes mellitus’/ab,ti) AND (‘cerebrovascular accident’/exp OR ‘stroke’/ab,ti OR ‘cardiovascular death’/exp OR ‘cardiovascular death’/exp OR ‘heart failure’/exp OR ‘myocardial infarct’/ab,ti OR ‘brain ischemia’/exp OR ‘heart failure’/exp OR ‘heart failure’/exp OR ‘death’/ab,ti OR ‘death’/exp OR ‘albuminuria’/exp) AND (‘controlled clinical trial’/de OR ‘controlled clinical trial (topic)’/de OR ‘controlled study’/de OR ‘double blind procedure’/de OR ‘major clinical study’/de OR ‘multicenter study’/de OR ‘observational study’/de OR ‘phase 3 clinical trial’/de OR ‘phase 3 clinical trial (topic)’/de OR ‘prospective study’/de OR ‘randomized controlled trial’/de OR ‘randomized controlled trial (topic)’/de)</td>
</tr>
<tr>
<td>Cochrane</td>
<td>(“type 2 diabetes mellitus” OR T2DM OR “non-insulin dependent diabetes mellitus”) AND (sodium glucose cotransporter inhibitor OR “sodium glucose cotransporter-2” OR “sodium glucose cotransporter-2” OR SGLT2) AND (cerebrovascular accident OR “stroke” OR “myocardial infarction” OR “heart failure” OR “albuminuria” OR “death”)</td>
</tr>
</tbody>
</table>

**Hand search:** Hand search included conference proceedings and articles published until 30th November 2019, and available results from clinicaltrials.gov database.

**Selection criteria**

**Inclusions criteria**
- RCTs including patients with T2DM ≥ 18 years of age on treatment with SGLT2i
- RCTs including patients with T2DM without established CV disease OR RCTs including patients with T2DM without established HF OR RCTs including patients with T2DM having microalbuminuria (>30 mg and <300 mg per day of albumin in the urine)
- RCTs published in English language

**Exclusion criteria**
- RCTs including patients with T2DM with a history of diabetic ketoacidosis, type 1 diabetes mellitus, pancreas or beta-cell transplantation, or diabetes secondary to pancreatitis or pancreatectomy only
- RCTs including patients with T2DM with a history of one or more severe hypoglycemic (i.e., very low blood sugar) episode within 6 months before screening only
- Smaller RCTs with a sample size < 1,000
- Studies for which the full-text articles are unavailable

Effect modification by baseline characteristics (ASCVD vs MRF, HF vs no HF, and eGFR level) was tested using random effects model, applying the method of restricted maximum likelihood estimation and Hartung-Knapp adjustment of the test statistic for five endpoints, viz., 3P-MACE, HHF, composite CV death or HHF, and composite renal.

**RESULTS**

**Selected Trials and Baseline Characteristics**

Five cardiac and renal outcome studies, CANVAS, EMPA-REG-OUTCOME, DECLARE-TIMI-58, CREDENCE, and DAPA-HF (15 primary and secondary publications with 43,467 patients) were selected for meta-analysis (Fig. 1). As all the studies were well-designed RCTs, the risk of bias was assigned as “low”. There was no heterogeneity between the studies for most outcomes.

The baseline characteristics of patients on SGLT2i are detailed in Table 2. The mean age of the population was between 62 and 67 years with 23–37% females. The mean duration of T2DM was 11–15.5 years. Patients with history of ASCVD at baseline ranged between 40.5 and 99.4% across the studies and those with HF ranged between 9.9 and 14.9% except for the DAPA-HF study (all patients had HF). All patients enrolled in CREDENCE study had baseline eGFR between 30 and 90 mL/min/1.73 m² [mean ± standard deviation (SD) 56.2 ± 18.2 mL/min/1.73 m²].

**3P-MACE**

In comparison with placebo, a significant risk reduction of 14% was observed in 3P-MACE when treated with SGLT2is (p < 0.001) in patients with a history of ASCVD; the risk was reduced by 6% in patients with MRF (p = 0.364). The treatment effects did not differ significantly between the subgroups (p for interaction = 0.318) (Fig. 2A). The 3P-MACE risk was reduced significantly in patients without a history of HF (HR 0.90, 95% CI 0.83–0.98; p = 0.018) but not in those with a history of HF (p for interaction = 0.865) (Fig. 2B). When stratified by eGFR categories, the benefit was higher in the patients having eGFR < 60 mL/min/1.73 m² (HR 0.82, 95% CI 0.71–0.95; p = 0.009; p for interaction = 0.484) (Fig. 2C).

**HHF**

In patients with ASCVD, SGLT2i use reduced the risk for HHF significantly by 30% (95% CI 0.61–0.79; p < 0.001) and in patients with MRF by 37% (95% CI 0.50–0.80; p < 0.001; p for interaction = 0.323) (Fig. 3A). Likewise, significant risk reductions in HHF were observed in patients irrespective of history of HF (p < 0.001; p for interaction = 0.822) (Fig. 3B). SGLT2is significantly reduced the risk of HHF in patients with eGFR categories < 90 mL/min/1.73 m² but not in those with eGFR ≥ 90 mL/min/1.73 m² (Fig. 3C).

**Composite of CV Death or HHF**

The reduction in composite endpoint of CV death or HHF was statistically significant (p ≤ 0.01) in patients with baseline ASCVD (HR 0.74, 95% CI 0.68–0.81) and patients with MRF (HR 0.81, 95% CI 0.69–0.95; p for interaction = 0.354) (Fig. 4A) with a low heterogeneity between the studies (I² = 17.50%). The HRs for composite of CV death or HHF in patients with and without a history of HF were 0.73 (95% CI 0.66–0.81) and 0.79 (95% CI 0.71–0.88); p = 0.001 for both; p for interaction = 0.510 (Fig. 4B) with a moderate heterogeneity between the studies (I² = 40.03%). Similarly, risk reduction per eGFR status was statistically significant in patients with eGFR < 60 mL/min/1.73 m² and 60–90 mL/min/1.73 m² (HR 0.74, 95% CI 0.64–0.85 and HR 0.80, 95% CI 0.71–0.89; p < 0.001) (Fig. 4C). No significant differences were found between the subgroups (p for interaction = 0.323).
Sodium-glucose Cotransporter-2 Inhibitors in Primary and Secondary Prevention

Renal Outcomes
Significant renoprotection (in composite renal-specific outcomes including worsening of renal function, end-stage renal disease, or renal death) was observed in patients with baseline ASCVD (HR 0.59, 95% CI 0.50–0.70; p < 0.001) and MRF (HR 0.57, 95% CI 0.46–0.71; p < 0.001; p for interaction = 0.786) (Fig. 5A). Risk reduction was also significant in patients regardless of baseline history of HF (HR 0.64, 95% CI 0.45–0.91; p = 0.013 vs HR 0.52, 95% CI 0.44–0.61; p < 0.001; p for interaction = 0.036) (Fig. 5B). When stratified by baseline eGFR, patients with eGFR ≥90 mL/min/1.73 m² showed the highest renoprotection (HR 0.44, 95% CI 0.32–0.59; p < 0.001; p for interaction = 0.107) (Fig. 5C).

Qualitative Summarization of Safety Outcomes
Safety outcomes from the included studies are qualitatively summarized in Table 3. SGLT2is increased the risk of genital infections in both males and females. A significant increase in the risks of amputations and fractures was evident with canagliflozin in CANVAS program, but this was not observed in other CVOTs.

Discussion
This meta-analysis builds on to the previous meta-analyses evidence of CVOTs demonstrating the significant effect of SGLT2is in reducing HHF and renal disease progression irrespective of existing ASCVD or HF.5,29–31 SGLT2is significantly reduced the risk of HHF and CV death or HHF irrespective of history of ASCVD at baseline (risk reduction of 19–37%) compared with placebo. Patients who had baseline ASCVD (secondary prevention group) were at lower risk of MACE, when treated with SGLT2is; however, this phenomenon was not observed in patients without a history of ASCVD. Thus SGLT2is are more likely to provide CV benefits in secondary prevention of CV outcomes in patients with ASCVD. Effects of SGLT2is on glycaemia, body weight, blood pressure, and lipids may possibly explain the CV risk reduction in patients with ASCVD.32

In our SRMA, SGLT2is significantly reduced the risk of majority of CV outcomes (HHF, CV death, or HHF) regardless of history of HF at baseline. A recent meta-analysis reported similar benefit of SGLT2is in reducing the risk of HHF in patients with HF (OR 0.68, 95% CI 0.55–0.83; p = 0.000; I² = 6.7%) and without HF (OR 0.71, 95% CI 0.60–0.83; p = 0.0000; I² = 0.0%).33

Unlike patients with ASCVD, SGLT2is did not reduce the risk of MACE in patients with HF; however, these outcomes were delayed in patients with no history of HF (10% risk reduction). Hupfeld and Mudaliar postulated that SGLT2 inhibition benefits are primarily because of their effects on HF and HHF. Our meta-analysis confirms this fact by demonstrating benefit of SGLT2is with respect to important CV outcomes such as 3P-MACE, HF, and composite of CV deaths and HHF in patients without HF at baseline.

In our SRMA, it was evident that SGLT2is reduced the risk of the composite of CV deaths or HHF irrespective of baseline eGFR categories. Furthermore, we observed that SGLT2is significantly delayed the worsening of composite renal outcomes compared with placebo, irrespective of risk categories at baseline, that is, HF, ASCVD, and eGFR status. This finding is consistent with the finding by Neuen et al. reporting renoprotective effects of SGLT2is such as a reduction in risk of dialysis, transplantation, or death due to kidney disease (relative risk 0.67, 95% CI 0.52–0.86; p = 0.0019).30

We observed maximum benefit of SGLT2is with respect to MACE (18% risk reduction) in the case of patients with reduced kidney function (eGFR between 60 and <90 mL/min/1.73 m² and <60 mL/min/1.73 m²). This observation is consistent with the observation by Arnott et al.30 as well as Lo et al.31 and various known mechanisms such as osmotic diuresis, restoration of homeostasis, and improved cardiac energy metabolism by which SGLT2is have beneficial cardiorenal effects.34

Our SRMA had various limitations such as diversity of patient subgroups across the trials; most patients (~85%) not having history of HF (except for DAPA-HF); diverse

Fig. 1: PRISMA flow diagram for study selection
CVOTs, cardiovascular outcome trials; GLD, glucose-lowering drugs; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; RCT, randomized controlled trials; SRMA, systematic review and meta-analysis
### Table 2: Baseline characteristics of patients in the SGLT2 inhibitor arm of the included outcome trials

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>EMPA-REG-OUTCOME</th>
<th>CANVAS</th>
<th>DECLARE-TIMI-58</th>
<th>CREDENCE</th>
<th>DAPA-HF*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Drug (N)</strong></td>
<td>Empagliflozin (N = 4687)</td>
<td>Canagliflozin (N = 5795)</td>
<td>Dapagliflozin (N = 8582)</td>
<td>Canagliflozin (N = 2202)</td>
<td>Dapagliflozin (N = 2373)</td>
</tr>
<tr>
<td><strong>Drug dose (mg/day)</strong></td>
<td>10, 25</td>
<td>100, 300</td>
<td>10</td>
<td>100</td>
<td>10</td>
</tr>
<tr>
<td><strong>Mean age (years) ± SD</strong></td>
<td>63.1 ± 8.6</td>
<td>63.2 ± 8.3</td>
<td>63.9 ± 6.8</td>
<td>62.9 ± 9.2</td>
<td>66.2 ± 11.0</td>
</tr>
<tr>
<td><strong>Female gender, n (%)</strong></td>
<td>1351 (28.8)</td>
<td>2036 (35.1)</td>
<td>3171 (36.9)</td>
<td>762 (34.6)</td>
<td>564 (23.8)</td>
</tr>
<tr>
<td><strong>Mean body mass index (kg/m²) ± SD</strong></td>
<td>30.6 ± 5.3</td>
<td>31.9 ± 5.9</td>
<td>32.1 ± 6.0</td>
<td>31.4 ± 6.2</td>
<td>28.2 ± 6.0</td>
</tr>
<tr>
<td><strong>Mean duration of diabetes (years) ± SD</strong></td>
<td>NR</td>
<td>13.5 ± 7.7</td>
<td>11.0 (6.0–16.0)**</td>
<td>15.5 ± 8.7</td>
<td>NR</td>
</tr>
<tr>
<td><strong>Mean glycated hemoglobin (%)</strong></td>
<td>8.07 ± 0.85</td>
<td>8.2 ± 0.9</td>
<td>8.3 ± 1.2</td>
<td>8.3 ± 1.3</td>
<td>NR</td>
</tr>
<tr>
<td><strong>Mean eGFR (mL/min/1.73 m²) ± SD</strong></td>
<td>74.2 ± 21.6</td>
<td>76.7 ± 20.3</td>
<td>85.4 ± 15.8</td>
<td>56.3 ± 18.2</td>
<td>66.0 ± 19.6</td>
</tr>
<tr>
<td><strong>Patients with eGFR &lt;60 mL/min/1.73 m², n (%)</strong></td>
<td>1212 (25.9)</td>
<td>NR</td>
<td>606 (7.06)</td>
<td>1297 (58.9)</td>
<td>962 (40.6)</td>
</tr>
<tr>
<td><strong>Patients with established ASCVD, n (%)</strong></td>
<td>4657 (99.4)</td>
<td>4127 (71.2)</td>
<td>3474 (40.5)</td>
<td>1113 (50.5)</td>
<td>NR</td>
</tr>
<tr>
<td><strong>Patients with history of HF, n (%)</strong></td>
<td>462 (9.9)</td>
<td>803 (13.9)</td>
<td>852 (9.9)</td>
<td>329 (14.9)</td>
<td>2373 (100)</td>
</tr>
<tr>
<td><strong>Previous antidiabetic therapies</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insulin, n (%)</td>
<td>2252 (48.0)</td>
<td>2890 (49.9)</td>
<td>3567 (41.6)</td>
<td>1452 (65.9)</td>
<td>274/993 (27.6)</td>
</tr>
<tr>
<td>Metformin/biguanides, n (%)</td>
<td>3459 (73.8)</td>
<td>4447 (76.7)</td>
<td>7020 (81.8)</td>
<td>1276 (57.9)</td>
<td>504/993 (50.8)</td>
</tr>
<tr>
<td>Sulfonylurea, n (%)</td>
<td>2014 (43.0)</td>
<td>2528 (43.6)</td>
<td>3615 (42.1)</td>
<td>612 (27.8)</td>
<td>228/993 (23.0)</td>
</tr>
<tr>
<td>DPP-4 inhibitors, n (%)</td>
<td>529 (11.3)</td>
<td>697 (12.0)</td>
<td>1418 (16.5)</td>
<td>378 (17.2)</td>
<td>161/993 (16.2)</td>
</tr>
<tr>
<td>GLP-1 receptor agonist, n (%)</td>
<td>126 (2.7)</td>
<td>222 (3.8)</td>
<td>397 (4.6)</td>
<td>89 (4.0)</td>
<td>11/993 (1.1)</td>
</tr>
<tr>
<td>Concurrent CV therapies</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antplatelet agents, n (%)</td>
<td>4162 (88.8)</td>
<td>4233 (73.0)</td>
<td>5245 (61.1)</td>
<td>1341 (60.9)</td>
<td>NR</td>
</tr>
<tr>
<td>ACE inhibitor or ARB, n (%)</td>
<td>3798 (81.0)</td>
<td>4645 (80.2)</td>
<td>6977 (81.3)</td>
<td>2201 ( &gt; 99.9)</td>
<td>ACE inhibitor 1332 (56.1); ARB 675 (28.4)</td>
</tr>
<tr>
<td>Beta-blocker, n (%)</td>
<td>3056 (65.2)</td>
<td>3039 (52.4)</td>
<td>4498 (52.4)</td>
<td>883 (0.1)</td>
<td>2278 (96.0)</td>
</tr>
<tr>
<td>Statin or ezetimibe, n (%)</td>
<td>3630 (77.4)</td>
<td>4329 (74.7)</td>
<td>6432 (74.9)</td>
<td>1538 (69.8)</td>
<td>NR</td>
</tr>
<tr>
<td>Diuretics, n (%)</td>
<td>2047 (43.7)</td>
<td>2536 (43.8)</td>
<td>3488 (40.6)</td>
<td>1026 (46.6)</td>
<td>2216 (93.4)</td>
</tr>
</tbody>
</table>

*Previous antidiabetic therapies*

Baseline characteristics of patients in the placebo are not presented; *At screening, 42% of patients enrolled in DAPA-HF trial in dapagliflozin arm and placebo arm had a history of T2DM, and an additional 3% of patients in each group received a new diagnosis of T2DM; **Data represented as median and range; ACE, angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blockers; DPP-4, dipeptidyl peptidase 4; GLP-1, glucagon-like peptide-1; NR, not reported

### Table 3: Qualitative summarization of safety outcomes

| Event | CANVAS CREDENCE EMPA-REG-OUTCOME DECLARE-TIMI-58 CREDENCE EMPA-REG-OUTCOME DECLARE-TIMI-58 DAPA-HF* |
|-------|--------------------------------------------------|---------------------------------|---------------------------------|---------------------------------|---------------------------------|---------------------------------|---------------------------------|
|       | (Incidence per 1000 patient-years) | (Incidence per 1000 patient-years) | n (% of events) | n (% of events) | n (% of events) | n (% of events) | n (% of events) |
| Diabetic ketoacidosis | 0.6 | 0.3 | 2.2 | 0.2 | 4 (0.1) | 1 (<0.1) | 27 (0.3) | 12 (0.1) | 3 (0.1) | 0 (0) |
| Amputation | 6.3 | 3.4 | 12.3 | 11.2 | NR | NR | 123 (1.4) | 113 (1.3) | 13 (0.5) | 12 (0.5) |
| Fracture | 15.4 | 11.9 | 11.8 | 12.1 | 179 (3.8) | 91 (3.9) | 457 (5.3) | 440 (5.1) | 49 (2.1) | 50 (2.1) |
| Acute kidney injury | 3.0 | 4.2 | 16.9 | 20.0 | 45 (1.0) | 37 (1.6) | 125 (1.5) | 175 (2.0) | 23 (1.0) | 46 (1.9) |
| Male genital infections | 34.9 | 10.8 | 8.4 | 0.9 | 166 (5.0) | 25 (1.5) | 76 (0.9)** | 9 (0.1)** | NR | NR |
| Female genital/mycotic infections | 79.4 | 18.1 | 12.6* | 6.1 | 135 (10.0) | 17 (2.6) | NR | NR |
| Urinary tract infection | 43.0 | 39.2 | 48.3 | 45.1 | 842 (18.0) | 423 (18.1) | 127 (1.5) | 133 (1.6) | 11 (0.5) | 17 (0.7) |

The data on safety were available as incidence per 1000 patient-years in CANVAS and CREDENCE program while it was available as percentages of events for EMPA-REG-OUTCOME, DECLARE-TIMI-58, and DAPA-HF studies; *At screening, 42% of patients enrolled in DAPA-HF trial in dapagliflozin arm and placebo arm had a history of T2DM, and an additional 3% of patients in each group received a new diagnosis of T2DM; **Values available as total genital infections including male and female genital infections; n, number of patients in the subgroup; NR, not reported
Figs 2A to C: Effect of SGLT2is on MACE
ASCVD, atherosclerotic cardiovascular disease; CI, confidence interval; eGFR, estimated glomerular filtration rate; HF, heart failure; HR, hazard ratio; MRF, multiple risk factors; NA, not available; N, number of patients in each arm; SGLT2i, sodium-glucose cotransporter-2 inhibitors
### Sodium-glucose Cotransporter-2 Inhibitors in Primary and Secondary Prevention

**Journal of the Association of Physicians of India, Volume 70 Issue 8 (August 2022)**

**Figs 3A to C: Effect of SGLT2is on HHF**

ASCVD, atherosclerotic cardiovascular disease; CI, confidence interval; eGFR, estimated glomerular filtration rate; HF, heart failure; HR, hazard ratio; MRF, multiple risk factors; NA, not available; N, number of patients in each arm; SGLT2i, sodium-glucose cotransporter-2 inhibitors; T2DM, type 2 diabetes mellitus

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### Table: Stratified by Baseline ASCVD

<table>
<thead>
<tr>
<th>Trial program</th>
<th>Patients</th>
<th>Rate per 1000 patient-years</th>
<th>Weight (%)</th>
<th>HR</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>EMPA-REG OUTCOME$^a$</td>
<td>4697</td>
<td>2333</td>
<td>9.40</td>
<td>14.50</td>
<td>24.79</td>
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<tr>
<td>CANVAS$^b$</td>
<td>3766</td>
<td>2900</td>
<td>7.30</td>
<td>11.20</td>
<td>21.64</td>
</tr>
<tr>
<td>DECLARE-TIMI 58$^c$</td>
<td>3747</td>
<td>3500</td>
<td>NA</td>
<td>NA</td>
<td>31.37</td>
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<tr>
<td>CREDENCE</td>
<td>1113</td>
<td>1167</td>
<td>20.80</td>
<td>33.20</td>
<td>16.12</td>
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<tr>
<td>Fixed effect model ($p=0.001$) Q Statistic = 1.97, $p=0.579$</td>
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</tbody>
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### Table: Stratified by Baseline Heart Failure

<table>
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<th>Trial program</th>
<th>Patients</th>
<th>Rate per 1000 patient-years</th>
<th>Weight (%)</th>
<th>HR</th>
<th>HR (95% CI)</th>
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</thead>
<tbody>
<tr>
<td>EMMA-REG</td>
<td>462</td>
<td>244</td>
<td>40.70</td>
<td>52.40</td>
<td>8.44</td>
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<tr>
<td>CANVAS$^d$</td>
<td>803</td>
<td>458</td>
<td>14.10</td>
<td>21.10</td>
<td>9.40</td>
</tr>
<tr>
<td>DECLARE-TIMI 58$^e$</td>
<td>852</td>
<td>724</td>
<td>NA</td>
<td>NA</td>
<td>22.43</td>
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<tr>
<td>Fixed effect model ($p=0.001$) Q Statistic = 2.21, $p=0.53$</td>
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<td></td>
<td></td>
<td>100.00</td>
</tr>
</tbody>
</table>

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### Table: Stratified by Baseline eGFR Status

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<tr>
<th>Trial program</th>
<th>Patients</th>
<th>Rate per 1000 patient-years</th>
<th>Weight (%)</th>
<th>HR</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>eGFR &lt;90 mL/min/1.73 m$^2$</td>
<td>1212</td>
<td>607</td>
<td>14.80</td>
<td>25.70</td>
<td>41.83</td>
</tr>
<tr>
<td>EMMA-REG OUTCOME</td>
<td>NA</td>
<td>NA</td>
<td>9.60</td>
<td>16.00</td>
<td>26.38</td>
</tr>
<tr>
<td>CANVAS$^f$</td>
<td>606</td>
<td>659</td>
<td>NA</td>
<td>NA</td>
<td>31.74</td>
</tr>
<tr>
<td>Fixed effect model ($p=0.001$) Q Statistic = 6.3, $p=0.061$</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>100.00</td>
</tr>
</tbody>
</table>

---

### Notes

- No heterogeneity was found between the subgroup (Q statistic = 2.00, $p=0.848$).
- $I^2 = 0.000$, $P_{het} = 0.323$.

- 41.1% of patients enrolled in DAPA-HF trial in dapagliflozin arm and placebo arm had a history of T2DM, and an additional 3% of patients in each group received a new diagnosis of T2DM.
- No heterogeneity was found between the subgroup (Q statistic = 3.942, $p=0.558$, $I^2 = 0.000$).

- No heterogeneity was found between the subgroup (Q statistic = 1.668, $p=0.498$, $I^2 = 0.000$).
Figs 4A to C: Effect of SGLT2is on composite CV death or HFH

ASCVD, atherosclerotic cardiovascular disease; CI, confidence interval; eGFR, estimated glomerular filtration rate; HF, heart failure; HR, hazard ratio; MRF, multiple risk factors; NA, not available; N, number of patients in each arm; SGLT2i, sodium-glucose cotransporter-2 inhibitors; T2DM, type 2 diabetes mellitus
Figs 5A to C: Effect of SGLT2is on composite renal-specific outcomes
ASCVD, atherosclerotic cardiovascular disease; CI, confidence interval; eGFR, estimated glomerular filtration rate; HF, heart failure; HR, hazard ratio; MRF, multiple risk factors; NA, not available; N, number of patients in each arm; SGLT2i, sodium-glucose cotransporter-2 inhibitors.
definitions of MRF and composite renal outcomes across the studies; limited number of renal events and most of the data emerging from secondary/post hoc analysis of CVDs; however, the data were homogenous and studies had low risk of bias.

To conclude, the SGLT2is reduced the risk of “CV death or HHF”, HHF, and composite renal-specific outcomes irrespective of ASCVD or HF at baseline. Greater benefit of SGLT2is was seen in primary prevention of 3P-MACE in patients with and without T2DM. However, in patients without a history of HF. As ASCVD outcomes are mostly driven by the incidence of HF, SGLT2is may hold value in primary prevention of CV outcomes in patients without ASCVD as well when compared with other glucose-lowering agents. More empirical evidences are necessary to understand the role of SGLT2is in the primary prevention of 3P-MACE in patients with and without T2DM with MRF.

Acknowledgments
The authors would like to thank AstraZeneca Pharma India Ltd. for providing medical writing support in collaboration with Neelam Joglekar, M.Sc., and Prajakta Nachane, M.Pharm. from Labcorp Scientific Services & Solutions Pvt. Ltd. for medical writing support, and Jyothi Subramanian, Ph.D. from LabCorp Scientific Services & Solutions Pvt. Ltd. for statistical analysis support in accordance with GPP3 guidelines (http://www.ismpp.org/gpp3).

References
The most extensively studied Indian dapagliflozin
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Overweight patients with IGT* and/or IFG*
Still progressing towards T2DM despite lifestyle changes for 3 to 6 months
PCOS Patients with Prediabetes, Women with History of GDM

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No additional safety concerns

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*English, Hindi, Bengali, Gujarati, Marathi, Punjabi, Tamil, Assamese, Kannada, Malayalam, Oriya and Telugu.
Assessment of Prevalence and Associated Risk Factors of NAFLD in People Living with Diabetes in India: A Retrospective, Multicenter, Electronic Medical Records Based Study

Sanjay Kalra1, Ashok Kumar Das2, Mangesh Tiwaskar3, Mohan Prasad V4, Manmohan Singh5*

Received: 30 April 2020; Accepted: 30 May 2022

ABSTRACT

Introduction: Nonalcoholic fatty liver disease (NAFLD) has become a leading cause of liver disease worldwide. The prevalence of NAFLD varies depending on population studied and type of diagnostic tools used to screen or diagnose the patients. There is a strong relationship between metabolic syndrome components and NAFLD prevalence. This study aims to understand the prevalence of NAFLD along with the associated risk factors and their interaction with other comorbidities among people living with diabetes in Indian context.

Materials and methods: It is a retrospective, observational study based on data retrieved from electronic medical records (EMRs) of people living with diabetes from more than 250 individual centers located in more than 30 cities across 14 states in India. Medical records of 171,996 adults living with diabetes were included in the analysis. The assessment of prevalence of NAFLD in diabetes was done using algorithm based on alanine transaminase (ALT) and aspartate aminotransferase (AST).

Results: Overall, 44.49% of people living with diabetes were found to have NAFLD. A significantly higher proportion of males (58.64%) had NAFLD compared to females (36.91%) (p < 0.001). Nonalcoholic fatty liver disease prevalence was >50% in seven of the states. People living with diabetes with dyslipidemia and hypertension had a significantly higher prevalence of NAFLD (p < 0.001). Obesity (57.1%), dyslipidemia (59.1%), and hypertriglyceridemia (42.3%) had significantly higher odds of NAFLD among people living with diabetes.

Conclusion: This study highlighted high-risk categories for NAFLD in diabetes, like young, obese, hypertriglyceridemia, poor glycemic control, etc. This information will help health care providers in prioritizing screening among high-risk diabetes population.

ORIGINAL ARTICLE

INTRODUCTION

Nonalcoholic fatty liver disease has become the leading cause of liver disease worldwide.1 It is a common hepatic disorder characterized by more than 5% of the accumulation of fat in the liver and refers to a spectrum of diseases ranging from pure steatosis to nonalcoholic steatohepatitis (NASH) and cirrhosis, in the absence of excessive or moderate alcohol consumption.

The prevalence of NAFLD varies depending on the population studied and the type of diagnostic tools used to screen or diagnose in studies. A meta-analysis (by Younossi et al.) of 86 studies from 22 countries, estimated a global prevalence of NAFLD as 25.2% [95% confidence interval (CI): 22.1–28.7%] and also highlighted obesity, type 2 diabetes, hypertension, hyperlipidemia, and metabolic syndrome as major comorbidities associated with NAFLD.2

Studies from India also showed marked variability in the prevalence of NAFLD ranging from 5 to 28%.3–6 People living with type 2 diabetes tend to have an increased risk of developing NAFLD and subsequent fibrosis, cirrhosis, and hepatocellular carcinoma.7 The link between NAFLD and diabetes is insulin resistance, leading to defective lipid metabolism and hepatic triglyceride (TG) accumulation in NAFLD and compensatory hyperinsulinemia leading to β-cell dysfunction in type 2 diabetes.8 A meta-analysis9 in 2019 covering 80 studies from 20 countries estimated the overall prevalence of NAFLD among type 2 diabetes mellitus (T2DM) to be 55.5%. The study also showed that the prevalence of NAFLD is more than two times higher in T2DM compared to that in the general population. The prevalence of NAFLD diagnosed with ultrasonography was 69.4% in 180 patients with T2DM as reported by Kalra et al. in 2013.6

The prevalence of NAFLD in India was found to be 44–72% in T2DM.3–5,6 The SPRINT report in 2014, one of the large-scale multicentric surveys from 101 cities across India concluded the overall prevalence of NAFLD to be 56.5% among 924 type 2 diabetes patients aged between 25 and 84 years. The prevalence was lowest in western India (44.1%) as compared to the northern states of India (72.4%).6,10 A study by Gupta et al. in 201711 reported the prevalence of NAFLD to be 69.3% in the patients with T2DM and the severity of NAFLD increased with increasing age.

Nonalcoholic fatty liver disease in T2DM is a risk factor for the development of cardiovascular disease and other vascular complications, irrespective of other known risk factors.12,13 In addition to the presence of diabetes, age (>45 years), obesity (body mass index (BMI) > 30 kg/m²), insulin resistance, elevated levels of ferritin, and hypertension are other clinical risk factors that contribute to higher risk of NAFLD progression.10,14 There is a strong relationship between metabolic syndrome components and NAFLD prevalence. Wong et al.,15 reported that each new metabolic syndrome component contributed significantly to the risk of NAFLD (prevalence of 4.5% in noncomponent subjects to 80.0% in all component subjects). Therefore, the patients with metabolic syndrome show high prevalence of NAFLD.
It is important to understand the prevalence of NAFLD along with the associated risk factors in patients living with diabetes in Indian context. This study aims to understand NAFLD prevalence patterns among T2DM patients across age, gender, states, and comorbidities, and to assess high-risk categories for NAFLD in Indian patients living with diabetes based on EMRs.

**Materials and Methods**

**Study Settings**

It is a retrospective, observational study based on data retrieved from EMRs of patients living with diabetes from over 250+ individual diabetes centers located in 30+ cities across 14 states in India. Medical records of 171,996 adult patients living with diabetes (age >18 years) were included in the analysis. Only first visit details were included from multiple visits to maintain uniformity across the analysis. The study was conducted in accordance with the Declaration of Helsinki and deidentified and anonymized data were used to maintain confidentiality of the patients.

**Inclusion Criteria**

Adult patients (age >18 years) with diabetes mellitus (DM) as per the EMR records, availability of at least one liver function test (LFT) report in medical records of patients were included and in case more than one data points were present for a subject, the first recorded LFT and concomitant lab parameters were used for the analysis.

Based on LFT algorithm (mentioned below), patients living with diabetes were categorized as with or without NAFLD. The algorithm used for identifying NAFLD patients with diabetes is given below:

- Serum glutamate pyruvate transferase (SGPT) or ALT levels between 25 and 150 IU/L, and
- Serum glutamic oxaloacetic transaminase (SGOT):SGPT (AST:ALT) ratio of less than 1.

Using the abovementioned algorithm, NAFLD prevalence patterns across baseline variables such as demographic (age and gender) and geographical (state and city) were assessed.

Nonalcoholic fatty liver disease prevalence rates across the following categories were assessed:

- Age categories: 18–40, 40–60, and >60 years.
- Body mass index categories: <23, 23–25 (overweight), and >25 kg/m² (obese).
- Hypertension—systolic blood pressure >140 mm Hg and/or diastolic blood pressure >90 mm Hg.
- Dyslipidemia—TG >150 and/or low-density lipoprotein (LDL) >130 and/or total cholesterol (TC) >200 and/or high-density lipoprotein (HDL) <40 mg/dL. If any of the criteria is positive (LDL or HDL or TC or TG).
- Hypertriglyceridemia >200 mg/dL.
- Duration of diabetes—less than 4 years, 4–8 years, 8–14 years, and 14 years and above.

Using the above parameters, prevalence rates and odds of developing NAFLD were estimated across the following categories:

- Nonalcoholic fatty liver disease prevalence rate in patients living with diabetes with and without obesity (overweight and obese categories were clubbed together).
- Nonalcoholic fatty liver disease prevalence rate in patients living with diabetes with and without dyslipidemia.
- Nonalcoholic fatty liver disease prevalence rate in patients living with diabetes with and without hypertriglyceridemia.
- Nonalcoholic fatty liver disease prevalence rate in patients living with diabetes with and without hypertension.
- Nonalcoholic fatty liver disease prevalence rate in patients living with diabetes with and without dyslipidemia and hypertension together.
- Nonalcoholic fatty liver disease prevalence rate in patients living with diabetes across age and gender categories.
- Nonalcoholic fatty liver disease prevalence rate in diabetes depending on the duration of diabetes and glycemic control.

**Statistical Analysis**

The data were analyzed using Microsoft Excel and R software. Descriptive tables for age, gender distribution, and geographical patterns of distribution of the overall NAFLD patient population are plotted. Nonalcoholic fatty liver disease prevalence is estimated across states and regions. Continuous variables like age, glycated hemoglobin (HbA1c), TC, and TG are presented as mean (standard deviation (SD)). Categorical variables like number of patients in each category according to age, gender, and state are presented as proportions. The prevalence rates are compared across different categories using the Chi-square/Fisher’s exact test. Continuous variables like lab parameters are compared using the Student’s t-test. Odds ratios (ORs) are calculated across various categories. P <0.05 is considered significant for statistical comparisons.

**Results**

Electronic medical records of 171,996 patients living with diabetes with average age of 53.18 years (SD: 12.51) were taken for the analysis. Baseline clinical and diagnostic parameters were compared (Table 1). Overall, 44.48% of the patients living with diabetes were found to have NAFLD. A significantly higher proportion of males (58.64%) in the study had NAFLD compared to females (36.91%) (p<0.001) (Fig. 1).

As shown in Table 2, NAFLD prevalence was >50% in seven of the states. The highest prevalence was seen in Telangana (54.54%) and Chhattisgarh (53.76%). Haryana (58.14%) had the highest prevalence although, the sample size for this was very small (Table 2).

Patients living with diabetes with NAFLD had a significantly higher BMI (27.54 vs 27.13, p<0.001) despite duration of diabetes (7.98 vs 10.10, p<0.001) was significantly lower in these patients in comparison to patients living with diabetes without NAFLD. These patients also had significantly higher levels of mean serum TGs (169.38 vs 144.09, p<0.001), LDL (108.66 vs 104.33, p<0.001), and TC (176.73 vs 170.47, p<0.001) and significantly lower mean levels of HDL (40.37 vs 42.93, p<0.001). However, HbA1c levels were not found to be significantly different between the two groups (Table 3).

The prevalence of NAFLD was significantly high in obese patients with dyslipidemia and hypertriglyceridemia. A higher prevalence of NAFLD was seen in the younger patients living with diabetes (18–40 years) in comparison to older adults (40–60 years) and elderly (>60 years) (58.35 vs 54.92% and 39.62%, p<0.001). Patients living with diabetes with both dyslipidemia and hypertension had a significantly higher prevalence of NAFLD (p<0.001) in comparison to those without. Similarly, patients living with diabetes with poor control had a significantly higher prevalence of NAFLD compared to patients with good control (54.26 vs 49.54%, p<0.001).

A comparison of prevalence of NAFLD among patients living with diabetes based on duration of diabetes showed that those with shorter duration of diabetes had a significantly higher prevalence compared to those with longer diabetes duration (60.52 vs 42.75%, p<0.001) of having NAFLD. Hypertension was not found to be significantly associated with NAFLD (Tables 4 and 5).

Obese and overweight individuals had significantly (57.1 and 33.5%) higher odds of having NAFLD among patients living with diabetes. Presence of dyslipidemia (59.1%) and hypertriglyceridemia (42.3%) among patients living with diabetes also had significantly higher odds of NAFLD. Among other major factors that had significantly higher odds of being associated with NAFLD were male gender, young age, poor glycemic control, and shorter duration of diabetes (Tables 6 and 7).
Assessment of Prevalence and Associated Risk Factors of NAFLD

The normal biochemical trend found in hepatic steatosis due to NAFLD is elevated transaminase levels, with levels of ALT exceeding AST levels (ALT > AST or AST:ALT < 1). This classical trend is particularly useful in distinguishing between NAFLD and alcoholic liver disease, which is associated with a high AST:ALT ratio. The moderate rise [50–150 U/L (1–3 times the upper limit of normal) with AST levels less than those of ALT] is associated with NAFLD. Also, >40 U/L has been considered of having 91.4% positive predictivity for NAFLD.15 After considering these studies, we had formulated an algorithm for NAFLD diagnosis with a transaminase rise ALT (25–150 U/L) and ALT > AST or AST:ALT < 1.

Table 1: Baseline parameters of the overall patients living with diabetes

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Total number of patients living with diabetes</th>
<th>Total number of NAFLD patients N (%)</th>
<th>Total number of patients without NAFLD N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>171,966</td>
<td>76,495 (44.48)</td>
<td>95,501 (55.52)</td>
</tr>
<tr>
<td>Gender</td>
<td>N (%)</td>
<td>Males: 39,013 (63.11)</td>
<td>Females: 32,36 (36.91)</td>
</tr>
<tr>
<td>BMI</td>
<td>N (%)</td>
<td>In persons with NAFLD: 27.34 ± 4.68</td>
<td>In persons without NAFLD: 25.8 ± 4.25</td>
</tr>
<tr>
<td>HDL</td>
<td>N (%)</td>
<td>N (%)</td>
<td>N (%)</td>
</tr>
<tr>
<td>LDL</td>
<td>N (%)</td>
<td>N (%)</td>
<td>N (%)</td>
</tr>
<tr>
<td>HDL (mg/dL)</td>
<td>N (%)</td>
<td>98,739 (50.71)</td>
<td>54.3 (53.76)</td>
</tr>
<tr>
<td>LDL (mg/dL)</td>
<td>N (%)</td>
<td>103,060 (53.41)</td>
<td>53.8 (54.9)</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>78.299 (44.8)</td>
<td>7.59 ± 2.13</td>
<td>7.8 ± 2.15</td>
</tr>
<tr>
<td>SGOT (IU/L)</td>
<td>171,996</td>
<td>35.63 ± 44.24</td>
<td>36.0 ± 44.3</td>
</tr>
<tr>
<td>SGPT (IU/L)</td>
<td>171,996</td>
<td>39.46 ± 47.09</td>
<td>40.0 ± 47.2</td>
</tr>
<tr>
<td>TC (mg/dL)</td>
<td>116,401</td>
<td>173.4 ± 42.12</td>
<td>173.6 ± 42.2</td>
</tr>
<tr>
<td>TGs (mg/dL)</td>
<td>106,611</td>
<td>156.67 ± 95.97</td>
<td>157.0 ± 96.0</td>
</tr>
<tr>
<td>HDL (mg/dL)</td>
<td>103,060</td>
<td>41.66 ± 10.30</td>
<td>41.7 ± 10.4</td>
</tr>
<tr>
<td>LDL (mg/dL)</td>
<td>98,739</td>
<td>106.48 ± 34.27</td>
<td>106.5 ± 34.3</td>
</tr>
</tbody>
</table>

*Others—Haryana, Uttar Pradesh, Gujarat, Goa, and Rajasthan

Fig. 1: Gender-wise distribution of NAFLD in patients living with diabetes

It was observed that young (18–40 years), obese (BMI >25 kg/m²), and normal TG levels. In comparison to overall patients living with diabetes population in the study, obese males had two times higher odds and males with elevated TG levels had 2.32 times higher odds of having NAFLD. A coexistence of the above three conditions (males, obese, and elevated TGs) was associated with 2.48 times higher odds of having NALFD (Table 8).

**Discussion**

The normal biochemical trend found in hepatic steatosis due to NAFLD is elevated transaminase levels, with levels of ALT exceeding AST levels (ALT > AST or AST:ALT < 1). This classical trend is particularly useful in distinguishing between NAFLD and alcoholic liver disease, which is associated with a high AST:ALT ratio. The moderate rise [50–150 U/L (1–3 times the upper limit of normal) with AST levels less than those of ALT] is associated with NAFLD. Also, >40 U/L has been considered of having 91.4% positive predictivity for NAFLD. After considering these studies, we had formulated an algorithm for NAFLD diagnosis with a transaminase rise ALT (25–150 U/L) and ALT > AST or AST:ALT < 1.

In the current study, the prevalence of NAFLD was found to be 44.48% among T2DM patients, based on the LFTs. This was consistent with the results reported by various studies, that came to be 44–72%. Prashanth et al. found a high prevalence of NAFLD and NASH in T2DM patients which increased with multiple variables such as age, duration of DM, degree of glycemic control, BMI, and waist circumference. In our study, the prevalence of NAFLD was found to be significantly higher in males (58.64%) in comparison to females (36.91%) (p < 0.001). Various studies also suggest that the incidence of NAFLD is higher in men than in women, and some longitudinal studies indicate that male gender is an independent predictor of NAFLD development.

In our study, seven states showed prevalence of over 50%, the highest seen in Haryana (58.14%) followed by Telangana (54.54%), Chhattisgarh (53.76%), West Bengal (53.41%), Andhra Pradesh (50.71%), and Tamil Nadu (50.38%). Other studies showed prevalence of NAFLD to be 41% in Kerala, 45% in Surat, and 54% in Hyderabad. We assessed the various risk factors associated with NAFLD in patients living with diabetes including age, BMI, blood pressure, duration of diabetes, and diagnostic parameters. In our study, the mean age of patients with NAFLD was 53.18 (±12.51) years. Among the different age groups, patients in the age group of 18–40 years had significantly higher odds [OR 2.13 (95% CI 2.02–2.25)] of having NAFLD.

It was observed that young (18–40 years), obese (BMI >25 kg/m²), and normal TG levels. In comparison to overall patients living with diabetes population in the study, obese males had two times higher odds and males with elevated TG levels had 2.32 times higher odds of having NAFLD. A coexistence of the above three conditions (males, obese, and elevated TGs) was associated with 2.48 times higher odds of having NALFD (Table 8).
Table 2: Geographical (state-wise) of NAFLD in patients living with diabetes in India

<table>
<thead>
<tr>
<th>States</th>
<th>Total number of patients living with diabetes, N</th>
<th>NAFLD, N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tamil Nadu</td>
<td>32,362</td>
<td>16,303 (50.38)</td>
</tr>
<tr>
<td>Karnataka</td>
<td>19,651</td>
<td>9053 (46.07)</td>
</tr>
<tr>
<td>Telangana</td>
<td>17,825</td>
<td>9722 (54.54)</td>
</tr>
<tr>
<td>Delhi</td>
<td>8671</td>
<td>3925 (45.27)</td>
</tr>
<tr>
<td>West Bengal</td>
<td>8453</td>
<td>4515 (53.41)</td>
</tr>
<tr>
<td>Maharashtra</td>
<td>6921</td>
<td>3028 (43.75)</td>
</tr>
<tr>
<td>Orissa</td>
<td>6326</td>
<td>2920 (46.16)</td>
</tr>
<tr>
<td>Andhra Pradesh</td>
<td>988</td>
<td>501 (50.71)</td>
</tr>
<tr>
<td>Chhattisgarh</td>
<td>932</td>
<td>501 (53.76)</td>
</tr>
<tr>
<td>Other*</td>
<td>672</td>
<td>370 (55.05)</td>
</tr>
<tr>
<td>Unknown</td>
<td>69,195</td>
<td>25,657 (37.08)</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>171,996</td>
<td>76,495 (44.48)</td>
</tr>
</tbody>
</table>

*Others—Haryana, Uttar Pradesh, Gujarat, Goa, and Rajasthan

Table 3: Comparison of clinical and diagnostic variables of NAFLD patients with non-NAFLD diabetes patients

<table>
<thead>
<tr>
<th>Clinical variables</th>
<th>NAFLD</th>
<th>Non-NAFLD</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMI (in kg/m²)</td>
<td>4908</td>
<td>4751</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>27.54 ± 4.45</td>
<td>27.13 ± 4.89</td>
<td></td>
</tr>
<tr>
<td>Systolic blood pressure (in mm Hg)</td>
<td>4958</td>
<td>4943</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>129.64 ± 18.19</td>
<td>130.77 ± 20.29</td>
<td></td>
</tr>
<tr>
<td>Diastolic blood pressure (in mm Hg)</td>
<td>4915</td>
<td>4901</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>81.38 ± 10.69</td>
<td>79.80 ± 10.83</td>
<td></td>
</tr>
<tr>
<td>Duration of diabetes (in years)</td>
<td>4158</td>
<td>3640</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>7.98 ± 7.77</td>
<td>10.10 ± 8.58</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Diagnostic variables</th>
<th>NAFLD</th>
<th>Non-NAFLD</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>HbA1c (%)</td>
<td>38,805</td>
<td>39,583</td>
<td>0.332</td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>7.712 ± 2.03</td>
<td>7.46 ± 2.16</td>
<td></td>
</tr>
<tr>
<td>HDL (in mg/dL)</td>
<td>51,331</td>
<td>51,827</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>40.37 ± 9.34</td>
<td>42.93 ± 10.68</td>
<td></td>
</tr>
<tr>
<td>LDL (in mg/dL)</td>
<td>48,955</td>
<td>49,883</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>108.66 ± 34.55</td>
<td>104.33 ± 34.08</td>
<td></td>
</tr>
<tr>
<td>TGs (in mg/dL)</td>
<td>53,080</td>
<td>53,627</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>169.38 ± 103.87</td>
<td>144.09 ± 91.05</td>
<td></td>
</tr>
<tr>
<td>TC (in mg/dL)</td>
<td>56,984</td>
<td>59,529</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>176.73 ± 42.46</td>
<td>170.47 ± 41.84</td>
<td></td>
</tr>
</tbody>
</table>

Statistical significance was considered at p < 0.005

in comparison to those >40 years of age. In a study by Targher et al. in 2018,23 the highest risk of NAFLD was seen among patients living with diabetes in the age group of >45 years. A different trend in our study can be attributed to the fact that as age advances, patients living with diabetes tend to effectively manage their diabetes. The mean BMI in patients living with diabetes with NAFLD in our study was 27.54 (±4.45) kg/m² compared to non-NAFLD subjects who had a mean BMI of 27.13 (±4.89) kg/m² (p-value < 0.001). In comparison to patients with normal BMI, overweight and obese patients had 33.5 and 57.1% higher odds of NAFLD, respectively. These findings are supported by a meta-analysis by Atan et al.24 which reported an increased risk of NAFLD in patients living with diabetes who have had a higher BMI. Another study by Bhatt et al.21 found that BMI was significantly higher in patients with NAFLD than the control group without NAFLD. Study by Gupta et al.11 also supports this finding in which the mean BMI was significantly high (p-value < 0.001) among patients living with diabetes with NAFLD (29.64 ± 4.36 kg/m²) in comparison to patients living with diabetes without NAFLD (25.94 ± 3.25 kg/m²).

Dyslipidemia in NAFLD is characterized by elevated plasma triglycerides (TGL), and low HDL cholesterol. In the Bhatt et al. study21 statistically significant difference in TGL value (175.47 ± 24.82 vs 128.53 ± 26.66 mg/dL, p < 0.001) was observed in the patients with fatty liver as compared to nonfatty liver which is in concordance to our study (169.38 ± 103.87 vs 144.09 ± 91.05, p < 0.001). Leite et al.25 found that the occurrence of hypertriglyceridermia (OR 3.7–4.1 (95% CI 1.2–13.3)) was independently associated with NAFLD in patients living with diabetes supporting the results of our study (OR 1.423 (95% CI 1.37–1.47)). Similar findings were reported in studies by Singh et al.26 who showed the mean TGL levels were considerably higher in T2DM patients with NAFLD as compared to non-NAFLD patients. In a meta-analysis by Dai et al.,27 the pooled prevalence of NAFLD in patients living with diabetes with dyslipidemia was 60.50% (95% CI 52.58–67.39). Dyslipidemia was found to be significantly (p-value < 0.001) associated factor with NAFLD in patients living with diabetes in our study as well [OR 1.59 (95% CI 1.52–1.65)]. Glycemic control of NAFLD was significantly poorer in our analysis, Zoppini et al.28 evaluated the relation between glycemic control and NAFLD and found that 75% (2725) of patients had poor glycemic control (HbA1c ≥6.5%) and 57.3% (2082) of patients had HbA1c values ≥7%. In our study, 54.26% patients had poor glycemic control (HbA1c > 8%) in NAFLD group as compared to 45.74% patients in non-NAFLD group. The mean HbA1c in NAFLD patients living with diabetes was 7.71 ± 2.03% which was more when compared to non-NAFLD patients who had a mean HbA1c of 7.46 ± 2.16%. A study by Gupta et al.11 supports this finding where the HbA1c among patients living with diabetes with NAFLD (7.73 ± 0.56%) was higher
Table 4: Prevalence of NAFLD among different profiles of patients living with diabetes

<table>
<thead>
<tr>
<th>Clinical/diagnostic variables</th>
<th>NAFLD, N (%)</th>
<th>Non-NAFLD, N (%)</th>
<th>Total number of patients, N</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (in years)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>18–40</td>
<td>4875 (58.35)</td>
<td>3480 (41.65)</td>
<td>8355</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>40–60</td>
<td>18,054 (54.92)</td>
<td>14,820 (45.08)</td>
<td>32,874</td>
<td></td>
</tr>
<tr>
<td>60–above</td>
<td>7529 (39.62)</td>
<td>11,474 (60.38)</td>
<td>19,003</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>30,458 (50.57)</td>
<td>29,774 (49.43)</td>
<td>60,232</td>
<td></td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>7693 (36.34)</td>
<td>13,474 (63.66)</td>
<td>21,167</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Male</td>
<td>21,303 (58.36)</td>
<td>15,201 (41.64)</td>
<td>36,504</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>28,996 (50.28)</td>
<td>28,675 (49.72)</td>
<td>57,671</td>
<td></td>
</tr>
<tr>
<td>BMI</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>575 (41.88)</td>
<td>798 (58.12)</td>
<td>1373</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Obese</td>
<td>3220 (53.09)</td>
<td>2845 (46.91)</td>
<td>6065</td>
<td></td>
</tr>
<tr>
<td>Overweight</td>
<td>756 (49.03)</td>
<td>786 (50.97)</td>
<td>1542</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>4551 (50.68)</td>
<td>4429 (49.32)</td>
<td>8980</td>
<td></td>
</tr>
<tr>
<td>Hypertension (mm Hg)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>1733 (49.30)</td>
<td>1782 (50.70)</td>
<td>3515</td>
<td>0.60</td>
</tr>
<tr>
<td>No</td>
<td>2813 (50.09)</td>
<td>2803 (49.91)</td>
<td>5616</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>4546 (49.79)</td>
<td>4585 (50.21)</td>
<td>9131</td>
<td></td>
</tr>
<tr>
<td>Dyslipidemia (mg/dL)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>20,737 (55.04)</td>
<td>16,940 (44.96)</td>
<td>37,677</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>No</td>
<td>5731 (43.49)</td>
<td>7447 (56.51)</td>
<td>13,178</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>4551 (50.68)</td>
<td>4429 (49.32)</td>
<td>8980</td>
<td></td>
</tr>
<tr>
<td>Hypertension + dyslipidemia</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>1283 (53.17)</td>
<td>1130 (46.83)</td>
<td>2413</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>No</td>
<td>537 (42.42)</td>
<td>729 (57.58)</td>
<td>1266</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>1820 (49.47)</td>
<td>1859 (50.53)</td>
<td>3679</td>
<td></td>
</tr>
<tr>
<td>TGs (mg/dL)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertriglyceridemia</td>
<td>12,783 (56.99)</td>
<td>9646 (43.01)</td>
<td>22,429</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>No hypertriglyceridemia</td>
<td>13,170 (48.22)</td>
<td>14,144 (51.78)</td>
<td>27,314</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>25,953 (52.17)</td>
<td>23,790 (47.83)</td>
<td>49,743</td>
<td></td>
</tr>
</tbody>
</table>

Statistical significance was considered at p<0.05

Table 5: Prevalence of NAFLD among different diabetic parameters of patients living with diabetes

<table>
<thead>
<tr>
<th>Diabetic parameters</th>
<th>Categories</th>
<th>NAFLD, N (%)</th>
<th>Non-NAFLD, N (%)</th>
<th>Total number of patients, N</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fasting blood sugar (in mg/dL)</td>
<td>126 or more</td>
<td>15,870 (55.16)</td>
<td>12,903 (44.84)</td>
<td>28,773</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>Up to 125</td>
<td>8171 (47.57)</td>
<td>9005 (52.43)</td>
<td>17,176</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Total</td>
<td>24,041 (52.32)</td>
<td>21,908 (47.68)</td>
<td>45,949</td>
<td></td>
</tr>
<tr>
<td>Postprandial blood sugar (in mg/dL)</td>
<td>200 or more</td>
<td>14,229 (54.86)</td>
<td>11,707 (45.14)</td>
<td>25,936</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>Up to 199</td>
<td>7257 (50.48)</td>
<td>7118 (49.52)</td>
<td>14,375</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Total</td>
<td>21,486 (53.30)</td>
<td>18,825 (46.70)</td>
<td>40,311</td>
<td></td>
</tr>
<tr>
<td>Glycemic control (%)</td>
<td>Good control (&lt;8)</td>
<td>11,290 (49.54)</td>
<td>11,498 (50.46)</td>
<td>22,788</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>Poor control (8 or more)</td>
<td>11,751 (54.26)</td>
<td>9907 (45.74)</td>
<td>21,658</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Total</td>
<td>23,041 (51.84)</td>
<td>21,405 (48.16)</td>
<td>44,446</td>
<td></td>
</tr>
<tr>
<td>Duration of diabetes (in years)</td>
<td>0–3</td>
<td>1300 (60.52)</td>
<td>848 (39.48)</td>
<td>2148</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>4–8</td>
<td>1211 (58.79)</td>
<td>849 (41.21)</td>
<td>2060</td>
<td></td>
</tr>
<tr>
<td></td>
<td>9–14</td>
<td>851 (49.25)</td>
<td>877 (50.75)</td>
<td>1728</td>
<td></td>
</tr>
<tr>
<td></td>
<td>14–above</td>
<td>796 (42.75)</td>
<td>1066 (57.25)</td>
<td>1862</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Total</td>
<td>4158 (53.32)</td>
<td>3640 (46.68)</td>
<td>7798</td>
<td></td>
</tr>
</tbody>
</table>

Statistical significance was considered at p<0.05

than those without NAFLD (7.06 ± 0.42%). In our study hypertension was not found to be significantly associated with NAFLD in patients living with diabetes. The prevalence of hypertension was 49.30% among NAFLD patients with diabetes. In contrast to our study Dai et al., found out that pooled prevalence of hypertension [66.50% (95% CI 57.63–74.82)] in patients living with diabetes...
### Table 6: Showing odds of having NAFLD among different subcategories of patients living with diabetes

<table>
<thead>
<tr>
<th>Category</th>
<th>Odds risk</th>
<th>95% CI (lower limit)</th>
<th>95% CI (upper limit)</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (in years)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>18–40</td>
<td>2.135</td>
<td>2.026</td>
<td>2.250</td>
<td>113.5% higher odds</td>
</tr>
<tr>
<td>40–60</td>
<td>1.857</td>
<td>1.790</td>
<td>1.925</td>
<td>85.7% higher odds</td>
</tr>
<tr>
<td>60–above</td>
<td>Baseline</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Gender</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>Baseline</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>2.455</td>
<td>2.370</td>
<td>2.542</td>
<td>145.5% higher odds</td>
</tr>
<tr>
<td><strong>Dyslipidemia</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>1.591</td>
<td>1.528</td>
<td>1.656</td>
<td>59.1% higher odds</td>
</tr>
<tr>
<td>No</td>
<td>Baseline</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>TGs (in mg/dL)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertriglyceridemia</td>
<td>1.423</td>
<td>1.374</td>
<td>1.475</td>
<td>42.3% higher odds</td>
</tr>
<tr>
<td>No hypertriglyceridemia</td>
<td>Baseline</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Hypertension + dyslipidemia</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>1.541</td>
<td>1.344</td>
<td>1.768</td>
<td>54.1% higher odds</td>
</tr>
<tr>
<td>No</td>
<td>Baseline</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Table 7: Showing odds of having NAFLD among different parameters of patients living with diabetes

<table>
<thead>
<tr>
<th>Category</th>
<th>Odds risk</th>
<th>95% CI (lower limit)</th>
<th>95% CI (upper limit)</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Glycemic control (%)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Good control</td>
<td>Baseline</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Poor control (HbA1c 8 or more)</td>
<td>1.208</td>
<td>1.164</td>
<td>1.254</td>
<td>20.8% higher odds</td>
</tr>
<tr>
<td><strong>Duration of diabetes (in years)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0–3</td>
<td>2.053</td>
<td>1.810</td>
<td>2.329</td>
<td>105.3% higher odds</td>
</tr>
<tr>
<td>4–8</td>
<td>1.910</td>
<td>1.682</td>
<td>2.169</td>
<td>91% higher odds</td>
</tr>
<tr>
<td>9–14</td>
<td>1.299</td>
<td>1.139</td>
<td>1.482</td>
<td>29.9% higher odds</td>
</tr>
<tr>
<td>14–above</td>
<td>Baseline</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Fasting blood sugar (mg/dL)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>126 or more</td>
<td>1.35</td>
<td>1.30</td>
<td>1.40</td>
<td>35% higher odds</td>
</tr>
<tr>
<td>Up to 125</td>
<td>Baseline</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Postprandial blood sugar (mg/dL)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>200 or more</td>
<td>1.192</td>
<td>1.144</td>
<td>1.24</td>
<td>19% higher odds</td>
</tr>
<tr>
<td>Up to 199</td>
<td>Baseline</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Table 8: Patient subgroups with higher odds of NAFLD

<table>
<thead>
<tr>
<th>Patient subgroups</th>
<th>Total number of patients, N (% of total similar population)</th>
<th>NAFLD, N (%)</th>
<th>OR (opposite group comparison)</th>
<th>Interpretation</th>
<th>OR (overall patient population comparison)</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Young, male, hypertriglyceridemia and obese</td>
<td>269 (3.3%)</td>
<td>232 (86.25%)</td>
<td>17.07</td>
<td>17 times higher odds</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Male and obese</td>
<td>3464 (43.2%)</td>
<td>2186 (63.11%)</td>
<td>4.007 (with respect to nonobese females)</td>
<td>4 times higher odds</td>
<td>2.078</td>
<td>2.00 times higher odds</td>
</tr>
<tr>
<td>Male + hypertriglyceridemia</td>
<td>2627 (32.82%)</td>
<td>1652 (62.89%)</td>
<td>3.060 (with respect to females with normal TGs)</td>
<td>3 times higher odds</td>
<td>2.321</td>
<td>2.33 times higher odds</td>
</tr>
<tr>
<td>Male + hypertriglyceridemia + obese</td>
<td>1762 (22.01%)</td>
<td>1170 (66.40%)</td>
<td>5.467 (with respect to nonobese females with normal TGs)</td>
<td>5.4 times higher odds</td>
<td>2.483</td>
<td>2.48 times higher odds</td>
</tr>
</tbody>
</table>
Assessment of Prevalence and Associated Risk Factors of NAFLD

with NAFLD was significantly higher than non-NAFLD patients living with diabetes. Another important finding in our study was that patients with shorter duration of diabetes (0–4 years) had 105.3% higher odds [2.05 (95% CI 1.81–2.32)] of having NAFLD than those with longer duration of diabetes (more than 9 years). This is contrary to the common belief that longer duration of diabetes poses a higher risk of developing NAFLD. Research studies have shown better control of diabetes and lipid levels with increasing duration of diabetes and this might be the plausible reason for lesser prevalence of NAFLD with increasing duration of diabetes.29 A subgroup analysis in Dai et al. meta-analysis27 found that the prevalence of NAFLD was significantly higher in T2DM patients with male gender (vs female gender), obesity (vs without obesity), and dyslipidemia (vs without dyslipidemia) which is similar to high-risk population identified in the current study.

Conclusions

The current study is one of the biggest real-world evidence studies, based on EMR data of diabetes patients in India. An assessment of NAFLD using LFT-based screening was done. The study comprehensively evaluates various epidemiological characteristics of the NAFLD in diabetes patients in India which have hitherto, not been done so extensively. This study highlighted high-risk categories of diabetes patients for NAFLD, such as young, obese, with hypertriglyceridemia, poor glycemic control, etc. This information will help health care providers in prioritizing screening among high-risk diabetes populations.

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References

Pregnancy-related Acute Kidney Injury in Public Hospital in South India: Changing Trends

Manisha Sahay1*, Priyashree2, Luvdeep Dogra3, Kiranmai Ismal4, Sharmas Vali5

Received: 27 July 2020; Accepted: 15 April 2022

ORIGINAL ARTICLE

Pregnancy-related Acute Kidney Injury in Public Hospital in South India: Changing Trends

Manisha Sahay1†, Priyashree2, Luvdeep Dogra3, Kiranmai Ismal4, Sharmas Vali5

INTRODUCTION

Pregnancy-related acute kidney injury is an important cause of acute kidney injury (AKI) in developing countries.1–3 Pregnancy-related acute kidney injury occurs in healthy young females and may result in significant morbidity in the form of chronic kidney disease (CKD) and even mortality. The incidence of PRAKI in the developing countries is declining, though it is still higher than the developed world.

Hyperemesis gravidarum and septic abortions can result in PRAKI in the first trimester.1 Pregnancy-related acute kidney injury is predominantly due to pre-eclampsia, antepartum hemorrhage, and thrombotic thrombocytopenic purpura (TTP) in the third trimester while puerperal sepsis, postpartum hemorrhage (PPH), and acute fatty liver of pregnancy (AFLP) constitute important causes of PRAKI postpartum.1 There is variable degree of hemolysis and thrombocytopenia in these disorders. Coagulopathy is absent in HUS and TTP. Renal biopsy is usually done in cases of nonrecovery of renal function in 3 weeks. Histology may reveal CN. Management includes treatment of hypertension in pre-eclampsia and magnesium sulfate to prevent and treat seizures, plasmapheresis in thrombotic microangiopathy (TMA), antibiotics in sepsis, and supportive therapy. Prompt delivery is indicated after assessment of fetal maturity. There is an emerging role of eculizumab therapy in PRAKI due to atypical HUS. In this study we have analyzed the records of PRAKI at our center.

MATERIALS AND METHODS

The records of PRAKI over the last 10 years were analyzed. Pregnancy-related acute kidney injury was defined as per the Kidney Disease Improving Global Outcomes (KDIGO) criteria. Medical history including the pregnancy details, comorbidities, timing of onset of PRAKI, other pregnancy complications, and mode of delivery was recorded. Outcomes for the mother and child were noted. Renal biopsy was done if there was no recovery at the end of 3 weeks. Patients were followed up for a minimum of 12 months period.

Variables are presented as the mean standard deviation or as frequencies (percentage). Continuous variables were analyzed using Student’s t-test or analysis of variance. Kolmogorov–Smirnov was used for testing normality. Nonparametric variables were compared using Mann–Whitney U or Kruskal–Wallis tests as appropriate. The Pearson’s X² test or Fisher’s exact test was used for categorical variables. A p-value of <0.05 was considered to indicate a significant difference. The statistical analysis was performed using SPSS software.

RESULTS

Over a 10-year period, 395 patients of PRAKI were seen constituting 8.1% of all AKI. Only 125 (49%) were on regular antenatal follow-up. Etiology of PRAKI is shown in Figure 1. Acute fatty liver was not seen. Eleven had underlying glomerulonephritis out of three had underlying lupus nephritis. Forty-five of 395 (11.39%) had hemolysis, elevated liver enzymes, low platelets (HELLP) syndrome, that is, 25.5% of those with pre-eclampsia. Sixteen (4.0%) had placental abruption. A total of 288 (72.9%) presented postpartum. Renal biopsy done in 103 (26%) showed patchy cortical necrosis (PCN) in 25 (22.3%), diffuse cortical necrosis (DCN) in 23 (20.3%), acute tubular necrosis (ATN) in 20 (19.4%), acute interstitial nephritis (AIN) in 10 (9.7%), while nine (8.7%) had thrombotic microangiopathy (TMA). Glomerular disease was seen in 11. Cortical necrosis (CN) was seen in 48 patients of which 10 (20.83%) had abruption placenta, 25 (52%) had puerperal sepsis, 11 (22.9%) had postpartum hemorrhage (PPH), and two (4.1%) had TMA. A total of 290 (73.4%) required dialysis. About 76% improved while 8.3% progressed to end-stage renal disease (ESRD).

Maternal mortality (MM) was 5%. There were 42 intrarneal deaths and 30 deaths in the neonatal period.

Discussion: Pregnancy-related acute kidney injury in developing countries is more common as compared to the West. Only 49% patients had booked pregnancy, that is, received regular antenatal care. Apart from pre-eclampsia which is also the major cause in the West and was the etiology in 44% of patients with PRAKI in our study, sepsis (33%) and maternal hemorrhage (19%) were also significant. Immediate recovery from PRAKI was 75% however about 8% develop end-stage kidney disease (ESKD) while in the west ESKD occurred in only about 2%.

Conclusion: Pregnancy-related acute kidney injury is an important cause of maternal and fetal morbidity and mortality. Pre-eclampsia emerged as the most common cause of PRAKI and CN was the most common histological lesion. Proper antenatal care and management may improve pregnancy outcomes.

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7 and 14 days, and 57 (14.4%) presented ≥14 days after delivery. Overall 288 (72.9%) presented postpartum. Total 142 (35.9%) were delivered vaginally while 253 (64.0%) had cesarean section. Thirty-four (8.6%) patients had retained product of conception. Total 140 (35.4%) had fever (>38.5°C), and 27 (6.8%) presented with shock. Seventy-nine (20.0%) needed blood transfusion. Transaminitis was observed in 105 (26.5%), and 144 (36.4%) had thrombocytopenia. Elevated uric acid was seen in 46 (11.6%), and 86 (21.7%) had coagulopathy. Thirty-two (8.6%) patients had disseminated intravascular coagulation. Three had posterior cerebral leukoencephalopathy.

Renal biopsy was done in 103 (26%) (Fig. 2). Cortical necrosis was seen in 48 patients of which 10 (20.83%) had abruptio placenta, 25 (52%) had puerperal sepsis, 11 (22.9%) had PPH, and two (4.1%) had TMA. About 73.6% required dialysis. The mean number of dialysis sessions was 8 ± 2.5. All of our patients with PRAKI-HUS underwent plasmapheresis. Complement was tested in five patients and it was low in two. Eculizumab was not used in any of the patients. Patients with puerperal sepsis received appropriate antibiotics and evacuation of retained products was done in 34 patients. Patients with glomerular disease and lupus nephritis were treated with steroids and went into remission. Renal outcomes and maternal and fetal outcomes are shown in Table 1. All patients with ATN and AIN on biopsy recovered completely. Anuria, sepsis, TMA, and CN on biopsy were predictors of nonrecovery of renal function.

**DISCUSSION**

Pregnancy-related acute kidney injury is an important cause of AKI in our setup. Our hospital is a tertiary care teaching hospital which provides free treatment to patients. In our study over a 10-year period 395 patients of PRAKI were seen constituting 8.3% of all AKI. Another Indian study by Chugh et al. in 1960s reported PRAKI contributed to 22% of all AKI. However, it declined to 9% during the period from 1981 to 1986.3,4 This decline was chiefly due to a fall in cases of septic abortion, puerperal sepsis, and postpartum hemorrhage. A similar trend was seen in a study by Prakash et al. where the contribution of PRAKI to total cases of AKI decreased significantly from 15.2% in 1982–1991 to 10.4% in 1992–2002 and further declined to 4.6% in the 2003–2014 period.5–7 The percentage of PRAKI in various Indian studies is shown in Table 2.6–15

Pregnancy-related acute kidney injury is also common in other Asian countries including Nepal, Pakistan, and Bangladesh.16–19

**Table 1: Clinical features and outcomes in PRAKI**

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>27 ± 3 years</td>
</tr>
<tr>
<td>Religion</td>
<td>Hindu 72.9% Muslims 20% Christians 7.1%</td>
</tr>
<tr>
<td>Multigravida</td>
<td>231 (58.6%)</td>
</tr>
<tr>
<td>Gestational age</td>
<td>29.33 ± 9.64 weeks</td>
</tr>
<tr>
<td>Timing of presentation</td>
<td>72.9% postpartum</td>
</tr>
<tr>
<td>Oliguria</td>
<td>297 (75.18%)</td>
</tr>
<tr>
<td>Anuria</td>
<td>39 (9.8%)</td>
</tr>
<tr>
<td>Shortness of breath</td>
<td>87 (22%)</td>
</tr>
<tr>
<td>Seizures</td>
<td>23 (5.8%)</td>
</tr>
<tr>
<td>Jaundice</td>
<td>16 (4%)</td>
</tr>
<tr>
<td>Edema</td>
<td>282 (71.3%)</td>
</tr>
<tr>
<td>Hemoglobin (gm/dL)</td>
<td>10.1 ± 1.8</td>
</tr>
<tr>
<td>Platelets (lakh/mm³)</td>
<td>1.9 ± 0.4 lakhs/mm³</td>
</tr>
<tr>
<td>White blood cells count (mm³)</td>
<td>9000 ± 1300</td>
</tr>
<tr>
<td>Sodium (meq/L)</td>
<td>137 ± 2.5 meq/L</td>
</tr>
<tr>
<td>Potassium (meq/L)</td>
<td>4.9 ± 1.2 meq/L</td>
</tr>
<tr>
<td>Uric acid (mg/dL)</td>
<td>7.9 ± 2.6</td>
</tr>
<tr>
<td>Bilirubin (mg/dL)</td>
<td>1.3 ± 0.3</td>
</tr>
<tr>
<td>Serum glutamic pyruvic transaminase (IU/L)</td>
<td>42</td>
</tr>
<tr>
<td>Serum glutamic oxaloacetic transaminase (IU/L)</td>
<td>46</td>
</tr>
<tr>
<td>Lactate dehydrogenase (U/L)</td>
<td>444</td>
</tr>
<tr>
<td>Prothrombin time/International normalized ratio</td>
<td>1.7</td>
</tr>
<tr>
<td>Renal replacement therapy (RRT)</td>
<td>73.6%</td>
</tr>
<tr>
<td>Live births</td>
<td>353 (89.3%)</td>
</tr>
<tr>
<td>Intrauterine death</td>
<td>42 (10.6%)</td>
</tr>
<tr>
<td>Preterm</td>
<td>45 (13.9%)</td>
</tr>
<tr>
<td>Low birth weight</td>
<td>56 (17.3%)</td>
</tr>
<tr>
<td>Neonatal deaths</td>
<td>30 (7.5%)</td>
</tr>
<tr>
<td>Maternal deaths</td>
<td>20 (5%)</td>
</tr>
<tr>
<td>Renal outcomes at 1 year among survivors</td>
<td></td>
</tr>
<tr>
<td>Complete recovery (CR)</td>
<td>285 (76%)</td>
</tr>
<tr>
<td>Partial recovery (PR)</td>
<td>59 (15.7%)</td>
</tr>
<tr>
<td>ESRD</td>
<td>31 (8.3%)</td>
</tr>
</tbody>
</table>
Pregnancy-related Acute Kidney Injury in Public Hospital in South India

Fig. 2: Histology of PRAKI (n = 103)

In a study from Bangladesh done from 2007 to 2008, PRAKI was seen in 21.6%.16 A study from Pakistan reported PRAKI in 30%.18 Pregnancy-related acute kidney injury in China was reported to range from 0.2 to 1.8%.19

Pregnancy-related acute kidney injury is also commonly reported from other developing countries like Africa20 and Brazil.21

Among the developed world, study from Australia reported paucity of data regarding frequency, causes, and outcomes of PRAKI.22 Pregnancy-related acute kidney injury was thought to be uncommon in developed world. However, the landscape of PRAKI in the developed world is changing, with recent studies reporting an increased incidence from 1.66 to 2.68 per 10,000 pregnancies from 2003 to 2010 in Canada23 and from 2.3 to 4.5 per 10,000 deliveries between 1998 and 2008 in United States.24 Much of the increase was attributed to the different coding of AKI (ascertainment bias) and increased surveillance during the study period. Some increase could have occurred due to older maternal age, pregnancies with hypertensive disorders, assisted reproduction, and underlying CKD in older females.

Though the incidence of PRAKI is decreasing in most Indian studies, most patients presented with severe AKI (AKIN 3) with 40–70% requiring dialysis.6,8-10 In another Indian study 20–25% needed dialysis.14 In our study about 75% needed dialysis. This is because our center is a tertiary care center and caters to the most severe cases of PRAKI. In contrast, in a study from developed world by Huang and Chen only 6% needed dialysis.19 In Canada, though PRAKI was increasing, the incidence of severe PRAKI requiring dialysis was low (<1 in 10,000 pregnancies).21

In our study 72% cases of PRAKI occurred postpartum. In a study in 1970s Chugh et al. reported that 59.7% of all PRAKI patients developed AKI in early pregnancy and 40.35% in late pregnancy.3,4 However, like in our study, most cases of PRAKI in recent studies are now seen to occur postpartum. Study by Prakash et al. also showed that early pregnancy postabortal AKI has decreased significantly.5 This shift from early pregnancy to postpartum has resulted from a decline in AKI due to septic abortions. This has occurred due to legalization of abortions.

The etiology of PRAKI in different studies is shown in Table 2. Pre-eclampsia (including HELLP) is the leading cause of PRAKI in Western studies.25,26 In Bangladesh, PE was identified as one of the main causes of PRAKI.17 In a study from Huang and Chen from China 69.9% PRAKI was due to PE while 9% had HELLP.19 Pre-eclampsia/HELLP syndrome-associated AKI was seen in 23% in 1982–1991 and 11.5% in 2003–2014 in studies by Prakash et al.5 In Pakistan among 43 PRAKI, pre-eclampsia accounted for only 11.6%. In our study, however, preeclampsia (PE) was the predominant cause of PRAKI.

Most Indian studies have reported puerperal sepsis as the predominant cause of PRAKI.5,10,14 A study from Pakistan reported PRAKI due to sepsis in 27.9%.18 In our study puerperal sepsis was the second most common cause of PRAKI after PE. Puerperal sepsis is most commonly associated with retained products of conception. This is in contrast to earlier eras where septic abortion was the most common cause of sepsis-related PRAKI ranging between 50 and 70% of cases.15

In our study PPH was one of the three common causes of PRAKI. In most studies from India, obstetric hemorrhage either PPH or antepartum hemorrhage (APH) is an important cause of PRAKI along with PE and sepsis (Table 2). In Pakistan, among 43 PRAKI, APH was seen in 18.6% and PPH in 37.2%.18 In a study from Nigeria the most common cause of PRAKI was obstetric hemorrhage in 50%, while sepsis (21.9%) and eclampsia (18.8%) were less common.

There were no patients with PRAKI due to AFLP in our series or in any other study from India. In a study from the West, hyperemesis constituted 5.9% of PRAKI.24 Hyperemesis has not been reported in India probably as it causes mild AKI which is not reported in developing world.

Lupus nephritis can present as PRAKI either due to lupus flare, superimposed pre-eclampsia, antiphospholipid antibodies, and thrombosis or lupus vasculopathy. In our study three patients who had PRAKI due to PE had underlying lupus nephritis.

Hemolytic uremic syndrome was seen in 8.7% in our study and all patients with HUS underwent plasmapheresis. Hemolytic uremic syndrome is associated with complement mutations and is called atypical HUS.27,28 Complement was tested in five and two had low complement.

Though acute pyelonephritis is an important cause of PRAKI, it was not seen in our study.

Two patients had postnatal AKI-1 due to obstruction by gravid uterus while the other had renal calculi. Both underwent stenting during pregnancy.

Only 125 (49%) were on regular antenatal follow-up. This shows that ensuring booking of each and every pregnant female might bring down the incidence of PRAKI. Pre-eclampsia cannot be prevented however the incidence of PRAKI due to septic abortion, hyperemesis, PPH, and puerperal sepsis can be reduced significantly by ensuring proper antenatal care. The program by government of registering every pregnancy may go a long way in reducing this dreaded cause of AKI which puts not one but two lives at risk.

About one-fourth of patients of PRAKI underwent renal biopsy in our study. Cortical necrosis was the most common histological lesion seen in 42.6% of all biopsies similar to most Indian studies (Table 3) and constituted 12.1% of all PRAKI. In an earlier study from our center among all causes of CN, PRAKI-related CN was seen in 39%.29 In a study by Prakash et al. incidence of CN was found to be decreasing from 17% in 1982–1991 to 1.4% in 2003–2014.30 The high incidence of CN in our study is probably due to referral of nonrecovering PRAKI to our center. In our study CN was due to puerperal sepsis (52%), PPH (22.9%), abruptio (20.8%), and TMA (4.1%). In a recent study by Ramachandran et al.31 among 21 cases of CN (17.5% of PRAKI), 33.3% patients had PPH, 42.8% had PPH, and 42.8% had sepsis. Mahesh et al. in their study reported CN in 4.6%.32

Journal of the Association of Physicians of India, Volume 70 Issue 8 (August 2022)
### Table 2: Comparison of PRABI in various studies

<table>
<thead>
<tr>
<th>Author (year)</th>
<th>No.</th>
<th>Incidence</th>
<th>Age</th>
<th>Parity</th>
<th>Mode of delivery</th>
<th>Time</th>
<th>Etiology</th>
<th>Pregnancy outcome</th>
<th>Renal outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Najar et al. (2008)</td>
<td>8</td>
<td>7%</td>
<td></td>
<td></td>
<td></td>
<td>Postpartum/third</td>
<td>Sepsis 33.3%</td>
<td>MM 20%</td>
<td>AKI RRT 60–94%</td>
</tr>
<tr>
<td>Arora et al. (2010)</td>
<td>57</td>
<td>25.6%</td>
<td></td>
<td></td>
<td></td>
<td>Postpartum 70.2%</td>
<td>Sepsis 33.3%</td>
<td>MM 28.1%</td>
<td>AKI RRT 60–94%</td>
</tr>
<tr>
<td>Sivakumar et al. (2011)</td>
<td>59</td>
<td>4.36%</td>
<td></td>
<td></td>
<td></td>
<td>Postpartum 74.5%</td>
<td>Sepsis 47.4%</td>
<td>MM 23.72%</td>
<td>AKI RRT 59.3%</td>
</tr>
<tr>
<td>Pahwa et al. (2014)</td>
<td>57</td>
<td>9.82%</td>
<td></td>
<td></td>
<td></td>
<td>Postpartum 3.59%</td>
<td>Sepsis 63.1%</td>
<td>MM 15.78%</td>
<td>Fetal death 49.12%</td>
</tr>
<tr>
<td>Godara et al. (2014)</td>
<td>57</td>
<td>9.82%</td>
<td></td>
<td></td>
<td></td>
<td>Postpartum 59.6%</td>
<td>Sepsis 63.1%</td>
<td>MM 15.78%</td>
<td>Fetal death 49.12%</td>
</tr>
<tr>
<td>Krishna et al. (2015)</td>
<td>98</td>
<td>3.39%</td>
<td></td>
<td></td>
<td></td>
<td>Postpartum 38%</td>
<td>Sepsis 46.9%</td>
<td>MM 18.36%</td>
<td>AKI RRT 100%</td>
</tr>
<tr>
<td>Gopalakrishnan et al. (2015)</td>
<td>130/5 years</td>
<td>7.9%</td>
<td></td>
<td></td>
<td></td>
<td>Postpartum 68%</td>
<td>Sepsis 21%</td>
<td>MM 18.36%</td>
<td>AKI RRT 100%</td>
</tr>
<tr>
<td>Huang and Chen (2017)</td>
<td>343</td>
<td>0.81%</td>
<td></td>
<td></td>
<td></td>
<td>Postpartum 38%</td>
<td>Sepsis 61.5%</td>
<td>MM 32.33%</td>
<td>AKI RRT 73.8%</td>
</tr>
<tr>
<td>Prakash et al. (2016)</td>
<td>15.5%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Postpartum 68%</td>
<td>Sepsis 61.5%</td>
<td>MM 20%</td>
<td>AKI RRT 83%</td>
</tr>
<tr>
<td>Prakash et al. (2016)</td>
<td>4.68%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Postpartum 68%</td>
<td>Sepsis 61.5%</td>
<td>MM 20%</td>
<td>AKI RRT 83%</td>
</tr>
<tr>
<td>Our study</td>
<td>395/10 years</td>
<td>8.1%</td>
<td></td>
<td></td>
<td></td>
<td>Postpartum 72.9%</td>
<td>Sepsis 132</td>
<td>MM 20 (5%)</td>
<td>AKI RRT 73.6%</td>
</tr>
</tbody>
</table>

AKI, acute kidney injury; APH, antepartum hemorrhage; CKD, chronic kidney disease; CR, complete recovery; ECC, eclampsia; GN, glomerulonephritis; HELLP, hemolysis, elevated liver enzymes, low platelets; MM, maternal mortality; MHD, maintenance hemodialysis; OU, obstruction; PE, preeclampsia; PPH, postpartum hemorrhage; PNM, perinatal mortality; PN, pyelonephritis; PR, partial recovery; PS, puerperal sepsis; RRT, renal replacement therapy; TMA, thrombotic microangiopathy
Thrombotic microangiopathy was seen in less than 10% in our study whereas in a study by Huang and Chen, only 6.1% of patients underwent dialysis as they have included PRAKI patients in all stages of severity. As ours is a tertiary care center, patients with severe AKI are referred, as a result almost three-fourths of PRAKI patients underwent dialysis. All our patients with pregnancy HUS underwent plasmapheresis. Eculizumab, the drug of choice for atypical pregnancy HUS underwent plasmapheresis. Patients with puerperal sepsis received appropriate antibiotics and evacuation of retained products was done. Patients with glomerular disease and lupus nephritis diagnosed in postpartum period were treated with immunosuppression as per KDIGO guidelines and went into remission. In our study 75.18% of PRAKI had recovered completely, 16.4% had nondialysis-dependent CKD at 1 year and 8.3% progressed to ESRD. In the study by Arrayhani et al., 40–75% of PRAKI had recovered completely, 16.4% had nondialysis-dependent CKD at 1 year and 8.3% progressed to ESRD. In a study by Prakash et al. MM mortality has been variously reported in recent Indian studies from 5 to 25% as shown in Table 2. In a study by Prakash et al. MM reduced to 5.79% from initial high value 20% in 1982–1991. In developing world however the numbers are still high. In a study by Krishna et al. 85% PRAKI had the highest mortality. In other Asian countries, that is, in China MM was reported as 4%. In Africa, a study from Nigeria showed alarmingly high MM up to 34.4%. Maternal mortality associated with PRAKI was reported as 0.13–0.23 per 10,000 deliveries in United States in a study by Mehrabadi et al. Pregnancy-related acute kidney injury in Hildebrand study from Canada exhibited higher MM than general population (4.3 vs 0.01%). This may be explained by older age of pregnant women, assisted reproduction techniques, etc. These reports are indicative of the new challenges facing the developed world, and highlight the need for ongoing studies in developed regions as well.

Pregnancy-related acute kidney injury is also associated with significant fetal mortality and morbidity. Intrauterine death was noted in 7.8% and neonatal deaths in 9.6% in our study (Table 1). Other studies from India have reported high perinatal mortality of 20–45% due to intrauterine death, stillbirth, and prematurity. In China, perinatal mortality was 17%, with higher mortality noted with PRAKI in the second rather than third trimester. In a Nigerian study fetal mortality was 50%. Severe PRAKI requiring dialysis in Canada was commonly associated with preterm deliveries, low birth weight, infants small for gestational age, and neonatal death.

**Table 3: Histology of PRAKI in different Indian studies**

<table>
<thead>
<tr>
<th>Study</th>
<th>% of PRAKI where was biopsy done</th>
<th>Biopsy findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mahesh et al., IJT (2017), Bangalore</td>
<td>16.3%</td>
<td>RCN 4.8%</td>
</tr>
<tr>
<td>Krishna et al., IJT (2015)</td>
<td>35.3%</td>
<td>RCN 34.7%</td>
</tr>
<tr>
<td>Gopalakrishnan et al., Renal Failure (2015)</td>
<td>35.3%</td>
<td>RCN 34.7%</td>
</tr>
<tr>
<td>Pahwa et al. (2014)</td>
<td>18</td>
<td>DCN 8</td>
</tr>
<tr>
<td>Prakash (2016)</td>
<td>48</td>
<td>RCN 61.9%</td>
</tr>
<tr>
<td>Gullipalli et al. (2015)</td>
<td>22.9%</td>
<td>RCN 12.5%</td>
</tr>
<tr>
<td>Godara et al. (2014)</td>
<td>36.8%</td>
<td>RCN 61.9%</td>
</tr>
<tr>
<td>Our study</td>
<td>26</td>
<td>RCN 25 (22.3%)</td>
</tr>
</tbody>
</table>

AIN, acute interstitial nephritis; ATN, acute tubular necrosis; CN, cortical necrosis; DCN, diffuse cortical necrosis; GN, glomerulonephritis; PCN, patchy cortical necrosis; RCN, renal cortical necrosis; TMA, thrombotic microangiopathy.
References

In hypertensive with CAD, initiate with

**Tazloc-Beta**

Telmisartan 40 mg + Metoprolol Succinate 25 mg / 50 mg PR

Celebrating

10 YEARS OF TRUST

1. No. 1 Rx brand by Cardiologist & Diabetologist
2. ODCA Technology
3. Economical
4. Preferred in multiple patient profiles
5. Cardio Protection
6. Recommended by latest guidelines
7. Trusted and clinically tested molecules
8. Prescribed as initiation therapy
9. 24 hours BP Control
10. Patient compliance
In patients with hypertension and diabetes,

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

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

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Higher time in Target Range

Time in Target Range

22% reduction in first CV event

If uncontrolled, Up-titrated to

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


In mild-to-moderate hypertension, initiate / add

Tazloc®
Telmisartan 40/40 mg

Tazloc®-H
Telmisartan 40 mg + Hydrochlorothiazide 12.5 mg

Tazloc®-Trio
Telmisartan 40 mg + Amlodipine 5 mg + Hydrochlorothiazide 12.5 mg

In hypertension

Amlopin
Amlodipine 5/10/20 mg

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

Amlopin®-AT
Amlodipine 5 mg + Atenolol 50 mg

For Intensive BP control with CV safety

For long-lasting BP control:
Heart Failure with Preserved Ejection Fraction: Management Guidelines (From Heart Failure Association of India, Endorsed by Association of Physicians of India)

Harikrishnan S1*, Abraham Oomman2, Uday M Jadhav3, Bagirath Raghuraman4, PP Mohanan5, Mangesh Tiwaskar6, GS Wander7, VK Chopra8

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ABSTRACT

Heart failure with preserved ejection fraction (HFpEF) accounts for 15–20% of patients with heart failure (HF) in India. Diagnosis is by clinical features supported by biomarkers and echocardiography. Lifestyle modifications, control of risk factors to optimum levels, and treatment of comorbidities are essential in the management of HFpEF. Spironolactone and sacubitril-valsartan (angiotensin receptor neprilysin inhibitor [ARNI]) are beneficial in subsets of HFpEF, especially with lower range of ejection fraction (EF). Sodium-glucose co-transporter-2 inhibitors (SGLT2i)—empagliflozin and dapagliflozin and probably sotagliflozin are the only currently available drugs which have shown benefits in HFpEF, mostly by reducing hospitalizations. The benefit of SGLT2i is evident in both diabetic and nondiabetic subsets.

Heart failure with preserved ejection fraction (HFpEF) is characterized by elevated left ventricular filling pressures and/or reduced cardiac output either at rest or on exertion. Cardiac output is maintained at the cost of abnormally elevated filling pressure which is responsible for the symptoms and signs. Neurohumoral activation (sympathetic and renin-angiotensin-aldosterone system activation) is present only in a group of HFpEF patients unlike in patients with heart failure with reduced ejection fraction (HFrEF).

The diagnosis of HFpEF is right heart catheterization which is cumbersome and not easily available. An invasively measured pulmonary capillary wedge pressure of ≥15 mm Hg (at rest) or left ventricular end-diastolic pressure ≥16 mm Hg (at rest) is generally considered diagnostic in presence of clinical features. If resting echocardiographic findings and laboratory parameters are equivocal, diastolic stress (exercise) test is recommended.

All patients with suspected HFpEF should undergo an electrocardiogram and a chest X-ray along with blood tests including blood cell counts, renal function test, thyroid function test, glycosylated hemoglobin, lipid levels, iron studies, and biomarkers like B-type natriuretic peptide (BNP/NT-proBNP) and troponin. Transesophageal echocardiogram with detailed evaluation for cardiac chamber enlargement, left ventricular hypertrophy, diastolic function assessment, and pulmonary hypertension is essential in the workup. Cardiac magnetic resonance imaging is recommended in patients with suspected infiltrative cardiomyopathy, hemochromatosis, or hypertrophic cardiomyopathy. The proposed diagnostic algorithm for HFpEF based on the universal definition of HF 2021 is attached below. The European Society of Cardiology (ESC) has proposed the PEFF algorithm for diagnosis of HFpEF, with a score >5 points are diagnostic and if the score is borderline, that is 2–4, we need to do stress testing or have to go for invasive hemodynamic testing (Flowchart 1).

Management of HFpEF

Till recently, no pharmacological therapy had been shown to significantly reduce mortality and morbidity in patients with HFpEF, although improvements had been reported in certain specific phenotypes of patients within the HFpEF spectrum. The recent data on SGLT2i have given hope to patients with HFpEF.

Phenotypes of HFpEF

Patients with HFpEF have varying presentations and clinical trajectories which resulted in categorizing patients based on pathophysiologic phenotypes. It is believed that this strategy may provide more targeted and efficacious therapies. Different phenogroups are based on clinical presentation, structural and functional alteration of cardiovascular system, hemodynamic patterns, exercise tolerance and capacity, and presence of comorbidities. While currently there is no consensus in defining the phenogroups, it is expected that it may occur in the near future.

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Heart Failure with Preserved Ejection Fraction: Management Guidelines

Flowchart 1: Algorithm for diagnosis of HFP EF. *LV mass index ≥95 gm/m² (female), ≥115 gm/m² (male), relative wall thickness >0.42 LA volume index ≥34 mL/m² (SR) >40 mL/m² (AF) PA systolic pressure—TR velocity at rest >35 mm Hg/>2.8 m/s at rest. On exercise TR velocity >3.4 m/s, E/E’ >15; BNP, B-type natriuretic peptide; E/E’ ratio, early filling velocity on transmitral Doppler/early relaxation velocity on tissue Doppler; LA, left atrial; LV, left ventricular; NT-proBNP, N-terminal pro-B-type natriuretic peptide; PA, pulmonary artery; SR, sinus rhythm; TR, tricuspid regurgitation

General Measures
Lifestyle modifications are important—structured cardiac rehabilitation and weight loss in the obese have shown to benefit patients. Dietary salt and fluid restriction help to minimize congestion and should be considered in patients who have features of volume overload. Tobacco cessation and restriction of alcohol consumption should be advised. Treatment of comorbidities is essential—control of hypertension, correction of anemia, and heart rate control especially in atrial fibrillation (AF) are very important. Myocardial ischemia should be assessed and treated.

Renal dysfunction is a common accompaniment of HFP EF and pharmacotherapy should be modified according to the renal function. Vaccination for influenza and pneumococcus should be considered whenever appropriate. Sleep pattern should be assessed to look for obstructive sleep apnea.

Use of organic nitrates (except to control angina), phosphodiesterase-5 inhibitors, or digoxin (except for ventricular rate control in AF), beta-blockers (except in relief of angina or rate control in AF) should be avoided in patients with HFP EF.

AF
Urgent cardioversion is recommended for patients with AF and hemodynamic compromise. Restoration of sinus rhythm by catheter ablation is preferred to rate control in HFP EF patients with AF, whenever feasible. Anticoagulation for CHA2DS2-VASc ≥2 in men and ≥3 in women, preferably with novel oral anticoagulant drugs, except in those with a prosthetic mechanical valve or significant mitral stenosis, is recommended.

Diuretics are needed for reducing congestion and symptoms. Diuretic therapy should be administered with caution to avoid excessive preload reduction and hypotension which can be detrimental in HFP EF. If there is objective evidence of hypervolemia, it should be treated with loop diuretics.

Other Drugs: Possibly Disease-modifying Agents
SGLT2i and HFP EF
Based on the success of SGLT2i in HFrEF these drugs were tried in HFP EF also. EMPEROR-Preserved trial tested the efficacy of empagliflozin compared with placebo and enrolled 5,988 patients with class II–IV HF and an EF of more than 40% to receive empagliflozin (10 mg once daily) or placebo, in addition to usual therapy. Empagliflozin reduced the combined risk of cardiovascular death or hospitalization for HF regardless of the presence or absence of diabetes. The result was mostly driven by reduction in hospitalizations.

The DELIVER trial tested dapagliflozin 10 mg once daily in patients with HFP EF. The results appear promising.

In a pooled analysis from the SOLOIST-WHe and SCORED clinical trials, sotagliflozin which is a dual (SGLT1 and SGLT2 blocker) was also found to benefit patients with HFP EF. But we must wait and see whether it is a class effect of SGLT2 inhibition or an effect of the dual blockade.

A subanalysis of the data of 4,005 subjects with LVEF >50% in the EMPEROR-Preserved cohort was presented in the American Heart Association Scientific Sessions 2021. There was a relative risk reduction of primary endpoint composite of cardiovascular death or hospitalization by 17% (p = 0.024) and first HF hospitalization by 22% (p = 0.013). There was also a significant improvement in quality of life and the slope of decline in glomerular filtration rate over time (difference vs placebo 1.24 mL/min/1.73 m² per year). This large-scale data will have clinical implications in patients of HFP EF with LVEF >50%.

Mineralocorticoid Receptor Antagonists (MRAs)
Mineralocorticoid receptor antagonists (spironolactone and eplerenone) prevent cardiac fibrosis, limit inflammation, and decrease left ventricular mass. We know that all these three abnormalities are common in HFP EF. Treatment with spironolactone was tested in the TOPCAT trial of 3,445 patients with symptomatic HF with EF ≥45%, which showed no difference in primary endpoints, but some subgroups showed benefits. In patients with symptomatic HFP EF and recent decompensation or elevated natriuretic peptide (NPs), MRAs may be initiated. Spironolactone or eplerenone can be started at dosages of 12.5 and 25 mg, respectively, and titrated up to 25–50 mg, while monitoring for hyperkalemia. There is no head-to-head comparison between spironolactone and eplerenone. Eplerenone has lesser side effects like gynecomastia but is much costlier.

ARNI—Sacubitril-valsartan
Angiotensin receptor neprilysin inhibitor is found to benefit patients with HFrEF without any doubt. The PARAGON-HF trial compared clinical outcomes with sacubitril-valsartan vs
valsartan in 4,796 HfPfEF patients with New York Heart Association class II–IV HF, LVEF ≥45%, and elevated natriuretic peptide levels. The study did not meet its primary endpoints, but benefit was shown in a few subgroups of HfPfEF like women, those with recent HF admission, and those with LVEF <57%. ARNI can be recommended in patients with HfPfEF who are already on MRA and who require additional medication for blood pressure control, particularly female patients with an LVEF less than 57%.

**Angiotensin-converting Enzyme Inhibitor (ACEI) and Angiotensin Receptor Blocker (ARB) in HfPfEF**

ACEI therapy has not shown any benefits in patients with HfPfEF in reducing mortality or morbidity. Prospective, randomized, placebo-controlled clinical trials using ARBs—candesartan, perindopril, and irbesartan in patients with HfPfEF failed to decrease cardiovascular mortality although there was some decrease in hospitalization for HF with candesartan largely in those patients who had HF with mildly reduced EF (HfMfEF, EF 41–49%). Based upon the CHARM trial, angiotensin receptor blocking agents are recommended for treatment of HfPfEF with a lower level of evidence and weaker recommendation.

**Management of Distinct Phenotypes**

Conditions like hypertrophic cardiomyopathy and cardiac amyloidosis have specific management pathways. Septal reduction therapies like surgical myectomy and alcohol septal ablation can help in hypertrophic obstructive cardiomyopathy. Myosin inhibitor like mavacamten has shown promise in hypertrophic cardiomyopathy.  

For the management of cardiac amyloidosis (especially the transthyretin variety), we have the drugs like tafamidis and patisiran. Tafamidis is recommended in the ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC) with the special contribution of the Heart Failure Association (HFA) of the ESC. Eur Heart J 2021;42(36):3599–3726.

**Summary**

Heart failure with preserved ejection fraction contributes to nearly 20% of patients with HF in India, though it is likely to be an underestimate. Diagnosis can sometimes be difficult and requires detailed evaluation with echocardiography and biomarkers. Lifestyle modifications and control of risk factors are very important in the management of HfPfEF. Treatment of comorbidities is essential. Spironolactone and ARNI are beneficial in some subsets of HfPfEF with lower range of EF. SGLT2i—empagliflozin, dapagliflozin and probably satogliflozin are the only currently available drugs which have shown benefit, mostly by reducing hospitalizations in both diabetic and nondiabetic patients with HfPfEF.

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Remission of Type 2 Diabetes: How, When, and for Whom?

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Abstract

Type 2 diabetes (T2DM) is conventionally considered a progressive disorder, with most patients requiring increasingly intensive therapy to control hyperglycemia over time. Recently, there has been a major paradigm shift towards trying to reverse T2DM. Emerging evidence suggests that remission of T2DM is feasible in a subset of patients. Identification and careful selection of candidates for remission are crucial for the success of these programs. Among various dietary strategies, low-calorie diets (LCDs) and low-carbohydrate diets (LCBDs) have been demonstrated as being effective in facilitating remission of T2DM in a targeted population within a clinical setting. Remission with LCBDs may be maintained in the absence of weight loss, however, long-term evidence is limited and remission may not be maintained without long-term carbohydrate restriction, which poses major challenges. In very low-calorie diets (VLCDs), weight loss of 15 kg or greater and maintenance of weight loss is the main driver and predictor of remission. However, most individuals with T2DM were unable to maintain remission beyond 2 years, despite being on VLCDs. More data are required on the long-term sustainability of remission in an ethnically diverse population like Asian Indians with T2DM who have less obesity and hence less weight to lose. Moreover, “re-reversal” or “relapse” of diabetes can occur in a large percentage of individuals who discontinue the dietary restrictions. Hence, regular follow-up by a multidisciplinary team to ensure sustainability of the lifestyle modification is crucial to the maintenance of remission of T2DM.

Definitions

As per the consensus report proposed by the International Expert Group convened by the American Diabetes Association (ADA), the term “remission” is to be preferred to “reversal,” and should be defined as a return of HbA1c to <6.5% (48 mmol/mol) and/or fasting plasma glucose to <126 mg/dL (<7.0 mmol/L) either spontaneously or following an intervention, and that persists for at least 3 months in the absence of glucose-lowering pharmacotherapy.

“Partial remission” is when an individual with T2DM achieves an HbA1c <6.5% and/or fasting glucose 100–125 mg/dL and is off all diabetes medication for more than 1 year.

“Complete remission” is when an individual with T2DM achieves an HbA1c <6.5% and/or fasting glucose <100 mg/dL and is off all diabetes medication for more than 1 year.

“Prolonged remission” is when an individual with T2DM achieves an HbA1c <6.5% and/or fasting glucose <100 mg/dL and is off all diabetes medication for 5 years and more.

The expert group suggested that testing of HbA1c to document a remission should be performed just prior to an intervention and no sooner than 3 months after initiation of the intervention or withdrawal of any

Introduction

Type 2 diabetes is conventionally considered a progressive disorder, with most patients requiring increasingly intensive therapy to control hyperglycemia over time, with around 50% of individuals requiring insulin therapy within 10 years.1,2

The global prevalence of diabetes in adults has been increasing over recent decades. The total number of people with diabetes is projected to increase from 537 million in 2021 to 784 million by 2045. India has more than 74 million people living with diabetes, the second highest number worldwide. This number is estimated to reach 92.97 million by 2030 and 124.87 million by 2045.3 India also ranks second in the world with 51.7% people with undiagnosed diabetes.4 In the Indian Council of Medical Research-IndianDiabetes (ICMR-INDIAB) study conducted in 15 states, the overall prevalence of pre-diabetes and diabetes were 10.3% and 7.3%, respectively.4

Increased prevalence of diabetes in India can probably be attributed to the higher than recommended consumption of carbohydrates especially simple carbohydrates such as polished white rice, refined wheat, and its products.5,6

Despite advancements in both pharmaceutical and technological treatments, diabetes management still remains suboptimal. The ICMR-INDIAB study data showed high mean hemoglobin A1C (HbA1c) levels (8.9 ± 2.1%) in subjects with self-reported diabetes. More than 60% of subjects had not had their HbA1c level checked in the past 1 year.7 Also, glycemic control tends to deteriorate even in those individuals who initially achieve good control, necessitating the addition of increasing doses of oral antidiabetic agents and ultimately insulin.8 This deterioration in control has been interpreted to mean that while T2DM is treatable and controllable, it is not curable or reversible. Indeed, it is fair to state that the major focus thus far has been on control of hyperglycemia and delaying the progression to the stage of complications. Current treatment guidelines for T2DM recognize this aspect of the natural history of disease by advocating stepwise addition of therapeutic agents so as to achieve glycemic targets.9

Most individuals having diabetes find taking medications life-long a hassle with worries about the long-term side effects of these medications. They wish to go off medications and be declared as “nondiabetic.”

Recently, the management of T2DM has undergone a sea change wherein, efforts are being focused on “reversing” the disorder completely. New evidence shows that it is possible to achieve remission of T2DM but, long-term data on sustainability are lacking. Reversal of glucose levels back into the normal range may be achieved due to modalities of treatment like bariatric surgery or by drastically changing diet and lifestyle to achieve profound weight loss resulting in drastic reduction in body fat (particularly hepatic fat), thereby improving insulin sensitivity. This article will review the literature available on remission of T2DM using dietary interventions such as low-carbohydrate diets (LCBDs) and low-calorie diets (LCDs).

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Remission of Type 2 Diabetes: How, When, and for Whom?

Dietary Strategies Involved in the Remission of T2DM are: LCD and LCBD

Low-calorie Diets (LCDs)
Dietary calorie restriction approaches for the remission of T2DM have used either LCDs (1000–1500 kcal/day) or very low-calorie diets (VLCDs) (<800 kcal/day) to achieve weight reduction.13

A VLCD regime usually involves the replacement of all food with a liquid diet formulation providing approximately 400–800 kcal/day for a period of 12–16 weeks, followed by a reintroduction phase which includes structured solid food tailored for weight loss maintenance. Most of the VLCD liquid formulae comprise approximately 50–60% of energy coming from carbohydrates (maltodextrins and sucrose) in order to prevent ketosis, essential fatty acids to meet the daily requirements, and high-biological-value proteins such (1.2–1.5 gm/kg body weight) to preserve loss of lean body mass. Liquid VLCD formulae typically contain very little fiber, are sweetened with artificial sweeteners, and are fortified with vitamins and minerals to meet the nutritional requirements. However, vitamin and mineral supplements are often suggested to meet the micronutrient needs for obese adults.14

Low-carbohydrate Diets (LCBDs)
Low-carbohydrate diets primarily work on the hypothesis that when LCBD is initiated, insulin secretion is lowered thereby reducing fat storage, facilitating weight loss, and improving cardio-metabolic function.

They are classified as:
- Low-carbohydrate diet—less than 26% of energy coming from carbohydrates or less than 130 gm carbohydrates per day
- Very low-carbohydrate diet—less than 10% energy coming from carbohydrates or 20–50 gm carbohydrates per day.15

Evidence for LCD and LCBD

LCDs
Evidence has shown a positive correlation between significant loss of weight and T2DM remission. The ADA guidelines recommend short-term (3-month) interventions focusing on lifestyle with the use of VLCDs (<800 kcal/day) to achieve >5% loss of body weight. To achieve this calorie deficit, meal replacement formulas can be advised by qualified health care professionals to selected patients with close monitoring. To sustain weight loss for a longer duration, such lifestyle intervention programs must include long-term weight-maintenance counseling and regular follow-up.16

In the COUNTERPOINT study, Lim et al.17 found improvement in hepatic insulin sensitivity and beta cell function in 11 individuals with T2DM (49.5 ± 2.5 years, body mass index (BMI) 33.6 ± 1.2 kg/m2) on a VLCD liquid diet of 600 kcal/day. A total of 510 kcal/day was contributed by a low-calorie liquid formulae providing carbohydrate 46.4%, fat 20.1%, protein 32.5%, vitamins, minerals, and trace elements, and 90 kcal/day from three portions of non-starchy vegetables daily for 8 weeks. Mean weight loss post dietary intervention was 15.3 ± 1.2 kg of initial body weight. It was observed that there was an increase in the first phase of insulin response. Remission of T2DM was noted in 8 weeks, with blood glucose levels returning to the normal range in 1 week. Hepatic triacylglycerol levels decreased to 2.9 ± 0.2% (baseline 12.8 ± 2.4%) (p = 0.003) and pancreatic triacylglycerol content reduced to 6.2 ± 1.1% (baseline 8.0 ± 1.6%) (p = 0.03) by week 8. Improvement in hepatic insulin sensitivity and regularization of beta cell function was attained by calorie restriction alone. Positive outcomes were achieved with a decrease in pancreatic and liver triacylglycerol stores.

This study showed that the aberrations underlying T2DM are reversible with reduction of body fat, weight, hepatic and pancreatic fat, and can be achieved by restriction of calories alone.

Table 1: Definitions of remission/reversal of T2DM

<table>
<thead>
<tr>
<th>Guidelines for remission</th>
<th>Reversal/remission</th>
<th>Glucose lowering agents</th>
<th>Glycemic parameters</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADA</td>
<td>Remission</td>
<td>No diabetes medication</td>
<td>HbA1c &lt;6.5% and/or fasting blood glucose &lt;126 mg/dL</td>
<td>&gt;3 months</td>
</tr>
<tr>
<td>Virta Health</td>
<td>Reversal</td>
<td>No medication or metformin alone</td>
<td>HbA1c &lt;6.5%</td>
<td>&gt;1 year</td>
</tr>
<tr>
<td>ABCD/PCD</td>
<td>Remission</td>
<td>No medication</td>
<td>HbA1c &lt;6.5%</td>
<td>&gt;1 year</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cessation of all diabetes medication</td>
<td>Fasting blood glucose &lt;126 mg/dL, HbA1c &lt;6.5%</td>
<td>&gt;6 months Occurs along with weight loss</td>
</tr>
</tbody>
</table>

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In the COUNTERBALANCE study, 29 people with T2DM, short-duration group (n = 15), having diabetes for <4 years, long-duration group (n = 14) having diabetes for >8 years, consumed VLCD of 624–700 calories comprising liquid replacements, vegetables, and 2 L water per day for a period of 8 weeks. Weight loss achieved in the short- and long-duration groups was found to be similar (14.8 ± 0.8% and 14.4 ± 0.7%, respectively; p = 0.662). About 87% of the individuals in the short-duration group and 50% of the individuals in the long-duration group achieved fasting plasma glucose levels in the nondiabetic range at 8 weeks.18

The COUNTERBALANCE study conducted in 30 individuals with T2DM by Steven et al.19 suggests that T2DM is potentially a reversible condition, and that remission can be achieved by a robust and sustainable weight loss program. This includes following a VLCD of 624–700 kcal/day for 8 weeks followed by return to isocaloric intake of normal food over 2 weeks in a stepwise manner followed by a structured, customized weight maintenance program over a period of 6 months. Weight decreased to 83.8 ± 2.4 kg from a baseline of 98.0 ± 2.6 kg and remained stable for 6 months (84.7 ± 2.5 kg). Similar weight loss was observed between the responders and non-responders (15.8 ± 0.5% vs 13.6 ± 0.7%, respectively). This study demonstrated that remission of T2DM was maintained in 40% of the responders for at least 6 months. Return to blood glucose levels in the non-diabetes range was sustained even while off all anti-diabetes agents and was characterized by improvement in acute insulin secretion. Improvement in hepatic insulin sensitivity was noted in both responders and non-responders. The structured and individualized weight maintenance program was seen to be effective in preventing weight regain. This also helped in continuing remission of T2DM by achieving fasting plasma glucose of <126 mg/dL for the 40% who responded to VLCD.

In the Diabetes Remission Clinical Trial (DIRECT-1), Lean et al. recruited 296 individuals with obesity (BMI of 27–45 kg/m²), aged 20–65 years, diagnosed with T2DM within the past 6 years, not on insulin therapy, and randomized them to intervention and control groups. Intervention consisted of withdrawal of all anti-diabetes and anti-hypertensive medications. They were initiated on complete meal replacement providing 825–853 kcal/day for 3–5 months, followed by stepwise food reintroduction (2–8 weeks), and structured support of long-term maintenance of weight loss. Remission of T2DM was achieved in 46% of the participants in the intervention group and 4% in the control group. At 12 months, 24% participants in the intervention group (and none in the control group) recorded weight loss of >15 kg.

Remission varied with the degree of weight loss in the entire study group. The intervention group showed an average weight loss of 10 kg while the control group showed an average weight loss of 1 kg. Almost half of the obese/overweight individuals with T2DM <6 years duration who had 10 kg weight loss, achieved diabetes remission.

Quality of life as measured by the EuroQol 5 dimensions visual analog scale, increased by 7.2 points in the intervention group and decreased by 2.9 points in the control group.20

Weight loss led to a decrease in liver fat, very low-density lipoprotein (VLDL)-triglyceride production, and intrapancreatic fat and it remained normalized even after 1 year of remission. Thus, obesity-related disordered fat metabolism seems to be responsible for development and remission of T2DM. Those achieving more than 15 kg weight loss sustained remission even after 2 years.21

Further analysis of the sustainability of the intervention done in the DIRECT trial showed that 17 (11%) participants in the intervention group achieved a sustained weight loss of a minimum of 15 kg and 53 (36%) participants in the intervention group sustained remission of T2DM after 2 years.

Thus, at the 2 years follow-up of the DIRECT trial, more than a third of people with T2DM were seen to sustain remission at 2 years. Continued remission was linked to the extent of sustained weight loss.22 Conversely, it may be stated that in two-thirds of participants with T2DM, despite VLCDs, remission could not be maintained beyond 2 years even in a structured clinical trial mode. Hence, in a real-life situation, sustained remission is likely to be extremely rare.

A VLCD was found to be safe and effective in achieving short-term remission in 20 Thai subjects with obesity and T2DM (<10 years duration). Intervention included 10 weeks of VLCD—600 kcal/day, followed by a stepped-up increase in calories at week 10—800 kcal/day, week 11—1000 kcal/day, week 12—1200 kcal/day, and week 13—1500 kcal/day. The average weight loss achieved during the dietary intervention of 14 weeks was 9.5 ± 1.8 kg, which was found to be equivalent to 13.3 ± 2.2% loss of initial body weight. Remission of T2DM was achieved in 79% of subjects in 8th and 12th week.23

In a single-arm study conducted on 20 individuals with T2DM, a personalized, very-low-calorie ketogenic diet (VLCKD) was administered for 8 weeks with protein supplementation as per lean body mass was given. The key findings were lean body mass preservation, abdominal fat reduction, improvement of metabolic profile, maintenance of resting energy expenditure, and T2DM remission. Weight loss achieved after 4 weeks was 11.07 kg and at 8 weeks was 15.77 kg. There was reduction in waist, abdominal, and hip circumference with 10% decrease in waist and abdominal circumference measurements. It was further seen that the weight loss resulted in reduction of truncal fat by –20.72%, and reduction of abdominal fat by –24.8%. There was reduction of 39.7% observed in fasting blood glucose and achievement of HbA1c <6.5% resulting in short-term remission.24

DIADEM-I trial was conducted to compare the impact of an intensive lifestyle intervention (ILI) vs routine medical care on weight loss and glycemic outcomes in 147 adults with obesity and T2DM, ≤3 years duration. The ILI group was put on a total diet replacement (VLCD diet) of 600 kcal/day which was then stepped up to 800 kcal/day at week 10, 1000 kcal/day at week 11, and 1200 kcal/day at week 12, and 1500 kcal/day at week 13 for a year using low-calorie meal replacement formulae followed by stepped-wise reintroduction of food combined with physical activity. This was followed by a maintenance phase for weight loss and it included structured lifestyle support.

Intensive lifestyle intervention led to significant weight loss at 12 months (11.98 kg in the VLCD arm compared to 3.98 kg in the control arm). This was associated with remission of T2DM in 61% of individuals in the VLCD group and 12% in the control group. The investigators concluded that lifestyle intervention allows for a large proportion of young individuals with early onset T2DM to achieve improvements in key cardio-metabolic outcomes, with potential long-term benefits for health and wellbeing.25

Bhatt et al. studied the effect of LCD in individuals with obesity and T2DM. Participants consumed LCD providing 1000 kcal/day [meal replacer formula (30 gm taken with 150 mL skimmed milk)] along with one regular meal and two to three small prespecified homemade snacks) for 12 weeks, which resulted in an average weight loss of 7 kg. About 50% of the study population (median baseline HbA1c 9%) attained HbA1c level in non-diabetes range with LCD despite discontinuing all anti-diabetes drugs. Improvement in liver fat, lipid profile, beta cell secretory capacity, indices of insulin resistance, and insulin sensitivity was also observed. There was a greater reduction (30%) in the median HbA1c of the responders as compared to the non-responders (21%)
with similar weight reduction. Improvement in liver fat was measured by ultrasound and a significant reduction was observed in levels of liver transaminases in responders. Non-responders had higher levels of insulin resistance, lower beta cell secretory capacity as well as lower insulin sensitivity at baseline. Those who achieved remission were younger with shorter duration of diabetes and originally required lesser medication for diabetes control compared to those who did not.

In the Look AHEAD study (2012), adults with obesity and T2DM were divided into two groups—ILI on 1200–1800 kcal/day, reduced total and saturated fat intake, and increased physical activity levels to a goal of ≥175 min/week or diabetes support and education (DSE) where there were three group sessions each year focusing on diet, physical activity, and social support. The ILI group lost more weight as compared to the DSE group in year 1 and year 4. The ILI group was more likely to experience any remission, with prevalence of 11.5% during year 1 and 7.3% in year 4, compared to 2.0% in the DSE group at both time points.

In the Look AHEAD trial, although carbohydrate intake was not specified, however, the goal for fat and protein intake was specified (<30% of total calories from fat, <10% from saturated fat, and at least 15% of calories coming from protein). A marked improvement in HbA1c at 1 year was observed, however, an increase was seen thereafter. This trial focused on weight loss as a key metric of success. Improvement in HbA1c, achieving desired blood glucose targets, reducing the risk of complications, and improving health outcomes, remain the central focus in individuals with T2DM.

The evidence for T2DM remission using LCD dietary interventions is summarized in Table 2.

It may be hypothesized that the individuals with long-term T2DM undergoing remission may have resilient beta cells and are able to endure metabolic stress for years and retain the ability to recover.

**LCBDs**

Low-carbohydrate diets have been in existence longer than LCDs. The link between high carbohydrate intake and diabetes was known to ancient Indian physicians. As early as the 5th century BC, the famous Indian surgeon Sushruta, in his work Samhita mentioned that diabetes is associated with excessive consumption of carbohydrate-rich foods such as cereals, rice, and sweet items. The LCBD is being primarily used since the 1920s as one of the modalities of treatment for intractable epilepsy and has gained prominence since 1970 for weight loss. Stern et al. conducted a study on 132 adults with obesity and T2DM or metabolic syndrome. They were put on either LCBD (carbohydrate intake <30 gm/day) or calorie restriction of 500 kcal/day with less than 30% of calories from fat (conventional diet) for a period of 1 year. Mean weight change was seen to be 5.1 ± 8.7 kg for LCBD after 1 year compared with 3.1 ± 8.4 kg for conventional diet. Participants on LCBD had more favorable outcomes at 1 year. In spite of similar weight loss, effects on atherogenic dyslipidemia and glycemic control were more favorable with LCBD.

Westman et al. studied the effect of low-calorie ketogenic diet (LCKD) (<20 gm of carbohydrate daily; n = 38) or low-glycemic index, calorie-restricted diet (LGID) (deficit of 500 kcal/day; n = 46) in 84 obese individuals aged 18–65 years with BMI 27–50 kg/m² and HbA1c >6% for 24 weeks. Mean weight loss was 11.1 kg (LCKD) vs 6.9 kg (LGID) of initial body weight. Both LGID and LCKD led to improvement in glycemic control, reduction/elimination of anti-diabetes medication, and loss of weight in individuals with overweight/obesity and T2DM over a period of 24 weeks. Greater improvements in glycemic control and reduction/elimination of anti-diabetes medication were seen in the LCKD group compared to the LGID group.

Based on a meta-analysis of 14 randomized controlled trials (RCTs) that included 1,416 obese individuals, there was a greater reduction in fat mass of 0.77 kg observed in the LCBD group compared to those individuals on a low-fat diet. The subgroup with LCBD showed an additional reduction in fat mass of 0.57 kg over a period of 12 months.

In a meta-analysis and systematic review of nine RCTs to study the efficacy of the LCBD compared to a high-carbohydrate diet (HCD) in individuals with T2DM, a significant reduction in HbA1c was observed in the LCBD group compared to the HCD group (weighted mean difference (WMD) −0.44). A positive effect on plasma triglyceride levels and HDL cholesterol in the LCBD group was also reported, however, no significant effects on total or LDL cholesterol were reported. Although LCBD reduced body weight initially, there was no significant effect seen in the long term.

Adoption of LCBD in obese individuals with T2DM showed that there was a spontaneous reduction in calorie intake resulting in weight loss associated with short-term improvement in optimization of glycemic control, insulin sensitivity, and lipid profile.

A recent meta-analysis of LCBD in >1,350 participants with T2DM, demonstrated that compared to other commonly recommended dietary strategies for management of T2DM (e.g., low-fat diets), the LCBD achieved greater rates of remission of T2DM, weight loss, and improvement in fasting insulin sensitivity and triglycerides was observed at 6 months, however, the effect was seen to be diminished at 12 months. In a recent systematic review of cohort studies, long-term LCBDs were found to be associated with increased mortality, therefore, clinicians may consider short-term LCBD for the management of T2DM, while actively monitoring and adjusting diabetes medication as and when needed.

Esposito et al. randomized 215 overweight recently diagnosed adults with T2DM to either low-carbohydrate Mediterranean diet (LCMD) (n = 108) or a low-fat diet (n = 107) for 4 years. Participants on LCMD were more likely to experience any remission (partial or complete), with a mean prevalence of 14.7% during year 1 and 5.0% during year 6 as compared to 4.1% in year 1 and 0% in year 6 in the low-fat diet group. In individuals with newly diagnosed T2DM, LCMD resulted in a greater reduction of HbA1c levels, a higher rate of T2DM remission, and a delayed need for diabetes medication compared to the low-fat diet.

In a study conducted by Unwin et al., 128 (27%) individuals with T2DM and 71 individuals with pre-diabetes opted to follow LCBD for a mean period of 23 months. Mean weight loss was 8.3 kg in individuals with T2DM and 8.4 kg in individuals with pre-diabetes. Remission of T2DM with the withdrawal of drugs occurred in 46% of participants. About 93% individuals with pre-diabetes attained a normal HbA1c. More research is warranted to study the effects of LCBD in achieving long-term glycemic control while ensuring positive metabolic health outcomes.

A pilot program at Norwood was initiated based on the principle that T2DM control depends on reducing the dietary glucose load. Eighty-five out of the 175 participants who were following LCBD for an average of 30 months achieved drug-free T2DM remission showing significant improvements in cardio-metabolic markers. Withdrawal of drugs led to significant savings. This can be the biggest motivational force to improve patient compliance.

Webster et al. assessed the status of diabetes, dietary intake, and personal experiences of 28 individuals with T2DM who followed a low-carbohydrate high-fat (LCHF) diet for a minimum of 6 months. The carbohydrate intake was found...
### Table 2: Evidence of LCD diets during remission

<table>
<thead>
<tr>
<th>Author/year/country</th>
<th>Subjects</th>
<th>Dietary intervention</th>
<th>Weight loss/remission</th>
</tr>
</thead>
</table>
| **Lim et al. (2011), Newcastle, UK** Counterpoint Study | 11 T2DM and controls matched for weight, age, and sex | Very low-energy liquid diet [46.4% carbohydrate, 32.5% protein, and 20.1% fat; vitamins, minerals, and trace elements (510 kcal/day) and three daily portions of non-starchy vegetables (90 kcal/day) for 8 weeks] | • 15 ± 1% weight loss of initial body weight  
• HbA1c decreased from 7.4 ± 0.3 to 6.0 ± 0.2%  
• Decreased hepatic and pancreatic triacylglycerol content  
• Increase in the first phase of insulin secretion |
| **Steven et al. (2015), Newcastle, UK** Counterbalance Study–1 | 29 participants with a T2DM short-duration group of ≤4 years n = 15, long-duration group of >8 years n = 14 | VLCD [43% carbohydrate, 34% protein, and 19.5% fat; up to 240 gm of non-starchy vegetables (624–700 kcal/day) for 8 weeks] | • 14.8 ± 0.8% and 14.4 ± 0.7% weight loss in short- and long-duration group, respectively  
• HbA1c decreased from 7.2 ± 0.2% to 6.1 ± 0.2% in the short-duration group and from 8.6 ± 0.4% to 8.0 ± 0.5% in the long-duration group  
• 87% short-duration group and 50% long-duration group achieved nondiabetic fasting plasma glucose levels |
| **Steven et al. (2016), Newcastle, UK** Counterbalance Study–2 | 30 participants with a T2DM duration of 0.5–23 years | VLCD [43% carbohydrate, 34% protein, and 19.5% fat; up to 240 gm of non-starchy vegetables (624–700 kcal/day) for 8 weeks] | • Weight loss achieved was similar between the responders and non-responders 15.8 ± 0.5% vs 13.6 ± 0.7%  
• HbA1c fell from 7.1 ± 0.3 to 5.8 ± 0.2% in responders and from 8.4 ± 0.3 to 8.0 ± 0.5% in non-responders |
| **Lean et al. (2018), Scotland and England** DIRECT Study–1 | 298 participants with T2DM (149 intervention and 149 control), 0–6 years duration—1 year follow-up | LCD replacement (825–853 kcal/day; 59% carbohydrate, 13% fat, 26% protein, and 2% fiber) for 3 months followed by structured food reintroduction of 2–8 weeks (about 50% carbohydrate, 35% total fat, and 15% protein) for 12–20 weeks | • At 12 months, weight loss of ≥15 kg in 24% participants (n = 36) in the intervention group and no participants in the control group  
• Mean HbA1c fell by 0.9% in the intervention group and increased by 0.1% in the control group  
• 46% remission in the intervention group and 4% in the control group |
| **Lean et al. (2019), Scotland and England** DIRECT Study–2 | 298 participants with T2DM (149 intervention and 149 control), 0–6 years duration—1 year follow-up | LCD replacement (825–853 kcal/day; 59% carbohydrate, 13% fat, 26% protein, and 2% fiber) for 3 months followed by structured food reintroduction of 2–8 weeks (about 50% carbohydrate, 35% total fat, and 15% protein) for 12–20 weeks | • At 24 months, weight loss of ≥15 kg in 11% (n = 36) in the intervention group and by 2% (n = 3) in the control group  
• 36% remission in intervention arm and 3% in control arm |
| **Umphonsathien et al. (2019), Bangkok, Thailand** | 20 participants with T2DM (BMI of 23–30 kg/m²), of <10 years duration | 10 weeks of 600 kcal/day followed by a stepwise increase in kcal/day at week 10 (800 kcal/day), week 11, (1000 kcal/day), week 12 (1200 kcal/day), and week 13 (1500 kcal/day) | • 9.5 ± 1.8 kg mean weight loss, equivalent to 13.3 ± 2.2% loss of initial body weight  
• 79% remission at 8th and 12th week |
| **Romano et al. (2019), Rome, Italy** | 20 participants with T2DM for 8 weeks | VLCKD with protein intake depending on lean mass and synthetic amino acid protein supplementation | • At 8 weeks, 15.77 kg weight loss of initial body weight in VLCKD diet  
• Reduction in waist, abdominal and hip circumference with 10% decrease in waist and abdominal circumference measurements  
• Short-term remission |
| **Taheri et al. (2020), Doha, Qatar** DIADEM-I | 147 adults with T2DM, ≤3 years duration (70 in the intervention arm; 77 in the control arm) | 12-week total diet replacement phase, 800–820 kcal/day diet meal replacement products (57% carbohydrate, 14% fat, 26% protein, and 3% fiber; followed by a 12-week structured food reintroduction phase) | • At 12 months, 11.98 kg weight loss in intervention and 3.9 kg in control group  
• 61% and 12% remission in VLCD and control arms, respectively |

(Contd…)

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**Journal of the Association of Physicians of India, Volume 70 Issue 8 (August 2022)**
Remission of Type 2 Diabetes: How, When, and for Whom?

Mechanisms of Remission of T2DM

The most commonly recognized mechanism of T2DM remission with LCD is based on the “Twin cycle” hypothesis by Roy Taylor. This hypothesis is based on the rationale that excess caloric intake, which happens in conjunction with insulin resistance, leads to ectopic fat accumulation in the hepatocytes and islets of Langerhans of the pancreas. This results in increased hepatic insulin resistance, shutting out of VLDDL, reduced first-phase insulin secretion, and increased inflammation. Excess fat in the liver affects hepatic insulin response, resulting in increased production of glucose. While in the pancreas, because of the fat-induced metabolic stress, beta cells seem to enter a mode of survival and fail to function optimally. Substantial weight loss leading to reduction of excess fat from the pancreas and liver is seen to normalize hepatic insulin response. This is associated with recovery of beta cells, thereby improving insulin secretion in individuals in the early years post diagnosis of T2DM, possibly by redifferentiation. These changes help in normalizing blood glucose levels.

Thus, reversing the cycle with calorie restriction results in the reduction of liver and pancreatic fat, thereby reducing insulin resistance and enhancing insulin secretion.

Mechanisms of Remission of T2DM with LCBD

The carbohydrate insulin model of obesity is the rationale behind using LCBD as a weight loss strategy. Diets high in carbohydrate (refined sugar and starches) stimulate post-prandial hyperinsulinemia which lead to fat deposition. Dietary carbohydrates have the most potent effect on insulin secretion, which differ based on the amount and type of carbohydrate.

The LCBD leads to a diminished supply of carbohydrates to the liver, reduced synthesis of fatty acids from excessive carbohydrates, and increased lipolysis. There is also a reduction in plasma insulin levels that decrease fat storage in adipose tissue, which ultimately manifests in progressive loss of body fat.

Post adoption of LCBD, gluconeogenesis, and ketogenesis are the two key metabolic processes that occur. A reduced supply of glucose to the liver, muscle, and brain leads to reduced glycojen synthesis and storage, thereby reducing the capacity for glycolysis. Diminishment of glycolysis results in augmentation of gluconeogenesis as they have a reciprocal and inverse relationship. Gluconeogenesis utilizes lactic acid, glycerol, and certain amino acids (alanine and glutamine) as substrates. Continuous gluconeogenesis over several hours may not be sufficient to provide the required glucose to the body due to limited supply of these substrates. In this scenario, ketone bodies are produced as an alternate fuel source to glucose via ketogenesis. LCBD is associated with low levels of serum insulin which leads to lipolysis. There is an elevated supply of fatty acids followed by conversion to acetoacetic acid and ketones—β-hydroxybutyric acid and acetone. With these physiological insights, LCBD reduces plasma insulin levels and promotes calorie utilization, thereby resulting in reduced storage of fat which in turn facilitates remission.

Which Dietary Strategy is Best for Inducing Diabetes Remission?

The controversy about LCBD or LCD approaches to remission of T2DM continues. Evidence has shown that both dietary strategies improve metabolic risk factors like BMI, glycemic control, and cardiovascular health. Both LCD and LCBD are effective in bringing about remission of T2DM, and if done under strict medical supervision, both dietary strategies may be considered safe.

Within 7 days of initiating a LCD of 800 calories/day, fasting plasma glucose is seen to normalize by either dietary intervention or bariatric surgery. There is a substantial reduction observed in hepatic fat content and improvement in hepatic insulin sensitivity. First phase and maximal rate of insulin secretion gradually return to normal over a period of 8 weeks and this change is associated with decreased pancreatic fat content.

As per the available evidence, VLCD is seen to help achieve 15 kg or greater weight loss. However, maintenance of weight loss is seen to be the main driver and predictor of remission.

If LCBD is sustained, remission of T2DM is seen to be maintained in the absence of weight loss. However, evidence is limited and relapse is likely to occur if carbohydrate restriction ceases. LCBD has shown reduction in fat mass and remission of T2DM for up to 6 months. Long-term studies with LCBD in the sustenance of remission of T2DM are warranted as efficacy of LCBD on weight loss and metabolic benefits beyond 6 months is found to be unsatisfactory.

Limitations of LCBD in the real world include sustainability in the long run due to restriction on food choices. Such diets can be nutritionally deficient, especially when done without medical supervision. Fat intake, especially saturated fat intake, is very high.

### Evidence for T2DM remission using LCBD dietary interventions is summarized in Table 3.

<table>
<thead>
<tr>
<th>Author/year/country</th>
<th>Subjects</th>
<th>Dietary intervention</th>
<th>Weight loss/remission</th>
</tr>
</thead>
</table>
| Bhatt et al. (2017), Pune, India | 12 participants with T2DM | 12-week low-calorie program—1000 kcal/day (using three servings meal replacement protein formula + one regular meal and two to three small prespecified homemade snacks, 60% carbohydrate, 30% protein, and 10% fat) | • Median weight loss of 7 kg  
• 50% remission |
| Gregg et al. (2012), USA Look AHEAD study | 4,503 obese adults with T2DM, 2,241 in intervention (ILI) group | Energy restricted low-fat diet (1200–1800 kcal/day) and increased PA to 175 min/week for 4 years | • ILI participants lost an average of 8.6% of initial body weight compared to a 0.7% weight loss in the DSE group at the end of 1 year  
• 11.5% remission at 1 year, 7.3% at 4 years in ILI group compared to 2% in DSE at both time points |
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It must be emphasized that both dietary interventions in a targeted population is seen as essential. Both LCD and LCBD need continuous support and follow-up by a multi-disciplinary health care team to prevent weight regain and re-reversal of diabetes.

**Who is the Right Candidate for Such Dietary Interventions?**

The implementation of these dietary interventions in a targeted population is seen to be more effective in a clinical setting and appears to be most appropriate for candidates with less than 6 years and ideally within 2 years of diagnosis of T2DM, preferably males, those with better glycemic control, who are on fewer anti-diabetes drugs, those with good beta cell function and insulin secretion, those with less visceral fat, and lastly with good mental health.

The ABCDEFG formula can help us identify individuals with T2DM most likely to achieve remission.

- **A:** A1c or HbA1c—those who do not have markedly elevated A1c are more likely to achieve remission.
- **B:** Body weight—greater the body weight, greater the chances of achieving remission.
- **C:** Lower visceral fat—greater the body weight, greater the chances of achieving remission.
- **D:** Early stage of diabetes—greater the chances of achieving remission.
- **E:** Diet adherence—greater the chances of achieving remission.
- **F:** Follow-up—greater the chances of achieving remission.
- **G:** Goals—greater the chances of achieving remission.

**Table 3:** Evidence of LCBD diets during remission

<table>
<thead>
<tr>
<th>Author/year/country</th>
<th>Subjects</th>
<th>Dietary intervention</th>
<th>Weight loss/remission</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stern et al. (2004), Philadelphia, USA</td>
<td>132 obese adults with T2DM or metabolic syndrome</td>
<td>LCBD carbohydrate intake &lt;30 gm/day (LCBD) or to restrict caloric intake by 500 calories/day with &lt;30% of calories from fat (conventional diet) for 1 year</td>
<td>Mean weight loss (5.1 ± 8.7 kg for LCBD) or 3.1 ± 8.4 kg for conventional diet</td>
</tr>
<tr>
<td>Westman et al. (2008), Durham, USA</td>
<td>84 participants with T2DM and obesity</td>
<td>LCKD group intervention (&lt;20 gm of carbohydrate) OR LGID group intervention (&lt;500 kcal/day) for 24 weeks</td>
<td>Meal weight loss (Weight loss of 11.1 kg (LCKD) vs 6.9 kg (LGID) of initial body weight)</td>
</tr>
<tr>
<td>Bogen et al. (2005), New Jersey, USA</td>
<td>10 obese participants with T2DM</td>
<td>Usual diet for 7 days followed by LCBD (20 gm carbs/day) for 14 days</td>
<td>Mean weight loss (1.65 kg)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Improved glycemic control with reduction in HbA1c from 7.3 to 6.8%</td>
</tr>
<tr>
<td>Esposito et al. (2014), Naples, Italy</td>
<td>215 overweight, middle-aged men and women with newly diagnosed T2DM</td>
<td>LCMD (n = 108, carbs &lt;50% of calories) or a low-fat diet (n = 107) for 4 years</td>
<td>Weight loss of 8.3 kg for T2DM and 8.4 kg in pre-diabetes</td>
</tr>
<tr>
<td>Webster et al. (2019), Cape town, South Africa</td>
<td>28 participants with T2DM</td>
<td>LCHF for 6 months and followed up for 15 months</td>
<td>Mean weight loss 16 kg (7–31 kg)</td>
</tr>
<tr>
<td>Unwin et al. (2020), South Port, UK</td>
<td>128 participants with T2DM and 71 with pre-diabetes</td>
<td>LCBD for 23 months</td>
<td>Mean weight loss of 8.3 kg for T2DM and 8.4 kg in pre-diabetes</td>
</tr>
<tr>
<td>Meng et al. (2017), China</td>
<td>Nine studies with 734 patients with T2DM or T2DM and obesity</td>
<td>A systematic review and meta-analysis of nine RCTs on the efficacy of the LCBD</td>
<td>Significant reduction in HbA1c in the LCBD group compared to the HCD group (WMD –0.44)</td>
</tr>
<tr>
<td>Hashimoto et al. (2016), Kyoto, Japan</td>
<td>Meta-analysis of randomized controlled studies</td>
<td>1,416 obese individuals, 15 RCTs (8–very LCBD – 50 gm/day or 10% of calories; 7–40% of calories from carbohydrates)</td>
<td>At 1 year, LCBD was not associated with decrease in body weight (~0.44 kg)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Very LCBD was associated with decrease in fat mass (~0.97 kg)</td>
</tr>
<tr>
<td>Goldenberg et al. (2021), USA</td>
<td>Systematic review and meta-analysis of published and unpublished randomized trial data in T2DM</td>
<td>23 trials, 1357 participants, studied LCBD (130 gm/day or &lt;25% of a 2000 kcal/day diet) and very LCBD (&lt;10% calories from carbohydrates) for at least 12 weeks in eligible adults with T2DM</td>
<td>At 6 months, 13% achieved remission</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>At 1 year, improvement in weight loss, fasting insulin sensitivity, and triglycerides diminished</td>
</tr>
</tbody>
</table>

with low dietary fiber intake predisposing an individual to dyslipidemia, hyperuricemia, poor bone health, renal calculi, insulin resistance, and gut dysbiosis. Such restrictive, extreme diets, if continued for a long time can also take a toll on mental, financial, and emotional status of the individual.30

In studies conducted on mice, if LCBDs are continued for a long time, the fat is seen to reappear. Therefore, more research is required to see the long-term effects of such diets in humans.

It must be emphasized that both dietary strategies work only for a targeted population and careful selection of the candidate needs to be done by health care professionals. Both LCD and LCBD need continuous support and follow-up by a multi-disciplinary health care team to prevent weight regain and re-reversal of diabetes.
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(15 kg or more weight loss is required to achieve T2DM remission).

• C: C-peptide—higher chances for remission are seen with better levels of C-peptide.
• D: Diabetes duration—greater the chance of remission with shorter duration of diabetes (<6 years).
• E: Enthusiasm—high motivation levels are needed for remission.
• F: Frequent follow-ups—individuals should be willing to follow-up frequently with the health care team

However, evidence of effectiveness beyond 2 years is limited and more data are required in an ethnically diverse population like Asian Indians with T2DM who have less obesity.

Adjustments of Dosage of Medications before initiating LCBD in Patients with T2DM

• Patients on hypoglycemic agents such as insulin or sulfonylureas may be at an increased risk of hypoglycemia. Hence, regular blood glucose monitoring/CGM along with reduction in dose/cessation of oral drugs/insulin is crucial to patient safety.
• Patients following LCBD who are on sodium-glucose co-transporter-2 (SGLT-2) inhibitors are at a higher risk of diabetic ketoacidosis. Hence, patients on SGLT-2 inhibitors must avoid following LCBD or discontinue SGLT-2 before following LCBD. This should be done under strict medical supervision.5
• The LCBD is associated with reduction in blood pressure levels; therefore, patients on anti-hypertensive drugs may require reduction in dosage or cessation of these drugs to avoid symptomatic hypotension.44

Early intervention and review of diabetes medications, especially insulin, sulphonylureas, and SGLT-2 inhibitors are essential in individuals following LCBD. Frequent follow-up and careful monitoring of cardiovascular risk factors are important.45

Irrespective of the initial effectiveness of the dietary intervention, “re-reversal” or “relapse” of diabetes can occur in a large percentage of people who discontinue the diet and lifestyle change. Patients should remember that diabetes has only gone into remission and has not been cured, and therefore it can reappear anytime. Hence, regular follow-up and sustenance of the lifestyle modification program are crucial.

CONCLUSION

While treating individuals with T2DM, we should try to identify the candidates likely to achieve remission. Accordingly, the possibility of and the need for achieving remission should be discussed with them. Both LCDs and LCBDs have demonstrated to be effective in remission of T2DM.

Hence, if appropriately supported and done under strict medical supervision, both dietary interventions may be considered reasonably safe. Normoglycemia can be achieved and maintained in the absence of weight loss in individuals following LCBDs, however, evidence is limited and relapse can occur if carbohydrate restriction is discontinued. In India, long-term carbohydrate restriction is a major challenge.

In VLCDs, weight loss (typically 15 kg or greater) and maintenance is the key driver and predictor of remission.

Use of dietary interventions in carefully selected individuals is seen to be more effective within a clinical setting. Dietary modification needs to be individualized and tailor-made for the individual after careful screening and assessment to ensure long-term adherence and remission.

“Re-reversal” or “relapse” of T2DM can occur in a large percentage of people who discontinue the dietary and lifestyle intervention. Hence, structured programs supporting people towards achieving remission need to be offered with regular support and follow-ups from the multi-disciplinary health care team especially a qualified dietitian and psychologist for long-term success.

It must also be emphasized that diabetes remission can happen only in individuals with T2DM and pre-diabetes. Type 1 diabetes is an autoimmune condition requiring insulin therapy for survival and at present, there is no evidence for remission or reversal of type 1 diabetes. Attempts to withdraw insulin in such patients can be potentially hazardous and life-threatening.

Finally, it should be understood that while T2DM can go into remission, re-occurrence may happen if the lifestyle and diet control are not maintained. Hence claims such as “cure” or “reversal” of T2DM may be inappropriate, particularly those made by different groups purporting to study the “metabolism” of the individual and instituting personalized “diabetes reversal” programs using unproven and unscientific “apps”.

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Rivaroxaban, a New Molecule with Potential to Balance Bleeding Risk and Ischemic Events in Patients with Chronic Coronary Syndrome

Lekha Adik-Pathak1*, Salil Shirodkar2, Amit Gupta3
Received: 17 May 2022; Accepted: 25 May 2022

Abstract
Globally, the prevalence of chronic coronary syndrome (CCS) increases with age. In India, there is a rapidly growing burden of coronary artery disease (CAD), which has become the leading cause of morbidity and mortality. Despite recommended medical therapy, patients with CCS are still at risk of ischemic events. Currently, dual antiplatelet therapy (DAPT) is recommended in the form of aspirin and a P2Y12 inhibitor or low dose rivaroxaban in patients with stable CAD and/or peripheral artery disease (PAD). A low dose of rivaroxaban in combination with aspirin is a promising approach; however, for patients who might benefit the most, it still remains a challenge. Clinical trial data on this new drug was certainly very encouraging, with evidence from the COMPASS trial and prespecified subgroups of COMPASS trials suggesting that the addition of rivaroxaban to aspirin was associated with a significantly lower risk of ischemic events, mortality, and tolerable bleeding profile in patients with CCS and high-risk factors. This combination is cost-effective and generally well tolerated in patients with CAD and/or PAD, as well as patients with CCS and multimorbidity or high-risk populations.

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Background and Rationale
The ESC 2019 guidelines have introduced a new term, CCS, for “stable” angina. CCSs include patients with suspected CAD and “stable” anginal symptoms and/or dyspnea, patients with new-onset of heart failure (HF) or left ventricular dysfunction and suspected CAD, asymptomatic and symptomatic patients with stabilized symptoms <1 year after an acute coronary syndrome (ACS), or patients with recent revascularization, asymptomatic, and symptomatic patients >1 year after initial diagnosis or revascularization, patients with angina and suspected vasospastic or microvascular disease, and asymptomatic subjects in whom CAD is detected at screening. All these patients have different risks for future cardiovascular (CV) events.1

Globally, the prevalence of CCS increases with age, both in men and women.2 The worldwide prevalence of CAD and PAD was reported in the range of 5–8% and 10–20%, respectively.4 In India, there is a rapidly growing burden of CAD, and it has become the leading cause of mortality and morbidity in the last three decades.4

Despite recommended medical therapy, including statins, beta-blockers, and calcium channel blockers, patients with CCS are still at risk of significant, and often clinically meaningful, ischemic events.1 Antiplatelet therapy is suggested in patients with stable atherosclerotic disease to prevent future CV events.5 The dual pathway concept is a novel approach that combines both antiplatelet and direct oral anticoagulants (DOACs) therapy. DOACs act by inhibiting factor Xa, which generates thrombin for platelet activation. Currently, DAPT in the form of aspirin and a P2Y12 inhibitor or low dose rivaroxaban is recommended in patients with stable CAD and/or PAD, based on evidence-based trials.5,7

Rivaroxaban, a novel DOAC with the dual-pathway mechanism of action, is accepted as a promising therapy for the prevention and treatment of venous thromboembolism (VTE), stroke, and systemic embolism in patients with atrial fibrillation (AF).6 A low dose of rivaroxaban in combination with aspirin is a promising approach in terms of reducing the composite of death from CV causes, myocardial infarction (MI), or stroke; however, for patients who might benefit the most, it still remains a challenge. This review is to discuss the potential role of low-dose rivaroxaban in terms of reducing CV events in patients with CCS based on the evidence from various clinical trials.

Rivaroxaban in a Nutshell
Pharmacokinetics and Pharmacodynamics Profile
Rivaroxaban has a low risk of drug-drug interaction, and it does not require regular monitoring for coagulation if given at fixed doses; owing to its predictable pharmacokinetics and pharmacodynamics properties.6 When the tablet is orally taken, it is quickly absorbed, and the maximum plasma concentration is achieved in 2–4 hours.6 An increased bioavailability was observed in case of 10 mg tablets regardless of food consumption; whereas, for 15 and 20 mg tablets, it is higher if consumed with food.6,8

Plasma concentration of rivaroxaban was eliminated with a terminal half-life of 5–9 hours and 11–13 hours in a healthy population of young and older individuals, respectively. The pharmacodynamic effects of rivaroxaban correlate well with its plasma concentration. Rivaroxaban is not associated with the inhibition of cytochrome P450 enzymes or known drug transporter systems. As rivaroxaban is eliminated via multiple pathways, there are no clinically relevant drug-drug interactions. Rivaroxaban is excreted from the body either through metabolic degradation or through the renal pathway. During renal elimination, 36% of the dose is excreted in the form of an unchanged active drug through active renal secretion (30%) and glomerular filtration (6%).6,12

Rivaroxaban showed dose-dependent pharmacodynamic properties in healthy subjects. A similar dose-dependent relationship was seen among different patient populations, including patients with AF (stroke prevention), patients with ACS, those undergoing deep vein thrombosis treatment, and those who underwent knee or total hip surgery (VTE prevention).13-15

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Rivaroxaban in CCS

Efficacy and Safety Profile (Evidence From Clinical Trials)

In clinical practice, it is challenging to develop strategies that will lower the risk of ischemic events without increasing bleeding events in patients with CCS. Recently more attention has focused on the use of rivaroxaban in such populations to improve clinical outcomes.

The COMPASS is a large trial that included more than 27,000 patients with stable CAD or PAD. Participants were randomly assigned to receive rivaroxaban (2.5 mg twice daily) plus acetylsalicylic acid (ASA) (once daily), rivaroxaban (5 mg twice daily) alone, or ASA (once daily) alone. Patients treated with rivaroxaban in combination with ASA experienced significant benefits compared with ASA alone. After a mean follow-up of 23 months, low-dose rivaroxaban in combination with ASA was significantly associated with lower rates of a composite of CV death, stroke, or MI than ASA alone (hazard ratio (HR): 0.76; 95% confidence interval (CI): 0.66–0.86; p < 0.001). Even though the bleeding risk was increased in the combination arm (HR: 1.70; 95% CI: 1.40–2.05; p < 0.001) without a significant increase in fatal or critical organ bleeding, combination therapy resulted in lower mortality and ischemic events compared to ASA monotherapy.

A VOYAGER trial was conducted in patients with PAD who underwent lower-extremity revascularization.

A significant reduction in terms of a composite of acute limb ischemia, major amputation for vascular causes, MI, ischemic stroke, or death from CV causes was observed with a combination therapy of rivaroxaban at a dose of 2.5 mg twice daily plus aspirin compared to aspirin alone (HR: 0.85; 95% CI: 0.76–0.96; p = 0.009).

According to the International Society on Thrombosis and Haemostasis major bleeding definition, bleeding was significantly higher in patients treated with rivaroxaban and aspirin (HR: 1.42; 95% CI, 1.10–1.84; p = 0.007); however, bleeding was comparable between both groups according to Thrombolysis in Myocardial Infarction (TIMI) major bleeding definition (HR: 1.43; 95% CI, 0.97–2.10; p = 0.070). Therefore, while interpreting, it is important to look for which definition is followed. Consistent benefits of rivaroxaban added to aspirin therapy were reported in patients with PAD undergoing lower-extremity revascularization.

A total of 15,526 patients with a recent ACS were included in anti-Xa therapy to lower CV events in addition to standard therapy in subjects with Acute Coronary Syndrome–Thrombolysis in Myocardial Infarction 51 (ATLAS ACS 2–TIMI 51) trial and administered with either 2.5 mg or 5 mg twice daily dose of rivaroxaban or placebo. In this trial, rivaroxaban was found to be associated with a reduced risk of the composite endpoint of death from CV causes, MI, or stroke. Rivaroxaban increased the risk of major bleeding and intracranial hemorrhage but not the risk of fatal bleeding.

A combination of aspirin with a P2Y12 inhibitor is the standard DAPT for ACS. When rivaroxaban is added to this DAPT, it reduces both mortality and ischemic events but increases bleeding risk. However, observations of the GEMINI-ACS-1 trial indicate that a low-dose rivaroxaban in combination with either ticagrelor or clopidogrel was established as a safe treatment approach for ACS without increasing major bleeding events. Moreover, mortality benefits were observed with rivaroxaban and aspirin combination in patients with CCS. There is an increased risk of CV morbidity and mortality in patients with PAD. However, a significant reduction in overall cause-specific CV mortality was observed with the rivaroxaban plus aspirin combination therapy compared with aspirin alone in patients with chronic CAD or PAD. Although absolute mortality rates were improved in high-risk patients, death due to HF remains unchanged.

A meta-analysis of the COMPASS and VOYAGER trials reported the beneficial use of low-dose rivaroxaban plus aspirin in terms of decreasing the number of events such as acute limb ischemia and major vascular amputation in patients with PAD compared to aspirin alone. In spite of the significant reductions seen in efficacy endpoints, the relative increase in major bleeding events raises concern about the tolerability of the above-mentioned combination; however, fatal or critical organ bleeding was low and nonsignificant.

The uniform results seen in these trials indicate the benefits of using this combination therapy across a wide range of patient populations with stable CAD or PAD. This combination provides significant benefits in terms of lower rates of a composite of CV death, stroke, or MI, acute limb ischemia, and major amputation for vascular causes.

There is limited data on the cost-effectiveness of rivaroxaban plus aspirin antplatelet therapy. An economic analysis conducted in Netherlands and Italy showed beneficial effects of rivaroxaban in combination with ASA in patients with stable CAD or PAD compared with ASA monotherapy.

Compared with aspirin alone, rivaroxaban plus aspirin is cost-effective in preventing recurrent CV events in all patients with CAD or PAD, from the Italian perspective. The cost-effectiveness of low-dose rivaroxaban in combination with aspirin was assessed in the entire COMPASS population and in all five subpopulations, including CAD, PAD, CAD and PAD, CAD with HF, and CAD with CKD, based on the specific health event risk and relative treatment impact.

Current Approval Status: Global and Indian

Rivaroxaban can be prescribed according to country-specific drug approval. Rivaroxaban was approved in the USA and Europe for various indications (Table 1). Food and Drug Administration approved rivaroxaban for patients with atherosclerosis, approval in India is expected in the near future.

Rivaroxaban 2.5 mg orally twice daily is recommended in chronic CAD or PAD in combination with aspirin (75–100 mg) once daily with or without food for prevention of risk of major CV events (CV death, MI, and stroke).

Use in Different Patient Populations

In recent clinical trials, rivaroxaban has been evaluated in CAD or PAD patients with other risk factors. However, it is too early to recommend a rivaroxaban plus aspirin regimen in patients with stable CAD and/or PAD for secondary CV prevention. A global COMPASS trial showed that rivaroxaban plus aspirin combination has greater benefits in terms of prevention of secondary CV events.

Table 1: Indications and approval of rivaroxaban

<table>
<thead>
<tr>
<th>Indication</th>
<th>Year of approval</th>
<th>Country</th>
</tr>
</thead>
<tbody>
<tr>
<td>DVT/PE prophylaxis in acute medical illness</td>
<td>2019</td>
<td>USA</td>
</tr>
<tr>
<td>PAD</td>
<td>2018</td>
<td>USA and Europe</td>
</tr>
<tr>
<td>Stable CAD</td>
<td>2018</td>
<td>USA and Europe</td>
</tr>
<tr>
<td>To reduce risk of VTE after 6 months of treatment</td>
<td>2017</td>
<td>USA and Europe</td>
</tr>
<tr>
<td>ACS</td>
<td>2013</td>
<td>Europe</td>
</tr>
<tr>
<td>DVT/PE treatment</td>
<td>2012</td>
<td>USA and Europe</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>2011</td>
<td>USA and Europe</td>
</tr>
<tr>
<td>DVT/PE prophylaxis in hip and knee surgery</td>
<td>2011</td>
<td>USA</td>
</tr>
<tr>
<td>DVT/PE prophylaxis in knee surgery</td>
<td>2008</td>
<td>Europe</td>
</tr>
</tbody>
</table>
in patients with stable CAD and/or PAD along with comorbidities when compared to aspirin alone. As reported in the COMPASS trial, rivaroxaban plus aspirin combination therapy was significantly associated with decreased risk of primary composite major adverse CV event outcome and composite major adverse limb event outcome in adult patients with stable CAD and/or PAD irrespective of the presence or absence of risk factors including age, gender, geographical region, eGFR status, and history of CV risk factors. Patients with HF having sinus rhythm were at high risk of stroke in the range of 1–2% year, and none of the guidelines have recommended anticoagulation or antiplatelet therapy due to lacking evidence of lower risk of stroke and considerable risk of gastrointestinal bleeding, especially in elderly patients. In the COMPASS trial, rivaroxaban use has shown clinically meaningful benefits in patients with HF and sinus rhythm; however, the COMMANDER-HF trial showed neutral benefits on ischemic risk but a substantial increase in mortality rate, which was not influenced by anticoagulation. Further subgroup analysis of the COMMANDER-HF trial demonstrated the possible benefit of rivaroxaban in stroke prevention among different conditions such as CAD, HF, and sinus rhythm. According to a subgroup analysis of COMPASS trials, the effect of low-dose rivaroxaban is consistent in patients with polypharmacy and multimorbidity and in patients with vascular disease, irrespective of comorbidities and BMI, respectively. Patients with LE-PAD with high-risk limb features (prior amputation, Fontaine III or IV symptoms, or prior peripheral artery revascularization) or high-risk comorbidities (diabetes, kidney dysfunction, HF, or polyvascular disease) included in the COMPASS trial suggested that the rivaroxaban plus aspirin combination is favorable in terms of absolute risk reduction for major vascular events compared to aspirin monotherapy. Moreover, a network meta-analysis suggested that compared with aspirin monotherapy, rivaroxaban plus aspirin combination therapy is the favored choice of long-term antithrombotic therapy, which showed an effective reduction in ischemic and bleeding events and all-cause mortality in patients with CCS and high-risk factors. In patients with chronic vascular disease, net clinical benefit (NCB) was assessed between low-dose rivaroxaban plus aspirin and aspirin alone, suggesting patients treated with combination therapy had fewer NCB events in terms of reduction in stroke and CV mortality and risk of major bleeding was not frequent. On the other hand, high-risk subgroups and patients with multiple comorbidities had more NCB as compared to the overall study population. Overall data indicate the use of rivaroxaban plus aspirin remains favorable in terms of

Table 2: Ongoing clinical trials of rivaroxaban for CCS

<table>
<thead>
<tr>
<th>Study identifier [ref.]</th>
<th>Phase</th>
<th>Intervention</th>
<th>Location</th>
<th>Patient population</th>
<th>Estimated sample size</th>
<th>Duration of study</th>
<th>Primary endpoints</th>
<th>Secondary endpoints</th>
</tr>
</thead>
<tbody>
<tr>
<td>NCT 049,90791</td>
<td>IV</td>
<td>Aspirin 75 mg</td>
<td>UK</td>
<td>CCS</td>
<td>48</td>
<td>14 days</td>
<td>Difference in bleeding time, measured at 2 hours postdose</td>
<td>Bleeding time predose Fibrin clot lag time by fibrin clot turbidimetry Fibrin clot lysis time by fibrin clot turbidimetry</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Aspirin 20 mg</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Frequency of further angioplasty Frequency of further heart attack, stroke or death</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Rivaroxaban</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Stroke or systemic embolism Major bleeding</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2.5 mg</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Major Adverse Cardiovascular Events Clinically driven coronary, peripheral or carotid revascularization Stent thrombosis</td>
</tr>
<tr>
<td>NCT 037,75746</td>
<td>IV</td>
<td>Clopidogrel</td>
<td>UK</td>
<td>ACS</td>
<td>150</td>
<td>30 days</td>
<td>The change in LT in the three treatment groups assessed using the GTT from admission to follow-up at 30 days</td>
<td>Occurrence stroke, myocardial infarction, cardiovascular death, coronary revascularization procedures (PCI, CABG), peripheral revascularization procedures, carotid revascularization procedures, minor bleeding complications (according to ISTH)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>75 mg</td>
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<td></td>
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<tr>
<td></td>
<td></td>
<td>Rivaroxaban</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>2.5 mg</td>
<td>Pakistan</td>
<td>ACS Left ventricular thrombus</td>
<td>320</td>
<td>12 weeks</td>
<td>Presence or absence of LV thrombus on transthoracic echocardiographic study</td>
<td>Occurrence stroke, myocardial infarction, cardiovascular death, coronary revascularization procedures (PCI, CABG), peripheral revascularization procedures, carotid revascularization procedures, minor bleeding complications (according to ISTH)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>90 mg</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Occurrence of stroke (at 1, 6, 12 months)</td>
</tr>
<tr>
<td>NCT 049,70576</td>
<td>IV</td>
<td>Warfarin</td>
<td>Pakistan</td>
<td>ACS Left ventricular thrombus</td>
<td>1000</td>
<td>12 months</td>
<td>Major Adverse Cardiovascular Events Clinically driven coronary, peripheral or carotid revascularization Stent thrombosis</td>
<td>Occurrence of stent thrombosis (at 1, 6, 12 months)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>CAD</td>
<td></td>
<td></td>
<td></td>
<td>Occurrence of stent thrombosis (at 1, 6, 12 months)</td>
</tr>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>PAD</td>
<td></td>
<td></td>
<td></td>
<td>Occurrence of myocardial infarction (at 1, 6, 12 months)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Occurrence of death from any cause (at 1, 6, 12 months)</td>
</tr>
</tbody>
</table>

ACS, acute coronary syndrome; CAD, coronary artery disease; CCS, chronic coronary syndrome; PAD, peripheral arterial disease
reducing the absolute risk of severe bleeding and improving NCB. This evidence suggests that there is a significant impact of rivaroxaban in high-risk patients who usually remain untreated owing to the high bleeding risk. 30

Use of Antiplaetate in Combination with Anticoagulation Agents among Diabetes Population with Cardiovascular Disease: COMPASS Trial

Diabetes mellitus is a common risk factor associated in patients with atherosclerotic disease. 31,32 Despite advances in the treatment of atherosclerotic disease, diabetes mellitus is considered as the main cause of the development of a prothrombotic state and residual CV risk. 33 Antiplaetate therapy, especially DAPT, has been reported without diabetes mellitus. 37 Furthermore, provided larger benefits in such population atherosclerosis and diabetes mellitus who should be warranted in patients with addition of low-dose rivaroxaban to aspirin. 34–36

More recently, findings from the subgroup analysis of the COMPASS trial showed similar effects of the combination of aspirin plus rivaroxaban 2.5 mg twice daily on coronary, cerebrovascular, and peripheral outcomes in patients irrespective of their diabetes status. 37 In the overall population, the baseline risk of diabetes mellitus was higher, and this combination therapy provided larger benefits in such population in terms of higher (3-fold) reduction in all-cause mortality compared to patients without diabetes mellitus. 37 Furthermore, the addition of low-dose rivaroxaban to aspirin in patients with stable atherosclerosis and diabetes mellitus was associated with significantly higher reductions in ischemic events compared to those without diabetes mellitus. Though there was a significant increase in nonfatal major bleeding with rivaroxaban and aspirin, the risk was similar in both patient groups. 37

Overall, the results indicate that the addition of low-dose rivaroxaban to aspirin should be warranted in patients with atherosclerosis and diabetes mellitus who are at an acceptable risk of bleeding.

Ongoing Clinical Trials

Several other ongoing trials are being conducted across the world to assess the efficacy and safety of rivaroxaban in combination with other antiplatelet therapy in patients with CCS (Table 2). 38

Conclusion

Clinical trial data on this new drug was certainly very encouraging, with evidence from the COMPASS trial and pre-specified subgroups of the COMPASS trials suggesting that the addition of rivaroxaban to aspirin was associated with a significantly lower risk of ischemic events, mortality, and tolerable bleeding profile in patients with CCS and high-risk factors. This combination is cost-effective and generally well tolerated in patients with CAD and/or PAD as well as patients with CCS and multimorbidity or high-risk populations. Therefore, on the basis of comorbidities and other risk factors, patients should be individually evaluated for polypharmacy approach and cost while considering the addition of rivaroxaban to the ongoing therapy.

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22. XARELTO (rivaroxaban) tablets, for oral use Initial U.S. Approval: 2011 Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/204395s025lbl.pdf Accessed on 1 December 2021


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Differential Physiological Sodium Iodide Symporter Expression in Lactating Breasts

Sudha Ramesh¹, Sandip Basu²*

A young female, mother of a 16-month-old baby and diagnosed case of differentiated classical papillary carcinoma of thyroid with metastasis to the regional lymph nodes, underwent total thyroidectomy with left modified neck dissection and central compartment clearance. The patient had a history of lactation and was advised to stop breastfeeding days before the planned preablation radioiodine ¹³¹I scintigraphy. The scan demonstrated iodine avid focus in the neck (marked). Another area of diffuse uptake was observed in the right chest region in addition to the left upper abdomen (corresponding to stomach uptake). This uptake in the right chest region had no obvious pathological explanation and corresponded to uptake in the right breast (Fig. 1).

Fig. 1: Radioiodine diagnostic scintigraphy illustrating tracer accumulation in the right breast only (arrow marked) with no corresponding uptake observed in the left breast in this lactating woman, who had stopped breastfeeding days before the study.

In view of the unusual unilateral breast uptake, the patient was enquired about her breastfeeding practice: she gave a history of unilateral breastfeeding from the right breast only to which the findings of the ¹³¹I scintigraphy corroborated.

Sodium iodide symporter (NIS) is an intrinsic membrane protein implicated in iodide uptake in the thyroid follicular cells. Physiological NIS expression in other cells/tissues include salivary gland ductal cells, breast tissue during lactation, epithelial and parietal stomach cells, intestinal enterocytes, placenta, and testicular cells. While the radioiodine uptake in the lactating mammary glands are typically observed bilaterally, the present case demonstrates an interesting phenomenon of differential physiological NIS overexpression unilaterally in a lactating woman related to her breastfeeding practice (from the same-sided breast).
Skeletal Features of Osteogenesis Imperfecta

Rudrajit Paul\textsuperscript{1,*}, Prasanta Kumar Mondal\textsuperscript{2}, Biplab K Gayen\textsuperscript{3}, Bikash C Seth\textsuperscript{4}, Rathindranath Sarkar\textsuperscript{5}

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Osteogenesis imperfecta (OI) is a genetic disorder associated mainly with brittle bones.\textsuperscript{1} This is the most common connective tissue disorder which affects the bone.\textsuperscript{2} There may also be other extraskeletal features like cardiac valvular disease, blue sclera, hearing loss, or hypercalciuria.\textsuperscript{3} The classification of OI has evolved over the years and presently, with newer data from medical genetics, OI is classified into at least 15 types.\textsuperscript{3} Type I is the most common variety and type III is the most severe variety which is compatible with survival.\textsuperscript{3} However, the mode of inheritance, clinical features, and prognosis vary widely among the different types.

A 38-year-old male was admitted to our hospital with generalized body ache. He was diagnosed with OI type III in another hospital. On examination, the patient was found to have triangular face, dentinogenesis imperfecta (discolored and eroded teeth with opalescent hue), pectus carinatum, saber tibia, and severe kyphoscoliosis (Fig. 1). X-ray of the chest revealed bent and deformed ribs with generalized cortical bone thinning (Fig. 2). X-ray of the skull revealed multiple wormian bones (Fig. 3). X-ray of the foot revealed thinning of metatarsals (Fig. 4). Computed tomography (CT) scan of the brain revealed typical features of basilar impression (Fig. 5). Lateral X-ray of the vertebrae revealed severe osteopenia with collapse in multiple sites (Fig. 6). There was no blue sclera and hearing was normal. The patient had no family history of similar disorder. He was born out of nonconsanguineous marriage. Unfortunately, due to poverty, he had not received medical supervision or any specific therapy like bisphosphonate from childhood. He had had multiple histories of fractures of long bones but each time, he had received only emergency care. At the time of presentation, he was bedbound and completely dependent on others for activities of daily living. He was referred to rehabilitation care.

Osteogenesis imperfecta is associated with multiple skeletal changes. Mutations in the alpha chain of collagen molecule make the bones excessively fragile.\textsuperscript{3} Also, prolonged immobilization and muscle wasting cause secondary bone loss.\textsuperscript{3} Osteopenia in X-ray is the universal finding, as in our case. Such bones are liable to fracture and bend easily. That is the reason for the markedly bent ribs seen in our patient and also the saber-like shape of tibia.

Basilar impression (BI) is a serious craniovertebral malformation seen in some cases of OI. There is upward displacement of basilar and clivus portion of occipital bone, causing infolding of foramen magnum and translocation of the upper cervical...
vertebrae in the brainstem region. This can remain asymptomatic, as in our case, or may give rise to serious neurological consequences. Thus, screening for BI in OI patients is needed, even if asymptomatic. Axial and/or sagittal CT scan or magnetic resonance imaging scan of the craniocervical region can diagnose the condition.

We present this case to sensitize clinicians to the various skeletal features of OI. These features may have serious consequences. Hence, early screening may be warranted.

**References**

Pretilachlor Poisoning: A Rare Case of Herbicide Poisoning with Neurotoxicity

Shaik Khasim1*, Sri Karan Uddeshula Tanugula2, Kasturi Ravinder Reddy3

Received: 8 May 2022; Accepted: 20 May 2022

CASE REPORT

Pretilachlor poisoning in humans is an understudied area. It is widely used as a herbicide in India; hence it is of paramount importance that we understand the various clinical presentations from its toxicity. Acute oral intoxication of pretilachlor can present with neurological and gastrointestinal manifestations. This case report adds to the scant evidence on how to recognize and manage pretilachlor toxicity.

Abstract
Pretilachlor poisoning in humans is an understudied area. It is widely used as a herbicide in India; hence it is of paramount importance that we understand the various clinical presentations from its toxicity. Acute oral intoxication of pretilachlor can present with neurological and gastrointestinal manifestations. This case report adds to the scant evidence on how to recognize and manage pretilachlor toxicity.

Introduction
Pretilachlor is a synthetic chloroacetanilide herbicide. Pretilachlor is a broad-spectrum systemic herbicide with the chemical name 2-chloro-2'-6'-diethyl-N-(2-prop-oxetyl) acetanilide. The mechanism of action of this group of herbicides is still not clearly understood but is known to act by inhibiting the biosynthesis of fatty acids, lipids, proteins, and flavonoids.

We report a case of a 58-year-old male who presented with neurological and gastrointestinal manifestations following oral ingestion of pretilachlor.

Case Description
A 58-year-old Indian male presented to the emergency department of Prathima Institute of Medical Sciences, Karimnagar with an alleged history of oral ingestion of 150 mL of undiluted pretilachlor (the said chemicals empty bottle was brought along by the attenders) following which the patient developed burning sensation in throat and two episodes of vomitings. The patient was initially taken to a local hospital within 1 hour, where gastric lavage was done with normal saline, and then shifted to our hospital for further management. On admission the patient was conscious and his initial vital parameters were as follows: blood pressure was 130/90 mm Hg, pulse rate was 105 beats per minute, respiratory rate was 29 breaths per minute, SpO2 90% on room air, capillary blood glucose level 210mg/dL, and had plenty of oral secretions. He was given benzodiazepines and anti-seizure medication (levetiracetam). On neurological examination, plantar reflex was extensor bilaterally, deep tendon reflexes were absent, adequate bilateral pupillary response was noted, and Glasgow Coma Scale (GCS) score was 5/15 (eye: 1, verbal: 2, and motor: 2). In view of poor GCS the patient was intubated, trachea was secured, and connected to mechanical ventilator. He was immediately started on intravenous (IV) fluids, antiemetics, IV benzodiazepines, and anti-seizure medication. The patient developed hypotension for which fluid challenge with normal saline was given, despite the fluid challenge the blood pressure did not improve; hence the patient was started on inotropic support.

Magnetic resonance imaging of the brain was normal. Serum sodium, potassium, and chlorides were within normal limits. Serum magnesium, serum phosphorous, and serum calcium were done and they were normal. Complete blood picture (CBP) showed neutrophilia. Liver function test (LFT) revealed hypoalbuminemia (2.5 gm/dL). Creatinine and blood urea nitrogen were normal. Chest X-ray was normal. Electroencephalogram findings revealed diffuse cerebral dysfunction with generalized seizure activity.

Over the next 2 days of hospitalization, supportive therapy was given as stated above, along with the addition of IV human albumin, regular chest physiotherapy, and endotracheal tube care. Daily monitoring of CBP, LFT, and creatinine was done. Over the next 48 hours, the patient’s clinical status improved. He was weaned off from mechanical ventilation and inotropic support was tapered and stopped. Over the next 2 days of hospitalization, his clinical parameters improved significantly. He was discharged from the hospital on the 7th day after behavioral counseling. After a week the patient came for follow-up visit and he was doing well.

Discussion
Pretilachlor is a synthetic chloroacetanilide. Chronic exposure to chloroacetanilide in vitro and in vivo studies has shown that it has a role in causing neurotoxicity, genotoxicity, and carcinogenicity. The literature has minimal data on how to treat chloroacetanilide poisoning. The cause of the central nervous system (CNS) manifestations might be the direct effect of pretilachlor or the solvents added in the herbicides. Central nervous system manifestations portend a grave prognosis, hence clinicians must be aware of the protean manifestations of its toxicity; this awareness would lead to earlier diagnosis and better-targeted treatment.

One study by Lo et al. in 113 patients with oral exposure to chloroacetanilides suggested that around 25% of the patients were asymptomatic, the rest had gastrointestinal manifestations like vomiting, gastritis, and CNS manifestations like seizures, coma, and stupor were reported along with three

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Pretilachlor Poisoning

In conclusion, pretilachlor poisoning causes neurotoxic symptoms which range from giddiness, seizures to coma. Education and awareness among the treating physician regarding the neurotoxicity of pretilachlor is an important aspect that needs to be noted from this case report. Initial stabilization, close monitoring, and supportive treatment are the mainstay of management for pretilachlor poisoning.

REFERENCES
Simultaneous Occurrence of Chicken Pox and Herpes Zoster with Facial Nerve Palsy in Immunocompetent Patient

Lalit Mohan Bhardwaj1*, Swapnav Borthakur2, Prabhas Chandra Bhattacharyya3

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ABSTRACT
Patients who earlier suffered from chicken pox may develop herpes zoster (HZ) due to reactivation in dorsal root ganglia. The occurrence of both clinical conditions at the same time is sporadic. Unusual presentation and a belligerent course are seen in immunocompromised hosts. The presence of both HZ and chicken pox in immunocompetent patients is infrequent and incoherent with the present understanding of pathogenesis. Here, we present a case of HZ involving the maxillary division of the right trigeminal nerve with simultaneous occurrence of varicella-zoster and right peripheral facial nerve palsy.

INTRODUCTION
Herpes zoster occurs due to reactivation of latent varicella-zoster virus (VZV) in dorsal sensory nerve root ganglion postprimary varicella infection (chicken pox). Association between HZ and varicella has been long established by Bokay, Ferryman, Campbell, Almeyda, Ward, Roxburgh, and Martin.1,2 They also described the simultaneous occurrence of both clinical entities in their case series within 5 days of zoster eruption. Many such reports are described in immunocompromised individuals like HIV, diabetics, corticosteroid use, cancer patients, syphilis, heavy metal poisoning, irradiation, and elderly population.3 Atypical presentation like toothache and complications like pulp necrosis and periodontitis is not uncommon in maxillary HZ. Unnecessary dental interventions should be avoided before a proper diagnosis is established. Subtle facial nerve palsy is frequently associated with HZ oticus due to anatomical predisposition. In our case, severe facial nerve dysfunction is seen with maxillary division of trigeminal HZ, which is very uncommon. Hematogenous dissemination theory has also been postulated for dissemination in an immunocompromised host. Still, the development of lesions typical of chicken pox along with HZ in the immunocompetent host is poorly understood (Figs 1 and 2).

CASE DESCRIPTION
A 48-year-old male patient with no history of hypertension or diabetes developed right upper molar toothache and fever. Initially, he consulted a dentist locally and was prescribed antibiotics and analgesics. But he developed rashes over his face and palate. On the 5th day of rash, he presented to us with high-grade fever, orofacial pain of burning character, papulovesicular rash distributed along with the maxillary division of trigeminal nerve, and vesicular lesions typical of chicken pox all over the body (Fig. 3). There was no eruption over the tympanic membrane, ear canal, pinna, tragus, and no earache. He also had conjunctival redness and increased lacrimation. He had no history of varicella illness. In due course, he also developed facial nerve palsy of lower motor neuron (LMN) type on the right side (Fig. 4). Other cranial nerves examinations were normal.

On clinical examination, temperature 102.6°F, pulse 90 bpm, blood pressure 120/88 mm Hg, general and systemic examinations were within normal limits.

Investigation
Random blood sugar (RBS) 116 mg/dL, hemoglobin 12.3 gm%, total count 6000/ cumm (P-63, L-25, M-10, E-02), erythrocyte sedimentation rate 15, hepatitis B and C screening test was negative, HIV-1/2 was nonreactive, liver function test was within normal limits, and swab for culture from facial lesions Staphylococcus aureus. Chest X-ray was normal, and Tzanck smear from vesicles was positive. Varicella-zoster IgM antibody was negative and IgG was positive, sent on the 10th day of fever.

Diagnosis and Treatment
The diagnosis was made based on the history of presenting illness, clinical picture, and laboratory investigations as the simultaneous occurrence of HZ of the maxillary division of trigeminal nerve and VZ with superadded secondary infection of S. aureus and peripheral type facial nerve palsy. He was managed over oral valacyclovir, gabapentin, IV ceftriaxone, and ayclovir ointment for skin lesions. He improved adequately and was then discharged. On follow-up after 2 weeks, his skin lesions healed by crusting, but painful sensation and paresthesia over right maxillary nerve distribution persisted, and facial palsy became obvious (Fig. 4). On subsequent follow-up after 3 months, facial palsy improved exclusively.

DISCUSSION
Herpes viruses like VZV and herpes simplex viruses (HSV) have the capacity for latency and later evade the host immune system and reactivate. The primary infection of VZV is chicken pox, and post-reactivation is called shingles (HZ). Immunosuppression and advanced age are risk factors for reactivation. Immune evasion of VZV is due to declining T cell-mediated immunity in the elderly population. Factors responsible for reactivation in immunocompetent hosts are largely unknown. Currently, vaccines are available, but the role in a non-elderly immunocompetent patient is debatable and not yet recommended. As healthcare facilities are improving and many patients are presenting in the pre-eruptive stage where a complete clinical picture is not yet appeared, diagnosis is often missed and may lead to unnecessary interventions; another issue is the poor response of medicine after 72 hours of development of rash; furthermore, postherpetic neuralgia also leads to comorbidity and poor quality of life in undiagnosed cases where treatment is delayed. All these factors emphasize rapid diagnosis and awareness of unusual presentations. Our patient presented with odontalgia to the dentist and later developed HZ and varicella. One should keep HZ as a differential diagnosis in patients with orofacial pain. Often herpes

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Simultaneous Occurrence of Chicken Pox and Herpes Zoster

Conclusions

In conclusion, a case of HZ affecting the maxillary division of the trigeminal nerve is reported along with peripheral facial nerve palsy and simultaneous occurrence of chicken pox in an immunocompetent patient. This case highlights the importance of a thorough history and examination in patients with toothache and indicates the necessity for a further inquest into pathogenesis. Herpes zoster should be considered as a differential diagnosis in patients presenting with a toothache. Additionally, physicians should be aware of the unusual presentation of VZV. Physicians are encouraged to identify the early symptoms of HZ and to administer antiviral therapy timely to prevent complications.

References

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Ludwig Albrecht Kossel (1853–1927) was born in Rostock, Germany in 1853. He passed the state medical examination in 1877, and earned his doctorate in 1878. He took an assistantship in Hoppe-Seyler’s Institute of Physical Chemistry in Strasburg and in 1881 qualified as Lecturer of Physiological Chemistry and Hygiene.

Kossel began to investigate a substance called “nuclein” in cell nucleus in 1879. It had remained a poorly defined substance which he showed to consist of a protein portion which he found as much like other protein. And a nonprotein substance—nucleic acid that was quite unlike any other substance known until that time. He used hydrolysis and other techniques to chemically analyze the nucleic acids and discovered that breakdown products were purines and pyrimidines nitrogen-containing compounds with atoms arranged in two rings and one ring, respectively. From 1885 to 1901, Kossel isolated two different purines adenine and guanine, and a total of three different pyrimidines thiamine, cytosine, and uracil. Kossel then went on to study protein in the spermatozoa cells, and isolated the amino acid histidine (1896). He did not realize that crucial components in spermatozoa (and in all cells) were the nucleic acids rather than the proteins. Kossel did recognize existence of carbohydrates among the breakdown product but the identification was done by his student Phoebus Levene (1869–1940) who showed a hitherto unknown five-carbon sugar ribose was to be found in one group and deoxyribose in other groups long before it was confirmed that DNA was the bearer of organism’s genetic material.

Kossel’s work even without him having realized the full importance of nucleic acids was impressive and he was appointed Professor of Physiology at Marburg and Director of the Institute of Physiology there in 1895. Here he worked until the spring of 1901. He was then called to the Chair in Heidelberg and presided as Chairman over the 17th International Congress of Physiology in Heidelberg (1907).

Albrecht Kossel received Nobel Prize in 1910 “in recognition of the contributions to our knowledge of cell chemistry made through his work on proteins, including the nucleic substances.” He died in 1927, after recurring attacks of angina pectoris.

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Sudden Quadriplegia in a Young Female

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Young Female

Spinal arteriovenous malformations (AVMs) are very rare causes of spinal space-occupying lesions. They can remain silent for a long time but they can also cause catastrophic consequences once symptoms begin. Improvements in interventional radiology and neurosurgery have led to better outcomes in the treatment of spinal AVMs, provided they are detected in time. We here report a catastrophic presentation of spinal AVM.

A 13-year-old female patient presented with sudden onset weakness of all four limbs. The patient was watching television on the couch when she had tingling sensation in her legs, followed by hands and this was rapidly followed by weakness of all four limbs over the next half hour. The patient was admitted to a nearby hospital where she was found to have complete flaccid quadriplegia with urinary retention. However, on the second day, she developed respiratory distress when she was transferred to our department. At presentation in our critical care unit, the patient was having tachypnea with power 0/5 in all four limbs. She was quickly scheduled for cervical spine magnetic resonance imaging (MRI) with contrast. On the second day, her dyspnea increased with single breath count of six and falling oxygen saturation. She was quickly intubated and put on mechanical ventilation. Meanwhile, the MRI reports were available, which showed (Fig. 1) AVM of the cervical spine and cervicomedullary junction with acute intraspinal bleed. Thus, the present case is notable for two atypical features: very young age of presentation and location in the cervical region. A case similar to ours was reported in 2013 from the UK where a young patient with cervical spine AVM (C1/C2) presented with paresthesia of left arm, followed rapidly by quadriparesis and respiratory failure. In our case, the AVM was present from foramen magnum up to C4. Spinal AVMs can present with sudden intra/extradural bleeding, as in our case, or the dilated vessels may cause chronic compression and myelomalacia.

Treatment options for such AVMs include microsurgery, embolization, or both. But in some cases, the location of the AVMs may preclude surgery. Now, newer technologies like Cyberknife are being used for such cases.

We present this case to sensitize clinicians to this rare cause of quadriplegia in the young. Such cases need urgent management by a multidisciplinary team.

References


Abstract

The changing scenario between society’s lookout toward the medical profession has taken a bad turn. The stress of education, practice starting, increasing to a peak of one’s performance in the early years and later on to maintain it after the age of 50 is a great challenge. Recent tragic events have brought up the role of social elements, media, press, politicians, police, and prosecutors under the lens. We as professionals and organizations must find out the weakest link which enforces someone to indulge in self-harm. We also should try to strengthen the chain of healthcare delivery system with the motto of “A healthy physician only can impart quality healthcare. His image, interests, and intentions must be protected by our own profession, society, policymakers—government agencies.”

Doctor–patient relationship has always been the foundation of healthcare system. Since the times of Hippocrates, relationship of doctor–patient has been extensively debated, receiving attention pertaining to its sociological, literary, and philosophical aspects. At present, doctor–patient–society relationship

Fig. 1: MRI with contrast of the cervical spine showing dural AVM (1) extending up to C4 level from foramen magnum, with intraspinal bleed (2) at C2–C4 level
is undergoing a progressively dangerous phase of distrust leading to increased violence against doctors. Especially after the spread of coronavirus disease pandemic in December 2019 (COVID-19), giving an altogether new dimension to it. The tragic suicide of Dr Archana Sharma has brought doctor–patient relationship into focus, whether positive? Or negative? Who is to decide? Over the last 2 decades, the trust which was gained over centuries and cultivated the relationship of doctors and their patients has started eroding and has been demonized during COVID-19 pandemic outbreak.

Magnitude of the Problem
Incidence of suicides in healthcare workers (HCWs) is a very serious issue as well as a big loss to family, community, and country. A 2022 report from Medscape states that around 1 in 10 physicians said they had thought about or attempted suicide. Recent studies have shown that the rate of suicidal thoughts among physicians is higher than in the general population (7.2 vs 4%).

Reality in India
Chhal et al. have reported 358 suicide deaths among medical students and residents in India between 2010 and 2020 whereas Kishor et al. reported grim reality of suicides in Indian HCWs.2,3 Das et al. report the prime cause of increasing suicides over the decade in our county as job-related stress and lack of proper infrastructure.4 How well the medical students and HCW can tackle it? The most recent incident from Rajasthan has shaken the whole community. It is not only Dr Archana Sharma, but it can be you or me, especially those doctors who are working in a small place and solo practices. The doctors working in small to midsize places, taluka or small business hubs, or districts are the backbone of primary and secondary healthcare. They are doing an exemplary work in grossly compromised present public healthcare system. They are in fact most vulnerable to stress and strains of medical practices, mostly facing various types of mild to extreme violence against doctors in small places.

Why do They Come to a Small Place?
Majority of them are middle or lower middle-class doctor couples in many combinations, with scarce financial resources or family support. The general ideology being that initial investment in starting small clinics is low, while hoping to gradually expand to multispecialty hospitals.

The Real Picture
*De facto* they do great public service especially to the unaffording category of society near to their home where there is a clear deficiency of public healthcare facilities.

Yet instead of support from government bodies, they have to face several legal hassles. Such as taking permission from different government bodies including municipality and local self-government, facing less qualified inspectors, expecting free consultations, medicines, gift—cash or kind, etc. It is very difficult to please or satisfy everyone in a small place especially the political or religious leaders, yellow journalists, and local goons with very high quotient of dissatisfaction and arrogance.

Few people gain proximity to doctors who become their pseudo advisors, pseudo advertisers, and pseudo protectors. They also incite unethical greedy professional competition creating a fertile ground for violence. Rather the honest and ethical doctor wants to stay away from such situations. In small towns or villages, the police, press, politicians, or religious leaders control the administration with the mindset of seeking an opportunity to flare up sentiments of one party against another. In any type of dispute and more dangerously in case of mishappening in a hospital and catching up to any opportunity as a broker-middlemen, agent to offer deal or blackmail one of the parties under the hypnotizing influence of cash or kind. Similar incident has allegedly happened in this index case. Where rather pacified relatives went home after death of a patient, but small-time politicians and yellow journalists incited the people resulting in demonstration in front of the hospital. Even after explaining the law to police by the doctors, police registered an FIR under section 302, against any logic or law point. Such blatant misuse of power resulted in scaring negative emotional impact on innocent and honest doctor to such an extent that she committed suicide than to face the shame as a murderer.

The Social Decline
Doctors are a part of society and the society too has social responsibility toward this noble profession. Unfortunately, there is a progressive loss of faith between doctors and patients which can be attributed to several factors. Especially to progressive degradation of social, moral, ethical, and cultural values in society under the hypnotizing influence of greed, consumerism, and excessive commercialization, where money has become GOD.

This ultimately is leading to collapse of healthcare system primarily affecting the doctors practicing solo or in small single doctors’ hospitals. Many rural physicians have experiences of similar kind. Over years of work in a sub-taluka industrial place on a highway and district not away from a metro city, one of the authors has similar experiences. Even in 2022, 4 out of 14 talukas in his district of Maharashtra do not have a resident practicing physician due to poor infrastructure, lack of support from local bodies and government authorities, pay divide, corruption, ransoms, and extortions in the name of social contributions. The society considers that doctors are the softest target.

Such a situation will lead to defensive practice where no doctor will be ready to take risk and lead to increased cost, investigations, and unnecessary referrals.

These doctors are lonely warriors, their problems and fate are different than those who are working in protected, corporate, and commercialized healthcare institutions. The society and fraternity may not be actually knowing the problems faced by grassroots doctors working in rather constrained facilities. Organizations can play a big role in advocacy and generating public opinion resulting in tougher laws for violence against doctors.

The Mental and Emotional Decline
Finally, who are they, susceptible, gullible for such an extreme action on their own life? Violence against healthcare professionals definitely affects the psyche of doctors. Resulting in depression, generalized anxiety, sleep disturbances, post-traumatic stress disorder, and extreme or irrational fear of entering open or crowded places. Such are the circumstances of fear and/or anxiety leading to work absenteeism and adversely affecting the family atmosphere.

These doctors are really intelligent, high-strung, and hard working, that are constantly affected emotionally by nonresponding patients. They are easily subjected to addictions like tobacco, alcohol, and sometimes recreational drugs to come out of this situation or temporary relief. We need to identify those who are “on the edge” and likely to be derailed emotionally. As a great friend of such persons, we as colleagues must try to identify people on the edge to raise their morale, and help them to come out of this negativity. This kind of friendship must be purely nonacademic, noneconomic, and noncompetitive. The good buddy role can be reversed in case if someone is a victim in other times. Yoga, pranayama, and self-actualization help you to be more balanced.

Role Models, Perfectionists, and Protectors
Previously, most of the medical intellectuals and teachers were very vocal about malpractices. They acted as role models so teaching ethics was not on agenda. But
now professionals with strong academic credentials are generally neither participating in pointing out deficiencies of medical profession nor suggesting measures to improve the situation. Most of the people feel that medical fraternity is currently facing the worst crisis. Due to absence of role models and inaction of medical intellectuals for letting the evil doctors thrive. We as peers must act quite quickly and positively!

The Young Victims
Other groups of the likely hood population are the newly joined residents from a small place to a high workload institution, often bullied, ragged by so-called 1–2 years senior resident big brothers, in many institutions the anti-ragging committees are just for NMC or UGC inspection sake only. And the juniors are threatened to write one prescription 50 times or get hardly 2–3 hours of sleep and suffer.

Community Spirit, Media, and Mob Mentality
Social intolerance and degradation are leading to dangerous influence. The greed, economic aspirations, stress, frustration, competitive society, and distorted moral, social, and cultural values are very important reasons for increasing intolerance in society ready to get violent even on mild or false provocation.

For few community opinion makers greed to make easy money or blackmail the healthcare professional, impart economic distress. For patients’ relatives added shock of huge medical bills often precipitates violence against healthcare professionals. Unfortunately, we Indians have no tradition to keep family health budget, precipitating economic stress in case of illness.5

Poor media projection and publication of all negative stories about doctors are adding fuel to fire. Important facts leading to general impression of branding healthcare professionals are the dangerous “villains, lutere, and extortionists” exploiting patient’s miseries for financial gains. Media seldom projects any good ethical doctor working for the benefit of the society. This can help improve the image of majority of doctors as ethical, empathic, and patient-friendly professionals.

Conclusion
The evidently impulsive, self-harming, very disturbing episode of the suicide of Dr Archana places the onus of prevention on two fronts, the intolerant society and its vicious manipulators AND the succumbing “on the edge,” the derailing Medical Doctors.

On the societal front, NO amount of “legal framing,” “protection acts,” and emergency task forces are going to bring down the rage and indecent and violent behavior, when unexpected loss of life episode happens. Only creating an understanding of the problem by very serious patient information and education systems will help.

Problem is who will do it?
Every specialty has serious unexpected complications occurring like PPH in obstetrics, major vessel and organ injuries in surgical cases, and unexpected SCD in stable medical cases.

All specialty associations like API, CSI, ASI, and FOGSI have to come out with very lucid and simple write-up in English, Hindi, and local state vernacular about the unexpected complications resulting in loss of life.

This print and audio-visual information should be made available to each member of the association. Formation of patient education, medicolegal support, and “emergency situation control” support cells by each association is essential, rather than mindless spending in huge conferences and academic unrealistic symposia.

Now, the second front—the healing touch, for the healers. How can it be done?
The touch actually has to start at the admission process of medical colleges.

Every batch has at least two to three casualties in the learning years under or postgraduate years. Entry-level counseling and having a constant monitoring of susceptible recognized students is the prevention.

At internship there should be a 1-month gearing up, psychosocial training, and knowledge sharing about regulations, different “acts,” and economic and infrastructure requirements for professional practice in clinic or hospital.

Finally, a change in the mindset of our colleagues, about stress and its obvious and unobvious reasons and acceptance of presence of mental ailments camouflaged by natural intelligence of the healer (doctor heal thyself) would be paramount in prevention of self-harm and bring courage to face mob or court or prison and fight for justice.

We need to have a system which ensures enforcement of law to award strong punishments to people responsible for violence against healthcare professionals. These measures will certainly help to curb the increasing tendency of younger population to shun medical profession. Such an effort and change seems to be an impossible task, but we need to shun the inertia and must make whatever efforts we can make before it is too late and beyond repair.

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References

Cerebral Mucormycosis in Context with COVID-19 Infection
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hino-orbital-cerebral mucormycosis (ROCM) is an uncommon infection caused by the angiotropic fungus belonging to the order Mucorales, which almost always occurs in immunocompromised hosts (uncontrolled diabetes mellitus, hematologic cancers, and solid organ or hematopoietic stem cell transplants). The suspicion or diagnosis of ROCM triggers a medical as well as surgical emergency, as delay in treatment increases morbidity and mortality.1 In India, after the second peak of COVID-19 infection, there was a surge in cases of mucormycosis implicating complex interplay of various factors such as an ideal environment of low oxygen, high glucose, acidic medium, high iron levels, and decreased phagocytic activity of white blood cells due to immunosuppression coupled with several other shared risk factors including prolonged hospitalization with or without mechanical ventilators.2 Here we present a clinical profile and outcome of ROCM at our institute.

After getting permission from the IECHR- PG research, an observational prospective study of 14 patients was carried out at a single-center tertiary care hospital over a period of 3 months. The significant findings of our study are:

- During the time of admission, 12 patients (85.71%) had SpO2 ≥90 and only two
patients had SpO₂ <90. The patients with high oxygen requirements had died (4–28.57%); whereas out of eight patients on room air, seven were discharged and only one died (p-value = 0.008). This finding suggests that patients with high oxygen requirements have higher mortality (Table 1).

- On radiological evaluation, computed tomography of the paranasal sinus (PNS) and magnetic resonance imaging of brain + orbit + PNS of six expired patients showed involvement of ≥3 sinuses (n = 5), cavernous sinus (n = 4) with proptosis (n = 2), and intraorbital extension. Whereas involvement of ≥3 sinuses (n = 5), frontal lobe (n = 5), optic nerve with intraorbital extension and other central nervous system (n = 8) without cavernous sinus involvement were seen in eight discharged patients. This suggests that patients in whom infection has extended to cavernous sinus had higher mortality.

- Six (75%) out of eight discharged patients had undergone sinuscopy and debridement, whereas three (50%) out of six expired patients had surgical intervention mentioned above. This result suggests that early surgical intervention could reduce mortality in ROCM however larger studies are required to throw further light.

Table 1: Association of COVID-19 infection with outcome in patients with ROCM

<table>
<thead>
<tr>
<th>History of COVID-19 infection</th>
<th>Discharged</th>
<th>Death</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Past COVID-19</td>
<td>7 (53.85%)</td>
<td>2 (15.39%)</td>
<td>9 (69.23%)</td>
</tr>
<tr>
<td>Recent COVID-19</td>
<td>–</td>
<td>4 (30.77%)</td>
<td>4 (30.77%)</td>
</tr>
<tr>
<td>Total</td>
<td>7 (53.85%)</td>
<td>6 (46.15%)</td>
<td>13</td>
</tr>
</tbody>
</table>

Past COVID-19—those patients who were COVID positive within past 6 months but not at the time of admission; Recent COVID-19—those patients who are COVID positive at the time of admission.

Other data collected during the study suggest that all 14 patients were diabetic (seven known cases and seven freshly diagnosed), with higher mortality among uncontrolled diabetics. Six patients received steroids (high dose methylprednisolone and low dose dexamethasone) as a part of COVID-19 treatment but no significant effect on mortality. The main presenting complaints were local symptoms such as orbital swelling, orbital pain, headache, and facial pain. Thirteen patients (92.86%) were COVID positive (recent and past) with 100% mortality in those having recent COVID infection, and only one patient had no past history of COVID (discharged). All 14 patients were not vaccinated for COVID-19 infection. Case fatality was 42.86% (six patients) and 57.14% (eight patients) were discharged.

On laboratory evaluation, almost all the patients had raised inflammatory markers (neutrophil-lymphocyte ratio, C-reactive protein, ferritin, and lactate dehydrogenase) with low serum albumin. All the patients had received lymphophylized amphotericin-B maximum for up to 28 days. The patients who developed nephrotoxicity and had estimated glomerular filtration rate <10 were given liposomal amphotericin-B. The major side effects on receiving amphotericin-B were hypokalemia (n = 13), nephrotoxicity (n = 9), hypocalcemia, and hypomagnesemia in decreasing order.

To conclude, in our study, we have observed that there was no significant difference in mortality among age group, gender, or severity of COVID-19 infection. Major presenting complaints were local symptoms involving orbit. Thirteen patients had history of COVID infection (recent and past). However, all the patients with recent COVID infection died (Table 1). Patients with higher oxygen requirements had higher mortality compared to those who were on room air. Cavernous sinus involvement in ROCM patients could be considered as a poor prognostic marker as observed in our study. However, this part of study should be explored further. We also observed that early surgical intervention and antifungal treatment are beneficial for patients in form of less morbidity and mortality among them. Major side effects of amphotericin-B were nephrotoxicity (64.29%) and dyselectrolytemia (50%).

Prevalence of Dyslipidemia in newly Onset Type II Diabetes Mellitus: A Cross-sectional Study

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diovascular disease (CVD) is the leading cause of death in diabetes mellitus (DM). Dyslipidemia is closely linked to CVD and is a modifiable risk factor for CVD.1 In DM, dyslipidemia is characterized by elevated triglyceride (TG), low high-density lipoprotein (HDL)—cholesterol, and elevated low-density lipoprotein (LDL)—cholesterol. The lipid changes associated with DM are attributed to increased free fatty acid flux secondary to insulin resistance. In DM, the increased CVD risk often persists for many years before the onset of biochemical hyperglycemia.2 During this period, obesity, hypertension, and dyslipidemia are usually present. After the development of DM even if we tightly control blood glucose (BG) one cannot effectively prevent CVD. So for holistic treatment of DM control of BG, blood pressure, and dyslipidemia is essential in management of DM. Prevalence of CVD in Asians is high and is increasing. Asians develop CVD at a younger age as compared to others. Besides this, Asians manifest CVD at a lower level of total cholesterol compared with other ethnic groups. In DM as compared to males, females have more risk of CVD and this is due to more burden and impact of cardiometabolic risk factors in females.3 Despite all these very little is known about the prevalence and pattern of dyslipidemia in newly onset DM from this (Eastern Uttar Pradesh) part of India. We conducted a cross-sectional study to know the prevalence and pattern of dyslipidemia in newly onset DM as it varies with ethnicity.

We enrolled 321 (male: 226 and female: 95) consecutive newly diagnosed diabetic patients attending our clinic between 2019 and 2021. Diabetes mellitus (fasting BG ≥126, postprandial BG ≥200 mg/dL, and A1C ≥6.5%) was diagnosed based on American Diabetes Association (ADA) criteria. Dyslipidemia was diagnosed based on ADA recommendation. Patients having serum TG ≥150 mg/dL, LDL-cholesterol ≥100 mg/dL, and HDL-cholesterol in males <40 mg/dL and in females <50 mg/dL were considered to have dyslipidemia. Patients with dyslipidemia were further subdivided into mixed dyslipidemia, combined dyslipidemia, and isolated single parameter dyslipidemia based on all three, any two, and any one parameter outside range, respectively.

Mean ± standard deviation (SD) of ages of male and female patients was 46.42 ± 11.33 and 46.89 ± 9.88 years, respectively. Mean ± SD of body mass index of male and female patients was 26.21 ± 3.87 and 26.92 ± 4.58 kg/m², respectively. Prevalence of central obesity in males and females was 83.19 and 94.75%, respectively (p < 0.005). Prevalence of dyslipidemia in males and females

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was 87.17 and 94.74%, respectively. Prevalence of dyslipidemia was significantly \((p < 0.044)\) more in females than males. Prevalence of raised LDL, raised TG, and low HDL in males and females was 54.42 and 67.37% \((p < 0.031)\), 61.06 and 54.74% \((p < 0.292)\), and 50 and 67.37% \((p < 0.004)\), respectively. Prevalence of raised LDL and low HDL were significantly more in females than males. In males, the prevalence of mixed dyslipidemia, combined dyslipidemia, and isolated single parameter dyslipidemia were 17.26, 43.81, and 26.11%, respectively. The most common type of dyslipidemia in males was combined dyslipidemia with raised TG and raised LDL. The second most common type of dyslipidemia in males was combined dyslipidemia with raised TG and low HDL. In females, prevalence of mixed dyslipidemia, combined dyslipidemia, and isolated single parameter dyslipidemia was 27.37, 40, and 27.37%, respectively. The most common type of dyslipidemia was mixed dyslipidemia and the second most common type of dyslipidemia was combined dyslipidemia with raised TG and low HDL and isolated raised LDL (Table 1).

It is clear from the study that prevalence of dyslipidemia is high in newly onset DM. Prevalence of dyslipidemia in females was more than in males and thus have more risk of CVD in future. More dyslipidemia in females in our study could be because of more prevalence of central obesity in females as compared to males. Since dyslipidemia often precedes the development of DM so early and aggressive management of dyslipidemia is urgently warranted in newly onset DM. Various data show that many diabetic patients with altered lipid levels are not on statin therapy and even those on statin therapy only 24.8% are on target. In our study majority of patients have either mixed or combined dyslipidemia so along with statin other lipid-lowering agents are needed to control dyslipidemia holistically. American Diabetes Association-European Association for the Study of Diabetes 2022 recommendations also endorse the individualization of lipid-lowering therapy. PCSK9 inhibitor, ezetimibe, and n-3 fatty acid are the other agents with proven cardiovascular benefits that can be given along with statin to control mixed and/or combined dyslipidemia.

### References


HIV coinfection and day-by-day increasing drug-resistant tuberculosis, the duration of active tuberculosis disease process is likely to increase with an additional expected increase in incidence of secondary renal amyloidosis in such patients.

A collective effort between clinicians, pathologists, and researchers can accelerate early diagnosis of renal amyloidosis by studies at protein and gene levels to address prediction models and treatment strategies in newer mode. This will not only enable early diagnosis of renal amyloidosis but also benefit those having end-stage renal disease with unknown etiology.

**References**


**Role of multiphasic Contrast-enhanced Computed Tomography in predicting WHO/ISUP histologic grading of Clear Cell Renal Cell Carcinoma**

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Dear Editor,

Renal cell carcinoma (RCC) is the most common (>90%) of adult renal neoplasms and is one of the most lethal urologic cancers with high mortality of rate of 140,000 per year. Clear cell variety comprises the major portion of RCC accounting for 70% of tumors, followed by papillar and chromophobe RCCs. A clear cell RCC needs to be labeled carefully as it carries a dampening 5-year survival rate of 44–69% and a higher risk of metastasis compared to papillary and chromophobe variety of RCCs.

Many large multicenter studies have shown tumor staging and grading are of utmost importance during tumor cancer diagnosis and treatment as it dictates the future course of action and the expected tumor behavior.

We studied the association between features on multiphasic contrast-enhanced computed tomography (CECT) and World Health Organization/International Society of Urologic Pathology (WHO/ISUP) histologic grading of clear cell RCC.

The WHO/ISUP grading system has four grades, with the degree of nuclear prominence assessed to determine grades I–III and the presence of highly atypical “pleomorphic” cells and/or sarcomatoid/rhabdoid morphology defining grade IV.

Differential enhancement of the tumor and renal cortex was calculated as the difference between attenuation in corticomedullary (CMP), nephrographic (NP), and excretory phases (EP) minus attenuation on unenhanced scan. The relative enhancement (RE) in abovementioned phases was calculated as the ratio of differential tumor and cortical attenuation.

There is a negative correlation between relative tumor enhancement in all phases with increasing tumor grades and the best association was shown in the NP phase with maximum area under the curve of 0.732 (p-value =< 0.001). As per receiver operating characteristic (ROC) calculations, the optimal cutoff points for RE ratios below which there is a high probability of grades III and IV tumors is 0.79 in CMP, 0.59 in NP, and 0.45 in EP phases. Again, the NP phase shows the best sensitivity of 77.1% and specificity of 73.1% for prediction of high-grade disease.

On subgroup analysis in NP phase with tumors more than 5 cm in size and having less than 50% necrosis the sensitivity and specificity to predict high-grade tumors was 95.5 and 80.0%, respectively. It was found that when individual RE ratios in CM, NP, and EP phases were less than the abovementioned cutoff points and existed together in a tumor the specificity increased to 80.7% with an odds ratio of 23.0 for prediction of grades III and IV neoplasms.

Lower grade tumors (grades I and II) showed homogenous enhancement when compared with higher grade (grades III and IV) neoplasms as high-grade tumors can have intratumoral necrosis, hemorrhage, or degeneration.

Since cystic tumors contain less malignant cells they are usually of lower grades when compared with solid tumors. Larger sizes translated to higher grade tumors. Tumor size emerges as an independent prognostic factor in solid tumors with a p-value of <0.001 which is in accord with previous study conducted by Yildiz et al.

As the tumor grade increased, there was a change in pattern of calcification from nil to subtle specks seen in lower grades to dense in high grades (p-value 0.006).

Tumor size had positive associations with tumor grade, volume of necrosis, and type of calcification.

Age, sex, and laterality were not meaningful parameters in predicting tumor grade.

In patients with anticipated short life expectancy due to other comorbidities presenting with renal mass, we suggest a size cutoff point of 5.4 cm which can be considered safe for active surveillance on the basis of ROC calculations.

In summary, RE values on multiphasic CECT when used together either in NP and EP or CMP phases have a specificity of 80.7% for predicting high WHO/ISUP histologic tumor grade. On subgroup analysis, there was further increase in sensitivity and specificity.

**References**

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¹. Pati S. et al. Prim Health Care Res Dev. 2020;21

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