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From the Desk of Editor-in-Chief

Esteemed members of API,

I am sure you must be surprised to find JAPI in a new get up. March 2018 issue of JAPI marks the beginning of my second tenure as Editor-in-Chief of JAPI. I am extremely grateful to one and all in API family for having reposed faith in me and putting me at the helm of JAPI for second time.

As you are aware JAPI is the medium of communication amongst all of in API. Over decades this platform has served as a binding agent and a feeling of belonging to API everytime you see a new issue on your desk each month.

When I took over as Editor-in-Chief of JAPI three years back in March 2015 with blessings and support of the likes of Dr. Siddharth N. shah, Dr. Y.P. Munjal and Dr. B.B. Thakur, I had some tasks and goals cut out for me. Firstly, I started online submission for authors and online referee work to make the task easy for everyone. Secondly, apart from free website access to articles which was already available, I made JAPI available to all the medical community in their hands on the go by launching JAPI app on android and i-phone platforms. As innovation I added some other features in the contents of the Journal. Many guidelines and recommendations for various diseases were published to assist you in day to day practise. Also, series on ‘Art of Writing’ and ‘Statistics in Medicine’ was published which was well received.

Two years back MCI made it mandatory for medical teachers to have publications as Research Papers while getting promotions. Due to this coupled with ease of online submission, the number of articles submitted in a year almost went up three times. I had made every effort to raise extra funds, a difficult task, to increase number of pages to cope with this to publish more Original Articles. However, due to this Case Reports had to be given a back seat which was commensurate with ongoing practise in international journals. I am trying my best to publish more number of Original Articles over last two years. I am also planning to publish soon a series on ‘Ethics in Research’ and ‘Preparing Research Protocol’.

All this was not possible without the rock solid support I received from my Editorial Board team; referees and authors. I will specially like to acknowledge support given by Drs. Sandhya A. Kamath, Shashank R. Joshi, Mangesh Tiwaskar, Amar R. Pazare and Agam Vora. Also, I will like to put on record the full hearted support received from all the Presidents of API over last three years, namely Drs. Rajesh Upadhyay, G.S. Wander and B.R. Bansode. All the members of Governing Body of API, Faculty Council of ICP and Board of PRF also supported me all throughout.

With your blessings, I am confident of carrying out new term as Editor-in-Chief with great Zeal and Vigour.

- Prof. Milind Y. Nadkar
Editor-in-Chief
Diabetes Mellitus (DM) is a metabolic affliction which is reflected by chronic hyperglycemia resulting from disturbances in insulin secretion, insulin action or even both, along with associated derangements of lipid, carbohydrate and protein metabolism at the background. Amongst the various types of diabetes encountered, type 2 diabetes mellitus (T2DM) accounts for almost 90% of all the cases. A 2 to 6 fold increase in cardiovascular morbidity and mortality is observed in those patients who develop T2DM, which further contributes to the adverse socio-economic burden of diabetes in the long term. Majority of these patients tend to also suffer from concomitant dyslipidemia, typically characterized by the atherogenic triad of elevated triglycerides (TG), low concentrations of high density lipoprotein cholesterol (HDL-C) and an increased number of small dense low density lipoprotein cholesterol (LDL-C) particles. Hypertriglyceridemia has been reported as an important risk factor for CVD and may be as prevalent as 50% in T2DM and is often also unresponsive to statin treatment. This typical dyslipidemic feature has been observed in diabetic as well as prediabetic patients and addressed by multiple terms like ‘Atherogenic Dyslipidemia’, ‘Atherogenic Diabetic Dyslipidemia’ or just ‘Diabetic dyslipidemia’ and has been associated with an increased cardiovascular disease (CVD) risk.

People with prediabetes are at a very high risk of developing T2DM. And as per recent updates in addition to the 425 million diabetics worldwide, there are 352.1 million adults with impaired glucose tolerance (IGT) or prediabetes, who have a very high chance of developing full blown diabetes in the future. Though out of these, not all become diabetic, the conversion rate varies from population to population and from region to region. In India, the ICMR-INDIAB study (2011), which included both urban and rural population across 4 major Indian states, identified a conversion rate from prediabetes to diabetes, ranging between 7.1% - 15.2%.

Prediabetes, if simply put, would be a metabolic disorder portrayed by insulin resistance along with primary or secondary beta cell dysfunction, which in turn increases the risk of T2DM. The American Diabetes Association (ADA) defines prediabetes as an impaired fasting glucose (IFG) between 100 mg/dL to 125 mg/dL OR as impaired glucose tolerance (IGT) [2-h PG during 75-g OGTT] between 140 mg/dL to 199 mg/dL OR Glycated Hemoglobin (HbA1c) levels between 5.7–6.4%. The common risk factors for prediabetes include family history of diabetes, excess body weight (particularly abdominal adiposity), dyslipidemia, age >45 years, gestational diabetes, high birth weight children, certain ethnic groups, hypertension, and physical inactivity. In a metaanalysis of 18 studies, Ford et al. had concluded that people with prediabetes in general have a 20% increased risk of CVD. Halting the progression from prediabetes to T2DM is therefore an important health intervention strategy which has the potential to improve the health of populations, and reduce health care costs associated with the management and prevention of diabetic complications.

Multiple interventions have been utilized and studied to prevent or delay the progression from prediabetes to T2DM, including pharmacological agents (oral antidiabetic drugs and antiobesity drugs), lifestyle modification (LSM), and herbal remedies. Three major randomized studies have shown a positive effect of LSM on DM prevention. The ADA, therefore recommends exercise as a major part of T2DM prevention. Diet and exercise interventions have demonstrated improvements in insulin resistance and decrease in the incidence of diabetes and cardiovascular events, although long term weight loss is difficult to maintain.

In clinical and research studies, pharmacological agents like metformin, α-glucosidase inhibitors, orlistat, glucagon-like peptide 1 (GLP-1) receptor agonists, and thiazolidinediones (PPAR-γ agonists) have each shown to prevent the incidence of diabetes to various levels in patients with prediabetes. But at present, none of them is approved by the U.S. Food and Drug Administration for diabetes prevention in particular. Metformin though, has a very strong evidence base and also has demonstrated long term safety as a pharmacologic therapy for diabetes prevention. Apart from metformin, PPAR-γ agonists (pioglitazone) have also shown a potential to decrease the incidence of diabetes, mostly due to their ability to address insulin resistance which lies as the root cause behind the hyperglycemia seen in both T2DM and prediabetes. Although, weight gain and edema were also reported with the glitazones.

As insulin resistance and dyslipidemia are generally identified as early offenders in the process of developing T2DM and also a part of the metabolic syndrome, the concept of the dual peroxisome proliferator activated receptor (PPAR) α/γ agonists or glitazars was born.

Consulting Physician & Diabetologist; Executive Editor. Journal of the Association of Physicians of India; Editor-in-Chief. API Textbook of Medicine -8th Edition; Director Elect: Physicians Research Foundation, API; Hon.Diabetologist : Bhatia Hospital, SL Raheja Hospital, Global Hospital & Saifee Hospital

Siddharth N Shah

The Road to Preventing Diabetes: Addressing Prediabetes and Concomitant Dyslipidemia

Siddharth N Shah
clinical trials (PRESS V & PRESS VI) and is presently available in India as Saroglitazar. Saroglitazar is presently approved for clinical usage in India since 2013 for the treatment of diabetic dyslipidemia not controlled by statin therapy alone. In the present issue, Bhosle D. et al. have attempted to assess the potential of Saroglitazar for the first time in a prediabetic population having concomitant dyslipidemia, where they have observed, that saroglitazar with its insulin sensitizing and triglyceride action plays a role in controlling the dyslipidemic and HbA1c parameters and thereby may play a part in delaying or preventing the progression of diabetes. This is a first-in-concept study with a relatively smaller sample size, carried out at a single center. There is no doubt though, that this avenue should be further explored in larger, randomized clinical trials to assess the true potential of this Indian molecule i.e. Saroglitazar in population with prediabetes.

References

Study of Saroglitazar in Treatment Of Pre-diabetes with Dyslipidemia: STOP-D

Deepak Bhosle1*, Vandana Bhosle2, Jyoti Bobde3, Abhijeet Bhagat3, Huzaif Shaikh4, Rajesh Kadam3

Abstract

Objectives: Patients with prediabetes are not only at increased risk of progression to type 2 diabetes, but they are also at high risk of developing cardiovascular risk compared to normoglycemic people. Further, prediabetes is also often associated with abnormal lipid levels (dyslipidemia). We therefore aimed to evaluate the effect of Saroglitazar in patients with prediabetes and dyslipidemia.

Methods: This was a prospective, single centre, single arm study involving patients with pre-diabetes and dyslipidemia. Subjects with baseline HbA1c 5.7-6.4% and dyslipidemia (Total cholesterol > 200mg/dl, LDL-C > 130 mg/dl, triglycerides > 150 mg/dl and HDL< 40 mg/dl) were enrolled in this study. Subjects with on-going medications affecting blood glucose or lipids were excluded from the study. Saroglitazar 4mg once daily was administered for a period of 24 weeks. The primary outcome was change in serum triglycerides and secondary outcome parameters included changes in other lipid parameters and HbA1c levels at 24 weeks follow-up.

Results: Forty patients with prediabetes and dyslipidemia were enrolled in the study. At 24 weeks follow-up, serum triglycerides was significantly reduced from 348 ± 86.98 mg/dl to 216.4 ± 72.34 mg/dl (P <0.0001). HbA1c was significantly reduced from 6.3 ± 0.16 % to 5.5 ± 0.30 % after 24 weeks of Saroglitazar therapy (P<0.0001). There were significant improvements observed in other lipid parameters at 24 weeks follow-up period. Saroglitazar was found to be safe and well tolerated, no serious adverse event reported during entire study period.

Conclusion: Saroglitazar is safe and effective in prediabetes with dyslipidemia by exerting its dual lipid lowering and glycemic actions.

Trial Registration: ctril.nic.in CTRI/2016/03/006778.

Introduction

Type 2 Diabetes Mellitus (T2DM) is on the rise with its many complications and high cost to the society, and its prevention is of primordial concern. According to International Diabetes Federation 2015 Diabetes Atlas (7th edition), in addition to the 415 million adults who are estimated to currently have diabetes, there are 318 million adults with impaired glucose tolerance (IGT), which puts them at high risk of developing the disease in the future. India is the second largest contributor of diabetes in the World with 69.2 million and 2040 projection estimates of 123.5 million, second only to China. India is already the largest contributor of IGT in the world with 36.5 million population affected with IGT in 2015.1

Prediabetes is the precursor stage to T2DM which is defined by American Diabetes Association (ADA) as impaired fasting glucose (IFG) of 100–125 mg/dl (5.6–6.9 mmol/l) or IGT of 140–199 mg/dl (7.8–11.0 mmol/l) after two hours postprandial. ADA also recommends glycosylated hemoglobin (HbA1c) prediabetic range of 5.7–6.4%.2 Prediabetes is not only associated with increased risk of progression to T2DM but also with increased cardiovascular disease (CVD) risk.3

Current consensus definition of metabolic syndrome incorporates hyperglycemia, obesity, hypertension, hypertriglyceridemia and reduced high density lipoprotein cholesterol (HDL-C).4 However, many researchers believe that insulin resistance is the core pathophysiology which mediates metabolic syndrome.3 Hence, there is an overlap between prediabetes and metabolic syndrome and prediabetes is often associated with dyslipidemia. The risk of diabetes is 5–7 fold higher in patients with IFG or IGT as compared to normoglycemic patients and for the patients with metabolic syndrome, the risk of developing diabetes is 5 fold more as compared to the patients who are not having metabolic syndrome.5 However, when prediabetes combines with metabolic syndrome, the risk is increased even more.

Saroglitazar, a dual peroxisome proliferator activated receptor (PPAR) α/γ agonist is approved in India for the treatment of diabetic dyslipidemia which is not controlled with statin alone. Pivotal phase III studies have shown triglyceride reduction by 45–46.7%, Non HDL-C reduction by 32.5%, Apo B reduction by 32% and HbA1c reduction by 0.3% from baseline at 12-24 week follow-up with Saroglitazar 4 mg once daily treatment.5,6 The safety and efficacy of Saroglitazar in prediabetes population with dyslipidemia had not been studied till date. Hence, we strived to evaluate the safety and efficacy of Saroglitazar in patients with dyslipidemia and meeting the criteria of prediabetes.

Material and Methods

This is an interventional, prospective, single center, single arm trial conducted in patients with pre-diabetes and
dyslipidemia to evaluate the safety and efficacy of Saroglitazar. The subjects were recruited at Deogiri Diabetes Centre, Aurangabad, Maharashtra, India. Subjects with baseline HbA1c 5.7–6.4% and dyslipidemia as per NCEP ATP III criteria (borderline high total cholesterol > 200mg/dl, low-density lipoproteins cholesterol (LDL-C) > 130 mg/dl, triglycerides > 150 mg/dl and HDL< 40 mg/dl) as per National cholesterol education programme-adult treatment panel III (NCEP ATP III) criteria (borderline high and above) were enrolled in this study. Institutional ethical committee approval was sought and granted by the MGM-ECRHS (Mahatma Gandhi Mission’s Ethics Committee for Research on Human Subjects) based at MGM Medical College, Aurangabad, India and the trial was in accordance with the revised Helsinki Declaration of 2000. Patient’s informed consent was taken prior to each patient enrollment after proper explanation of the study details and interventions to the patient in their own regional language. The trial was registered in Clinical Trials Registry- India (CTRI) with CTRI number CTRI/2016/03/006778.

The inclusion criteria of the study were patients of either sex with age group of 20-60 years, patients with prediabetes (HbA1c 5.7–6.4%) and deranged lipids as per NCEP ATP III criteria.

Participants with borderline high and above range of dyslipidemia i.e. total cholesterol > 200mg/dl, LDL-C > 130 mg/dl, triglycerides > 150 mg/dl and HDL< 40 mg/dl were included in the study. Patients with Type I DM, Type II DM, secondary hypertension, bronchial asthma, chronic obstructive pulmonary disease or any other respiratory disorders and any hepatic or renal diseases were excluded from the study. Also, subjects with on-going medications affecting blood glucose or lipids were excluded from the study.

After fulfillment of inclusion criteria and informed written consent, subjects were enrolled into study and Saroglitazar 4mg once daily was administered for a period of 24 weeks. Saroglitazar is available in only 4 mg strength in the market. The primary outcome was change in serum triglycerides and secondary outcome parameters included changes in HbA1c, serum total cholesterol, serum LDL-C, serum HDL-C and Non HDL-C at 24 weeks follow-up. Serum urea and creatinine as Kidney function test (KFT), Alanine aminotransferase (ALT) and Aspartate aminotransferase (AST) as Liver function test (LFT) and electrocardiography (ECG) were also assessed at baseline and at 24 weeks follow-up to evaluate the safety of Saroglitazar.

The results were analyzed by using paired student “t-test” with SPSS (statistical package for the social science) software (version 22). P value < 0.05% was considered as significant.

**Results**

A total of 40 participants were enrolled in the study. The mean age was 48.15 years with 28 male participants out of the total 40. The baseline demographic profile is tabulated in Table 1.

The mean baseline HbA1c and triglycerides were 6.3 ± 0.16 % and 348 ± 86.98 mg/dl respectively (Table 2). All subjects were given Saroglitazar 4mg once daily for 24 weeks. There was no loss to follow-up as all 40 enrolled subjects completed the study. All participants who got enrolled in the study were hypertensive and they were on anti-hypertensive drug therapy. Hence, they were advised to continue the same. The participants were also provided routine dietary advice at enrollment.

The change in lipid parameters, HbA1c, liver enzymes, and kidney functions were evaluated at 24 weeks by using paired t-test.

At 24 weeks, there were significant improvements in lipid parameters and HbA1c level (Table 2). Serum triglycerides was significantly reduced from 348 ± 86.98 mg/dl to 216.4 ± 72.34 mg/dl (P <0.0001) with 38.7 ± 10.72 % change from baseline. Other lipid parameters like total cholesterol, LDL-C and non HDL-C were also reduced significantly (P<0.0001) by 17.1 ± 2.48 %, 15.7 ± 8.47 % and 19.9 ± 10.35 % respectively and HDL-C was increased by 9.6 ± 5.54 % (P<0.0001). In addition to significant changes in lipid parameters, there was significant improvement observed in glycemic parameter as well. Mean HbA1c reduced from 6.3 ± 0.16 % at baseline to 5.5 ± 0.30 % after 24 weeks of Saroglitazar therapy (P <0.0001). These results signify the dual role of Saroglitazar in reducing both lipid and glycemic parameters.

Apart from the above parameters, lipid and kidney function were also assessed in the study. The results are depicted in Table 3. After 24 weeks of Saroglitazar therapy, ALT significantly reduced by 6.7% ± 23.14 (P =0.024) and serum urea reduced by 2.5% ± 26.17 though, not statistically significant (P =0.2217). There was no serious adverse event reported with Saroglitazar during the entire study period. The ECG reports of all subjects were within normal limits with no QT prolongation. One patient reported with an episode of diarrhea which was resolved with antimicrobials without interrupting study medication. There was no adverse effect on liver enzymes or kidney function at week 24. There was no weight gain or edema reported. Mean baseline weight of 74.02±3.66 kg was reduced to 73.9±3.92 kg. (P=0.3468) (Table 3).

**Discussion**

The incidence and prevalence of T2DM has been progressing rapidly worldwide over the last few decades posing as a major public health problem. Moreover, the disease manifestations start at an earlier stage, even before it gets established as a full blown condition, the pre-stage to T2DM called prediabetes.

South East Asia has 42.2 million people with IGT and is at increased risk of developing T2DM in the future and projected 2040 estimates are 73.9 million people. India constitutes over 86% of adults amongst South East Asia population.

Much of the socioeconomic burden of diabetes is due to the complications of this disease, notably from CVD. This increased risk for cardiovascular morbidity and mortality is mostly an indirect manifestation of cardio-metabolic abnormalities, including lipid abnormalities. In general, people with diabetes tend to have elevated concentrations of triglycerides and Apo-lipoprotein B, low concentrations...
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Table 2: Change in lipids and HbA1c after 24 weeks treatment with Saroglitazar

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<th>Baseline (n=40)</th>
<th>24 weeks follow-up (n=40)</th>
<th>Absolute change from baseline</th>
<th>% change from baseline</th>
<th>P-value</th>
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<tbody>
<tr>
<td>Total cholesterol (mg/dl)</td>
<td>324.7 ± 43.39</td>
<td>270.1 ± 43.61</td>
<td>-54.6 ± 5.73</td>
<td>-17.1 ± 2.48</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Triglycerides (mg/dl)</td>
<td>348.0 ± 86.98</td>
<td>216.4 ± 72.34</td>
<td>-131.6 ± 48.64</td>
<td>-38.7 ± 10.72</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>LDL-C (mg/dl)</td>
<td>209.8 ± 47.67</td>
<td>177.9 ± 47.56</td>
<td>-31.9 ± 14.22</td>
<td>-15.7 ± 8.47</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>HDL-C (mg/dl)</td>
<td>44.8 ± 5.71</td>
<td>49.0 ± 6.13</td>
<td>4.2 ± 2.39</td>
<td>9.6 ± 5.54</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Non-HDL-C (mg/dl)</td>
<td>276.8 ± 42.38</td>
<td>224.1 ± 47.15</td>
<td>-54.5 ± 25.11</td>
<td>-19.9 ± 10.35</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>6.3 ± 0.16</td>
<td>5.3 ± 0.30</td>
<td>-0.7 ± 0.25</td>
<td>-</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

All values are in Mean ± SD

Table 3: Change in kidney, liver function and weight after 24 weeks treatment with saroglitazar

<table>
<thead>
<tr>
<th>Laboratory parameters</th>
<th>Baseline (n=40)</th>
<th>24 weeks follow-up (n=40)</th>
<th>Absolute change from baseline</th>
<th>% change from baseline</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum urea (mg/dl)</td>
<td>22.0 ± 4.21</td>
<td>20.9 ± 4.74</td>
<td>-1.1 ± 5.73</td>
<td>-2.5 ± 26.17</td>
<td>0.2217</td>
</tr>
<tr>
<td>Serum creatinine (mg/dl)</td>
<td>1.0 ± 0.17</td>
<td>1.0 ± 0.14</td>
<td>0.0 ± 0.18</td>
<td>6.1 ± 19.46</td>
<td>0.21</td>
</tr>
<tr>
<td>Alanine aminotransferase (U/L)</td>
<td>26.9 ± 6.16</td>
<td>24.6 ± 6.61</td>
<td>-2.3 ± 6.12</td>
<td>-6.7 ± 23.14</td>
<td>0.024</td>
</tr>
<tr>
<td>Aspartate aminotransferase (U/L)</td>
<td>25.2 ± 6.11</td>
<td>26.5 ± 6.39</td>
<td>1.4 ± 8.33</td>
<td>11.3 ± 38.81</td>
<td>0.311</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>74.02 ± 3.66</td>
<td>73.9 ± 3.92</td>
<td>-0.125 ± 0.26</td>
<td>-0.182</td>
<td>0.3468</td>
</tr>
</tbody>
</table>

All values are in Mean ± SD

of HDL-C and an elevated number of small dense LDL-C particles. Findings from the National Health and Nutrition Examination Survey 1988–1991 to 2005–2008 reveal that participants with prediabetes had worse lipid profiles than those with diagnosed diabetes. Hence, prediabetes and dyslipidemia might be needed to be addressed and interventions sought in order to prevent their progression to frank diabetes and its chronic complications.

Asian Indians have a phenotype which is generally a combination of characteristics that predisposes more to the development of insulin resistance, T2DM and CVD. A study by the ICMR–INDIAB (Indian Council of Medical Research-IndiaDIAbetes) Collaborative Study Group showed that the onset of T2DM is earlier and at lower levels of BMI in Asian Indians compared with Caucasians. In spite of a relatively lower rate of obesity as defined by BMI cut points, Asian Indians tend to have larger waist measurements and waist-to-hip ratios, indicating a greater degree of central body obesity. This is associated with a characteristic metabolic profile with a greater degree of insulin resistance, a premature loss of beta cell function, metabolic syndrome or prediabetes.

Diabetic dyslipidemia (DD) is condition where in there is increased triglycerides, low HDL-C and increased proportion of small dense LDL-C. Hypertriglyceridemia has been reported as an important risk factor for CVD. Hypertriglyceridemia may be as prevalent as 50% in T2DM and is often unresponsive to statin treatment. In an article by Anders Berg Jorgensen et al, using data from 75,725 participants in two general-population studies, it was ascertained that participants with non-fasting TG <90 mg/dl had 60% lesser risk of CV events compared to participants with non-fasting TG >350 mg/dl. Hence, triglyceride management becomes important along with reduction of other lipid parameters not only in diabetes but in prediabetes as well.

Phase III trials of Saroglitazar have shown significant reductions in triglycerides and other lipid parameters along with effective reductions in glycemic parameters in diabetes patients suffering from dyslipidemia. Similar efficacy and safety results were further reiterated in a post marketing study where at 3 months follow-up, use of Saroglitazar 4 mg in patients with diabetic dyslipidemia led to significant reduction in triglycerides (35.8%), LDL-C (16.4%), total cholesterol (19%) and non-HDL-C (23.4%). Addition of Saroglitazar to baseline antidiabetic medications showed a significant 0.9% absolute reduction in HbA1c with significant improvement in fasting and post prandial plasma glucose.

All studies till date on Saroglitazar have been on diabetes patients with dyslipidemia. This is the first study which was solely conducted on subjects with prediabetes and dyslipidemia. The results are encouraging and in lines with the previous studies on Saroglitazar with significant reduction in triglycerides (38.7 ± 10.72 %), LDL-C (15.7 ± 8.47 %), total cholesterol (17.1 ± 2.48 %) and non-HDL-C (19.9 ± 10.35 %) as well as 0.7 ± 0.25 % reduction in HbA1c levels.

In a recent study data on pioglitazone, a PPAR γ agonist, it was found to almost half the progression to Type 2 DM in people with insulin resistance and CVD. It was hypothesized that its metabolic actions mediated through PPAR-γ in adipocytes, skeletal muscle, and the liver might have led to such impressive results. In this study, Saroglitazar having agonistic action on PPAR γ, following a similar trend might have resulted in 0.7 ± 0.25 % reduction in HbA1C levels from baseline 6.3 ± 0.16 % to 5.5 ± 0.30 % thus halting the progression of diabetes. However, to establish the efficacy of Saroglitazar in the prevention of diabetes, evidences based on larger randomized controlled trials are warranted.

In addition to above, there were no major adverse events reported. The one reported adverse event of diarrhea was also unrelated to the drug and easily managed with medication. Liver, kidney parameters and ECG were within normal limits and not adversely affected by Saroglitazar.

Strength and limitations: This is the first study to examine the effect of first approved dual PPAR α/γ agonist, Saroglitazar in patients with prediabetes and dyslipidemia. The study was however limited by its sample size and other limitations such as single centre study and absence of comparator group. Also, blood glucose levels were not included as part of trial which could have added more dimension over and above HbA1c. A more robust study with a larger sample size is required to further establish the results of this study.

Conclusion

This study concluded that Saroglitazar is safe and effective in prediabetes with dyslipidemia by exerting its dual lipid and glycemic lowering benefits.

Acknowledgement

This study was presented in poster session (1133 P-“ Study of Saroglitazar in Treatment of Pre-diabetes with Dyslipidemia”) of American Diabetic
References


Study of Correlation of Serum Vitamin D Levels with Arterial Stiffness and Cardiovascular Morbidity in Elderly Individuals of Western Rajasthan

Om Prakash Suthar¹, Shyam Mathur², Vikas Gupta³, Harish Agarwal⁴, Arvind Mathur⁵, Pradeep Singh⁶, Sohan Lal Sharma⁶

Abstract

Introduction: Vitamin D deficiency is highly prevalent condition in western countries as well as in India. Lower level of vitamin D is associated with increased arterial stiffness by activating renin–angiotensin–aldosterone system leading to increased cardiovascular morbidity and mortality including increased risk of coronary artery disease, stroke, peripheral vascular disease, hypertension, diabetes mellitus and metabolic syndrome. Our aim was to study the correlation between serum vitamin D level, various measures of arterial stiffness and cardiovascular morbidity in elderly individuals.

Material and Method: The present study was conducted in collaboration with Department of Medicine, Department of Cardiology and Regional Geriatric Centre, NPHCE, MDM Hospital attached to Dr. S.N. medical college Jodhpur. Total 100 elderly individuals 60 yrs and above attending hospital for minor short illness, acute illness or for routine health checkup or with acute coronary events are included in the study. Vitamin D level was assessed by chemiluminescent immunoassay. Pulse Wave Velocity was determined by Periscope.

Results: In subjects with coronary artery disease, 28.30% were vitamin D deficient, 49.05% were vitamin D insufficient and only 22.64% are vitamin D sufficient. In healthy subjects, 25.53% were vitamin D deficient, 23.40% were vitamin D insufficient and 51.04% were vitamin D sufficient. The difference between these groups was statistically highly significant. (p value-0.006). Various measures of arterial stiffness including Rt baPWV, Lt baPWV, cf PWV and pulse pressure are more in vitamin D deficient group as compared to vitamin D sufficient group. The difference was statistically significant.

Conclusion: Vitamin D deficiency is quite common condition in elderly individuals which besides its bone mineralization action is also involved in cardiovascular functions. Deficiency of vitamin D may cause increase in arterial stiffness and widening of pulse pressure which are the predictor of atherosclerosis and cardiovascular morbidity and mortality.

Abbreviation: NPHCE-national program for health care of elderly, Rt baPWV-Right brachio-ankle pulse wave velocity, Lt baPWV- left brachio-ankle pulse wave velocity, cfPWV- carotico-femoral pulse wave velocity

Introduction

Vitamin D deficiency is highly prevalent condition in western countries as well as in India. However the best-characterized consequence of vitamin D deficiency involve the musculoskeletal system but many evidences suggests that low levels of suboptimal level of vitamin D is associated with increased arterial stiffness leading to cardiovascular morbidity and mortality including increased risk of coronary artery disease, stroke, peripheral vascular disease, hypertension, diabetes mellitus and metabolic syndrome. Vitamin D affects arterial stiffness by certain mechanism such as it affects vascular wall by regulating renin–angiotensin–aldosterone system (RAAS). Vitamin D inhibits renin gene expression by sequestering C-AMP response element binding protein, a necessary factor for transcription of renin mRNA. Vitamin D deficiency activates RAAS system, causes proliferation of vascular smooth muscle cells, activates macrophages invasion of vascular cell, promotes calcification and increased PTH release. These effects can be ameliorated by vitamin D supplementation. Rehman et al. demonstrated that matrix metaloproteinase protein that contribute to aberrant cardiomyocytes remodeling in response to injury and atherosclerosis were up-regulated in vitamin D receptor knockout mice and impaired cardiac relaxation and contractility and developed left ventricular hypertrophy.

Vitamin D modulates endothelial function by decreasing expression of adhesion molecules, providing protection against advanced glycation products.

Substantial evidence indicates that atherosclerosis is an inflammatory disease and inflammation plays a role in major CV disease events, and efforts to reduce inflammation may

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Original Article
be warranted.7 Low 25(OH)\textsubscript{2}D and increased PTH levels increases the risk of inflammation, as documented by elevated levels of C-reactive protein and interleukin-10. Administration of 1,25(OH)\textsubscript{2}D in the setting of vitamin D deficiency has been shown to down-regulate inflammatory biomarkers such as C-reactive protein.

In small clinical trials, vitamin D supplementation has shown reduction in blood pressure, left ventricular hypertrophy and inflammatory cytokines.9 Population-based studies have partially, but not consistently, documented that low vitamin D status is associated with an increased risk of adverse cardiovascular events and cardiovascular mortality.9 Meta-analyses support the finding that low 25-(OH)\textsubscript{2}D concentrations are associated with increased risk of cardiovascular diseases.10

However, data regarding correlation between vitamin D and arterial stiffness in elderly are lacking in context of Indian population. Our aim was to find out association between arterial stiffness and vitamin D level in elderly individuals in western Rajasthan.

**Aims and Objectives**

1. To study correlation between serum vitamin D level and cardiovascular morbidity.
2. To establish relationship between serum vitamin D level and various measures of arterial stiffness in elderly individuals.

**Material and Method**

The present study was conducted in collaboration with Department of Medicine, Department of Cardiology and Regional Geriatric Centre, NPHCE, MDM Hospital attached to Dr. S.N. Medical college Jodhpur.

Participants, after making them understand study protocol and procedure, were asked to give written consent for study. It was conducted according to principles expressed in declaration of Helsinki.

**Study Population**

Present study was carried out in the group of elderly subjects (age>60yrs) attending MDM hospital for their acute illness (cardiac and noncardiac) or for routine health checkup.

**Study Design**

An observational cross-sectional hospital based study.

**Inclusion Criteria**

1. Healthy elderly people 60 yrs and above attending hospital for minor short illness, acute illness or for routine health checkup.
2. Elderly subjects 60 yrs and above presenting with acute coronary events.

**Exclusion Criteria**

1. Person <60 yr of age.
2. Previous known case of diabetes, hypertension, ischemic heart disease, chronic kidney disease, hepatic dysfunction, prior history of peripheral vascular disease, chronic obstructive pulmonary diseases, HIV etc.
3. Persons on oral calcium, vitamin D, bisphosphonates supplementation, steroids treatment or on any other long term undefined medication.
4. Any past history of malignancy, sarcoidosis, tuberculosis, any chronic granulomatous diseases.

Methodology: After written informed consent from subjects comprehensive clinico-epidemiological data were collected. Diabetes, hypertension, hypercholesterolemia was defined as per ADA guidelines, JNC 8, and Adult Treatment Panel 4 respectively. Relevant laboratory investigations were done. Arterial stiffness, ABI and pulse wave velocity were assessed by Periscope – window based vascular analysis system. Vitamin D level was assessed by chemiluminescent immunoassay (CLIA).

Method: Pulse Wave Velocity was determined by Periscope (M/S Genesis Medical System, Hyderabad, India). It is an 8-channel real time PC-based simultaneous acquisition and analysis system. It is dedicated hardware module connected to 4 ECG electrode and 4 blood pressure measuring cuffs. The device was validated and found to have good reproducibility in PWV measurement in healthy as well as CAD subjects.11

Data evaluation: In this observational study, the data was analyzed by Epi info statistical and multivariate analysis method.

**Observations**

The present study comprised of 100 elderly individuals who attended Medical OPD, Cardiology OPD or Geriatrics centre for their acute coronary events or minor illnesses at MDM Hospital. Jodhpur.

**Result**

In the study population, 21% were females and 79% were males (Table 1). Mean values of left brachio-arterial pulse wave velocity (Lt ba PWV), carotico-femoral pulse wave velocity (cf PWV) and Pulse Pressure found to increase with age with minimum value in 61-70 yrs age group (Lt ba PWV 1384.01±744.48 cm/sec, cf PWV 1095.48±694.63 cm/sec, Pulse Pressure 60.22±19.4) and maximum in >80 yr age group (Lt ba PWV 1635.74±1222.6 cm/sec, cf PWV 1151.83±787.72cm/sec, pulse pressure 67.33±21.46). There was no correlation of ABI with age in our study (Table 2).

In subjects with coronary artery disease, 28.30% were vitamin D deficient, 49.05% were vitamin D insufficient and only 22.64% are vitamin D sufficient. In healthy subjects, 25.53% were vitamin D deficient, 23.40% were vitamin D insufficient and 51.04% were vitamin D sufficient. The difference between these groups was statistically highly significant (p value-0.006) (Table 3).

Pulse Pressure was abnormal in 66.66% of vitamin D deficient individuals, 43.24% vitamin D insufficient individuals and in only 25% of vitamin D sufficient individuals. Correlation of Pulse Pressure with serum vitamin D level was statistically significant (p value 0.004) (Table 4). It was highest in vitamin D deficient group (mean value-70±19.93) and lowest in vitamin D sufficient group (mean value-56.05±14.02). Pulse Pressure was 56.05±14.02 in vitamin D insufficient group. The difference between these groups was statistically highly significant (p value-0.0132).

In this study, right brachioarterial pulse wave velocity (Rt ba PWV) was abnormal in 55.55% of vitamin D deficient individuals, 43.24% of vitamin D insufficient individuals and in only 25% of vitamin D sufficient individuals. Correlation of Rt ba PWV with serum vitamin D level was statistically
The vitamin D deficiency was highest in vitamin D deficient group (mean value-1363.67 ± 284.75 cm/sec) and lowest in vitamin D sufficient group in (mean value-796.78 ± 490.58 cm/sec). The difference between these groups was statistically highly significant (p value-0.0014).

**Discussion**

Vitamin D deficiency is highly prevalent condition in India as well as worldwide. Besides its function of bone mineralization, now a-days research has explored its involvement in variety of others functions affecting cardiovascular system. Vitamin D affects blood pressure, insulin resistance, cytokine profile as well as psychological functions which ultimately affect arterial stiffness, predisposed individuals for various adverse cardiovascular events and increases morbidity and mortality.

In recent years, with development of readily available non-invasive techniques of measuring arterial stiffness, especially of large and medium arteries, has gathered pace. These include measurement of PWV, use of ultrasound and applanation tonometer to detect arterial waveforms. Most widely used technique is to estimate the distensibility and stiffness of aorta and proximal vessels by PWV and pulse pressure. In our study we used Periscopic, which records simultaneously pressure wave forms from all four limbs to calculate PWV. The device was validated and found to have good reproducibility in PWV measurement in healthy as well as CAD subjects.

The correlation between vitamin D level and pulse wave velocity was validated in Baltimore longitudinal study of ageing in 1228 healthy volunteers (50% males; age, 70±12 yr). There was a significant inverse association between central PWV and 25-OH D levels.

In a study, Lee et al. reported that low 25-OH D levels independently predicted PWV (P <0.001) in individuals with type 2 diabetes (n = 305) after adjustment for other risk factors such as age, smoking, hypertension, C-reactive protein, diabetes duration, hypertension duration, glycosylated hemoglobin, and BMI.

Ageing characterized by widening of Pulse Pressure and in older subjects Pulse Pressure relates more closely to cardiovascular events than systolic or diastolic blood pressure. Third national health and nutrition exam survey found increased pulse pressure, a nonspecific marker of arterial compliance and vitamin D deficiency. ABI has been suggested to be unsuitable for assessing PAD...
in subjects with diabetes, older age, history of intervention for PAD, or advanced chronic kidney disease (CKD). In particular, increased arterial stiffness might interfere with ABI measurements and affect the sensitivity of ABI for detecting PAD among dialysis subjects.

Vitamin D deficiency is more common in acute myocardial infarction. S Karur et al. found that 83.5% of acute MI subjects had low Vitamin D level. Chowdhury et al. showed in a meta-analysis of seven studies, including 47,809 individuals and 926 cerebrovascular events that, under consideration of established cardiovascular risk factors, the risk for cerebrovascular disease was significantly lower in subjects with high 25(OH)D levels compared to those with insufficient vitamin D status.

**Conclusion**

Vitamin D deficiency is quite common in elderly individuals which besides its bone mineralization action is also involved in cardiovascular functions. Deficiency of vitamin D may cause increase in arterial stiffness and widening of pulse pressure which are the predictor of atherosclerosis and cardiovascular morbidity and mortality. Supplementation of vitamin D may be helpful in old age.

**Study Limitations**

Our study was a cross-sectional, observational study which precludes definitive conclusions regarding the causal relationship between arterial stiffness and vitamin D levels. In addition, we did not explore the putative mediating effect of alcohol consumption and inflammatory status. Despite the aforementioned limitations, our study has several unique strengths. First, this study measured carotid-femoral PWV, which is the “gold standard” for the noninvasive assessment of arterial stiffness. Second, this study was performed in the context of a normative aging study that included both sexes with careful assessment of several potential confounders of the arterial stiffness/vitamin D status relationship.

**References**

Clinical Profile and Outcome of Acute Pancreatitis: A Hospital-Based Prospective Observational Study in Subhimalayan State

Nitesh Negi¹, Jatinder Mokta², Brij Sharma³, Rajesh Sharma⁴, Anupam Jhobta⁵, Vishal Bodh⁴, Asha Ranjan⁶*

Abstract

Background: Prospective and population-based studies on the incidence of acute pancreatitis (AP) are lacking. We aimed to determine the incidence, etiology, severity, and outcome of AP.

Material and Methods: This was an observational prospective study done on 123 patients with AP during one year period in IGMC, Hospital Shimla. Detailed clinical history was recorded and examination and lab investigations were done. Severity of AP was assessed using modified Atlanta classification.

Results: In this study, 123 patients were included- 89 men (72.35%) and 34 women (27.65%). Median age of presentation was 42 years. The most common presentation was abdominal pain followed by vomiting. The major etiological groups were as follows: alcohol 73 cases (59.3%), gallstones 40 (35.6%); postendoscopic retrograde cholangio-pancreatography 1 (0.8%), hypertriglyceridemia 3 (2.9%), autoimmune 1 (0.8%) and idiopathic 5 cases (4%). Alcohol was the most common cause of AP and followed by gallstone. Mortality was seen in 7(5.7%) patients. Out of seven patients who died in hospital, 5(71.42%) had severe pancreatitis and 2(28.57%) patients had moderately severe pancreatitis. When compared, patients with BMI ≥25, HCT≥44% and CRP ≥150mg/l had an increased risk of developing a severe form of AP.

Conclusions: Alcohol and gallstones were the most common etiology of AP. HCT, CRP and BMI done at admission are useful predictors of severe pancreatitis.

Introduction

Acute pancreatitis (AP) is an inflammatory process of the pancreas with varying involvement of regional tissues or remote organ systems¹,² and with potentially devastating consequences. The diagnosis of mild disease may be missed and death may occur before diagnosis in 10% patients with severe disease. AP runs a benign course in Asian countries and the etiology is different from that of the western population. Gall stones and alcohol abuse account for 70% of cases of AP. The risk of developing AP in patients with gallstones is greater in men, but more women develop this disorder since gallstones occur with increased frequency in women. The incidence of AP increases with age. More recently, biochemical markers, such as C-reactive protein³, interleukin-6 and trypsinogen activation peptide⁴,⁵ have been used as predictors of severity in AP. C-reactive protein is a useful marker only 48 h after the onset of acute episode¹ and overall usefulness of the remaining markers is restricted by their limited availability or elevated cost. Thus, so far, no early, accessible and economical predictive marker for severe AP has yet been described. Hematocrit (Hct) is routinely assessed in every AP case at admission and is an accessible and low-cost test. Recent studies have proposed that hemoconcentration can constitute a good marker for severity of AP, but others were unable to find a significant correlation with the development of organ failure, pancreatic necrosis or death.⁶,⁷ Thus, the value of hemoconcentration in the initial assessment of AP patients and its implications in prognosis remain controversial. Recently, several studies have identified obesity as a negative prognostic factor in AP.⁸,⁹,¹⁰ However, in Asian populations, morbidity and mortality also occur in patients with low body mass indexes (BMIs). In this background, the present study was undertaken to study the etiology, clinical profile, severity and outcome of AP in Hilly State.

Material and Methods

This was a prospective observational study done in the department of Medicine and Gastroenterology, IGMC Shimla during one year period from 1st July 2014 to 30th June 2015. All the patients above 18 years of age presenting in inpatient department with AP (2 of the 3 criteria- abdominal pain suggestive of AP, serum amylase or lipase activity >3UNL, characteristic radiological findings) were included in the study. Patients with chronic pancreatitis (history of chronic abdominal pain/ maldigestion with weight loss/ radiological evidence of chronic pancreatitis) and immunocompromised patients were excluded. Institutional ethical clearance and written informed consent was obtained from the patients. Detailed history and clinical examination was done and laboratory tests performed included haemogram, serum amylase, lipase, liver function tests, serum triglyceride, blood urea nitrogen, serum creatinine, blood glucose, lactate dehydrogenase, serum calcium, arterial blood gas analysis. All cases were

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The study included 89 (72.35%) male patients and 34 (27.65%) female patients, and male to female ratio was 2.6:1. The age of patients ranged between 18 to 81 years. The mean age was 42.89 ± 12.53 years. There was considerable variation in the numbers of patients with mild and severe acute pancreatitis. Although the overall mortality of acute pancreatitis is static at 1 to 2% but second attack predisposing to a severe attack. Although the overall mortality of acute pancreatitis is static at 1 to 2% but second attack predisposing to a severe attack. Although the overall mortality of acute pancreatitis is static at 1 to 2% but second attack predisposing to a severe attack. Although the overall mortality of acute pancreatitis is static at 1 to 2% but second attack predisposing to a severe attack. Although the overall mortality of acute pancreatitis is static at 1 to 2% but second attack predisposing to a severe attack. Although the overall mortality of acute pancreatitis is static at 1 to 2% but second attack predisposing to a severe attack. Although the overall mortality of acute pancreatitis is static at 1 to 2% but second attack predisposing to a severe attack. Although the overall mortality of acute pancreatitis is static at 1 to 2% but second attack predisposing to a severe attack.

A total of 123 patients with acute abdominal pain who were diagnosed as AP based on elevated serum amylase and/or lipase levels and radiological findings with ultrasound and CT abdomen were included in the study. The study included 89 (72.35%) male patients and 34 (27.65%) female patients, and male to female ratio was 2.6:1. The age of patients ranged between 18 to 81 years. The mean age was 42.89 ± 12.53 years. There was considerable variation in the numbers of patients with mild and severe acute pancreatitis. Although the overall mortality of acute pancreatitis is static at 1 to 2% but second attack predisposing to a severe attack. Although the overall mortality of acute pancreatitis is static at 1 to 2% but second attack predisposing to a severe attack. Although the overall mortality of acute pancreatitis is static at 1 to 2% but second attack predisposing to a severe attack. Although the overall mortality of acute pancreatitis is static at 1 to 2% but second attack predisposing to a severe attack. Although the overall mortality of acute pancreatitis is static at 1 to 2% but second attack predisposing to a severe attack. Although the overall mortality of acute pancreatitis is static at 1 to 2% but second attack predisposing to a severe attack. Although the overall mortality of acute pancreatitis is static at 1 to 2% but second attack predisposing to a severe attack. Although the overall mortality of acute pancreatitis is static at 1 to 2% but second attack predisposing to a severe attack. Although the overall mortality of acute pancreatitis is static at 1 to 2% but second attack predisposing to a severe attack.

### Results

A total of 123 patients with acute abdominal pain who were diagnosed as AP based on elevated serum amylase and/or lipase levels and radiological findings with ultrasound and CT abdomen were included in the study. The study included 89 (72.35%) male patients and 34 (27.65%) female patients, and male to female ratio was 2.6:1. The age of patients ranged between 18 to 81 years. The mean age was 42.89 ± 12.53 years. There was considerable variation in the numbers of patients with mild and severe acute pancreatitis. Although the overall mortality of acute pancreatitis is static at 1 to 2% but second attack predisposing to a severe attack. Although the overall mortality of acute pancreatitis is static at 1 to 2% but second attack predisposing to a severe attack. Although the overall mortality of acute pancreatitis is static at 1 to 2% but second attack predisposing to a severe attack. Although the overall mortality of acute pancreatitis is static at 1 to 2% but second attack predisposing to a severe attack. Although the overall mortality of acute pancreatitis is static at 1 to 2% but second attack predisposing to a severe attack. Although the overall mortality of acute pancreatitis is static at 1 to 2% but second attack predisposing to a severe attack. Although the overall mortality of acute pancreatitis is static at 1 to 2% but second attack predisposing to a severe attack. Although the overall mortality of acute pancreatitis is static at 1 to 2% but second attack predisposing to a severe attack. Although the overall mortality of acute pancreatitis is static at 1 to 2% but second attack predisposing to a severe attack.

### Discussion

AP is a common emergency, accounting for 3% of all patients admitted with acute pain abdomen. The spectrum of the disease is wide ranging from mild attacks with mild epigastric discomfort to multi-organ dysfunction and death. The mild attacks often go undiagnosed predisposing to a severe second attack. Although the overall mortality of AP is static at 1 to 2% but in severe acute pancreatitis mortality is 10 to 30%.

Ours was a hospital based prospective study of 123 patients. The mean age of patients was 42.89 ± 12.53 years. There was considerable variation...
in the age distribution of the study population. Majority of the patients in our study were in the age group of 41-60 years (47.15%) followed by patients between 18 to 40 years (43.91%) and 11 (8.94%) patients were above 60 years of age. Alcohol consumption is more common in middle age males as compared to other age groups, it could explain the preponderance of middle age in our study. This is comparable to the studies done by W.Uhl11 and Raghu M Get al,12 where it was 50 years & 42.9±15.9 years respectively. In our study, males outnumbered females and the male to female ratio was 2:6:1. This is comparable with the studies of W.Uhl10 of 302 patients, with a male to female ratio of 1.85:1 and A de Beaux et al,13 where male to female ratio was 1:6.1. Alcohol consumption being more common in male compare to female in this hilly state, it could be explained the male preponderance in our study. Pain abdomen was the most common presenting complaint in all patients (100%). The presentation in our study correlates with studies by Mitchell S 14 and Rao B S et al,15 where it was seen in 95% and 100% of cases respectively. Vomiting was seen in 42.27%, fever and pleural effusion were seen in 11.38% and 21.13% patients respectively. It correlates with study by Rao B S et al.15 Alcohol was the commonest cause of pancreatitis (59.34%) followed by gall stone pancreatitis (32.52%). Baig SJ, et al1 in their study of aetiology of gall stone pancreatitis (32.52%). Baig al.15 Alcohol was the commonest cause correlates with study by Rao B S et al,13 where overall mortality rate was 4.6%. In our study fifty percent of the patients with severe pancreatitis had BMI of ≥ 25 kg/m2, while 28.42% of patients with mild to moderate pancreatitis had BMI of ≥25 kg/m2. The sensitivity, specificity, positive predictive value and negative predictive value of BMI ≥25 kg/m2 in predicting acute severe pancreatitis at admission was 50%, 71%, 34.14% and 82.9% respectively. Statistically analysis of the data yielded a p value of <0.03. Our study is comparable to other studies for obesity as a risk factor for severe AP. In a study by Su Mei CHEN et al16 in their 12 clinical studies with a total of 1483 patients were included in the analysis. They found that obese patients (BMI ≥25) had a significantly increased risk of severe AP compared with non-obese patients. In our study the evaluation of serum HCT level at admission for the detection of severity of AP showed the sensitivity, specificity, positive predictive value and negative predictive value was 67.86%, 85.26%, 57.57%, 90% and 81.30% respectively & the values were found to be statistically significant (p=0.00). Brown et al19 in their study in 128 patients found that the test at admission had a sensitivity, specificity, positive predictive value and negative predictive value of 72%, 83%, 68% and 85% respectively. In our study the evaluation of serum CRP level at admission for the detection of severity of AP showed a sensitivity, specificity, positive predictive value, negative predictive value and accuracy of 67.86%, 93.67%, 76%, 90.8% and 87.80% respectively. This test at admission was statistically significant (p=0.00). Which is comparable with a study by Anna Gurda-Duda et al20 and Pongprasobchai S. Erythrocyte sedimentation rate and C - reactive protein for the prediction of severity of acute pancreatitis. Pancreas 2008; 37:367-372. In a study by S Macro et al,14 the most common etiology was alcohol consumption (39.3%) followed by gallstones (24.1%). High prevalence of alcohol consumption and gall stone disease among general population in this hilly state could explain the higher prevalence of alcohol and gall stones induced pancreatitis in our study. Out of total 123 patients, 116 patients recovered and 7 patients died. So overall mortality in our study is 5.7%. Out of 7 patients who died, 5 had severe pancreatitis and 2 had moderate pancreatitis. Hence the overall mortality in severe pancreatitis in our study is 17.85% and in moderately severe pancreatitis is 4.08%. It correlates with study by Bota S et al,17 where overall mortality rate was 4.6%. In our study fifty percent of the patients with severe pancreatitis with low mortality and morbidity and 22.76% patients present as severe pancreatitis with organ failure leading to higher mortality and morbidity. HCT, CRP and BMI done at admission are useful predictors of severe pancreatitis.

References

Evaluation of Endothelial Dysfunction in Idiopathic Dilated Cardiomyopathy Patients

Mukul Kumar¹*, Yashpaul Sharma², Ajay Bahl²

Abstract

Background: Endothelial dysfunction has early been characterized in ischemic cardiomyopathy patients. The study was aimed to study evaluation of endothelial dysfunction in idiopathic cardiomyopathy patients (DCM).

Methods: Thirty newly diagnosed patients (age >18 years) of DCM were enrolled in the study from cardiology OPD, PGIMER, Chandigarh from January 2011 to June 2012. Age-and sex-matched 30 healthy controls were also enrolled. Idiopathic DCM was diagnosed by presence of left ventricular dilatation and systolic dysfunction (LVEF<40%) on echocardiography in the absence of coronary artery disease, hypertension or valvular disease. All patients underwent echocardiography and coronary arteriography. Flow mediated dilation (FMD) and carotid intima media thickness (IMT) were compared between patients and controls.

Results: There was no significant difference in mean IMT between patients (0.73±0.04 mm) and controls (0.74±0.03 mm) (P=0.18). There was significant difference in left IMT in NHYA class (P=0.010). There was significant difference in mean percentage of FMD (patients vs. controls; 4.37% vs. 8.35%; P=0.001) while baseline FMD was different (patients vs. controls; 3.6 mm±0.26 mm vs. 3.72±0.32 mm; P=0.13). There was no significant difference in percentage NMD (P=0.057) and mean NMD (P=0.26) between patients and controls. There was no correlation between FMD and IMT.

Conclusion: Endothelial dysfunction occurs in IDC patients. Also, there is a positive correlation with NHYA class; however, IMT is not affected in dilated cardiomyopathy.

Introduction

An insult to vascular endothelium is likely a preliminary event in most vascular diseases. Endothelial dysfunction has been found to be implicated in a number of diseases from diabetes mellitus and essential hypertension, to vasospastic conditions such as systemic sclerosis and primary Reynaud’s phenomenon.¹ Furthermore, it has been postulated that endothelial dysfunction is a precursor to atherosclerosis; indeed, it has been identified in vivo in healthy individuals exposed to various cardiovascular risk factors like cigarette smoking, obesity, increasing age etc. Cardiovascular disease (CVD) is currently a leading cause of morbidity and mortality in the Western world, a fact which has provided a drive for the development of methods, facilitating in vivo evaluation of endothelial function.¹

Arterial physiology has recently been studied using a non-invasive ultrasound technique, brachial artery flow-mediated dilation (FMD).² Nitric oxide released from arterial endothelial cells mediates the dilatation response with increased blood flow. Brachial FMD response is also found to be correlated with coronary endothelial function as tested by invasive methods.

Endothelial dysfunction results in the inability of a vessel to dilate in response to endothelium-derived relaxing factors after physiological stimuli, like increases in blood flow (an early characteristics of coronary atherosclerosis).³ Major risk factors for atherosclerotic vascular disease (e.g., hypertension, diabetes, smoking, hypercholesterolemia and obesity) have been associated with endothelial cell dysfunction.⁴ Carotid intima-media thickness (IMT) is considered as a marker of early atherosclerosis, it predicts future risk of cardiovascular disease, and it has been found to be high in individuals with coronary heart disease and myocardial infarction. Whether it is related to cardiomyopathy, this needs evaluation.⁷

Several studies have used the measurement of IMT at the common carotid artery, obtained by non-invasive high-resolution B-mode ultrasonography.⁸ An increased IMT of the carotid artery wall is considered to be an early atherosclerosis index; evidences suggest an association between extra cranial carotid artery disease and incidence of coronary heart disease. As endothelial dysfunction and increased IMT are interrelated, indicative of different aspects of the atherosclerotic process, their early detection could have strong implications for cardiovascular prevention. Some studies have already related endothelial dysfunction and IMT in patients with atherosclerosis or coronary artery disease, but few data are available in cardiomyopathy patients. The purpose of present study was to study endothelial dysfunction in by FMD and assessment of correlation between endothelial dysfunction and carotid intima media thickness in idiopathic cardiomyopathy (DCM) patients.

Subjects and Methods

Thirty newly diagnosed patients (age >18 years) with idiopathic DCM were enrolled in the study from Department of cardiology, Post Graduate Institute
of Medical Education and Research, Chandigarh from January 2011 to June 2012. Age-and sex-matched 30 healthy controls (family members of the patients) were also enrolled. The study was conducted following approval from Institutional Ethics Committee (IEC). All the subjects were included in the study after their consent.

Idiopathic DCM was diagnosed by presence of left ventricular dilatation and systolic dysfunction (LVEF<40%) on echocardiography in the absence of coronary artery disease, hypertension or valvular disease. Subjects with coronary artery disease, diabetes mellitus, cancer, hypercholesterolemia, concomitant infection, on sildenafil treatment, pregnancy, peripheral vascular disease, renal failure or autoimmune disease, rheumatic heart disease, hypertrophic cardiomyopathy, hypertensive heart disease, evidence of restrictive or constructive physiology, smoking, and alcohol intake >60 g/day were excluded from study. None of the subjects had family history of ischemic heart disease, history of smoking etc.

**Echocardiography**

Echocardiography was performed for all the subjects and ejection fraction was calculated using modified Simpsons method in apical 4 chamber view. Patients with ejection fraction less than 40% were enrolled in study. Normal value for EF was taken as 55-70%, end diastolic volume as 65-240 ml, end systolic volume as 16-143 ml.

**Coronary Arteriography**

The patients enrolled for the study underwent coronary arteriography during the course of hospitalization. Selective coronary arteriography of left and right coronary arteries was performed and multiple cineangiographic views were selected to delineate coronary artery anatomy. Patients with normal coronaries were included in the study.

**Brachial Artery Flow-Mediated Dilatation Measurement**

FMD was measured for all the patients using a non-invasive method (ultrasound system), fitted with a high frequency vascular transducer operated at 10 MHz. All vasodilator drugs were withheld for at least 4 times their half-life period before the vascular studies. The measurement was conducted after overnight fasting with patients in supine position at a room temperature of 22 to 25°C after resting for 30 minutes. Transducer was placed approximately 5 cm proximal to elbow joint at a fixed point for imaging brachial artery in the longitudinal plane. A segment with clear anterior and posterior intimal interfaces was selected for continuous 2-D gray scale imaging. Diameter measurement was selected from one intimal surface to the other, measured at end diastole taking beginning of R wave on ECG interface. Brachial artery flow was measured from the midpoint of the lumen using pulse Doppler. After taking baseline measurements, blood pressure cuff tied at forearm was inflated to about 50 mmHg above systolic blood pressure. After 5 minutes of cuff inflation, the cuff was deflated rapidly. For diameter measurements, readings were taken every 15 second from 15 to 120 seconds after cuff deflation and the greatest diameter was considered.

**Nitroglycerin-mediated Dilatation (NMD)**

After a 10-minute rest, 25 mg GTN (glyceryl trinitrate) was given sublingually and, after waiting for 3 minutes to achieve plateau response to the drug, brachial artery images were recorded for 1 minute. Both FMD and GTN responses were expressed as percentage change, calculated as follows:

\[
\text{Maximum brachial diameter - baseline brachial diameter} \times 100/\text{Baseline brachial diameter}
\]

**Statistical Analysis**

The data were presented as mean ± SD or median as appropriate. Student t-test was used for normally distributed data. Pearson χ² test or Fisher’s exact test was used for analysis of categorical variables with two categories. A P value of <0.05 was considered to indicate statistical significance. Correlation was presented as coefficient. A P value of <0.05 was considered as statistical significance. All calculations were performed using SPSS version 15 (Statistical Packages for the Social Sciences, Chicago, IL).

**Results**

The subjects’ characteristics have been summarized in Table 1. 50% patients were in New York Heart Association (NYHA) class I followed by 46.6% patients in class II. There was no patient in NYHA class IV.

**Carotid Intima Media Thickness (IMT)**

Our study found that there was no significant difference (P=0.18) in mean IMT between the patients (0.73±0.04 mm) and the controls (0.74±0.03 mm) (Table 2). Amongst patients, mean IMT in right side was 0.74±0.04 mm (range 0.67-0.82 mm) and on left side was 0.72±0.04 mm (range 0.7-0.8 mm). Amongst controls, mean IMT in right side was 0.75±0.03 mm (range 0.7-0.8 mm) and on left side was 0.74±0.03 mm (range 0.7-0.8 mm). There was no sex-based significant difference between in mean IMT (0.72±0.032 vs. 0.70±0.171 female vs. male; P=0.551) in the DCM patients group. There was significant difference in left IMT in NYHA class (P=0.010).

**Brachial Artery Flow Mediated Dilatation and Nitroglycerin-mediated Dilatation**

There was significant difference in mean percentage of FMD (patients vs. controls; 4.37% vs. 8.35%; P=0.001) while baseline FMD was different (patients vs. controls; 3.6 mm±0.26 mm vs. 3.72±0.32 mm; P=0.13). There was no significant difference in percentage NMD (P=0.057) and mean NMD (P=0.26) between patients and controls (Table 3).

**Relationship of FMD and IMT**

There was negative correlation between baseline FMD and NYHA class with correlation coefficient of -0.259 (P=0.167) and no correlation FMD and IMT (P=0.185).

**Discussion**

This study was conducted to know about endothelial dysfunction in idiopathic DCM patients. The study showed that mean age was similar in both the groups. Patient group had 20 males (66.7%) and 10 (33.3%) females whereas control group had 16 (53.3%) males and 14 (46.7%) females.

Most of the patients were in NYHA class I (50%) and class II (46.7%) and only 1 (3.3%) was in class III and none in class IV. Our study found no significant difference in mean IMT between patients and controls. Badran et al have shown significantly increased carotid diameter and IMT were in ischemic cardiomyopathy in comparison to non ischemic DCM and control (P < 0.001). Shah et al measured common IMT and showed no difference in IMT between controls and patients with DCM, however, increased in IHD patients;
because IMT is an early and sensitive marker of atherosclerosis, unlike coronary angiography, which could be unremarkable until a relatively advanced stage of atherosclerosis, these data indicated that our subjects with DCM had no significant excess underlying atherosclerosis. Tamura et al have that mean IMT was significantly higher in ischemic cardiomyopathy than controls. On the other hand, findings by Shah et al., are consistent with those previously reported by Stolten et al., who found that patients with DCM had FMD responses similar to those of healthy control subjects, despite a decrease in myocardial perfusion reserve in the former group. In a study by Sigtes et al, FMD was significantly impaired in the DCM group as compared to the control group, while NTG vasodilation was not different in the 2 groups. There were no differences between the 2 groups in baseline brachial artery diameter or in reactive hyperemia. There was weak negative correlation between FMD and NYHA class in our study with correlation coefficient of -0.23 which implies that FMD decreases as NYHA class increases. However, Shah et al suggested that there was no relationship between FMD and NYHA functional class. This may be either no such relationship exists, or because our study was underpowered to detect the presence of such a relationship. Our study did not find any correlation between FMD and IMT. On the other hand, Shah et al found a strong inverse relationship between FMD and common carotid IMT. Collectively, these data suggest that FMD is influenced much more importantly by atherosclerotic load than by heart failure.

Conclusion
Endothelial dysfunction occurs in DCM patients. Also there is a positive correlation with NYHA class; however, IMT is not affected in DCM. There is no correlation of IMT or FMD with NYHA class in our study. Our study has limitations including relatively unable to study any patients in NYHA class IV which could have provided more information about vascular function in subjects with severe heart failure, unblind study, short follow-up period, and inclusion of only patients with DCM; the results therefore should not be extended to patients with other causes of impaired LVEF, such as hypertension or ischemic heart disease.

References
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Diabetes, Hypertension and Kidney Disease Combination “DHKD Syndrome” is common in India

Suresh Chandra Dash¹, Sanjay Kumar Agarwal², Ansuman Panigrahi³*, Jayanti Mishra⁴, Debadutta Dash⁵

Abstract

Objective: The study was designed to find out frequency of (i) Diabetes mellitus (DM) as a cause Chronic Kidney Disease (CKD), (ii) Association between diabetic-CKD (diabetic patients who subsequently developed CKD as complication), hypertension (HT) and obesity. Further assessment was made to (iii) Identify percentage of diabetics attending medical and nephrology OPD had prior testing for proteinuria and or creatinine.

Methods: After ethical consideration this prospective observational study was conducted on consecutive 6175 patients who gave consent to participate in two major referral hospitals one in Delhi and other in Bhubaneswar (BBSR). Primary hypertension was defined as blood pressure of ≥140/90 mmHg detected before onset of DM or detected together in the absence of CKD (elevated serum creatinine S Cr ≥1.7 mg/dL and or proteinuria > 0.3g/24H). Upper limit of serum creatinine was kept at 1.7 mg for this study. Mean value of three estimations on different days was recorded. Detail clinical history of DM and HT was taken. Body Mass Index (BMI), ocular fundi examination, urine analysis, serum creatinine, lipid profile, blood glucose, Hba, C tests were conducted in all patients. They were regularly followed up in renal clinic at about 2 month interval for repeat investigations. Blood pressure in nondiabetic-CKD patients was recorded for comparison.

Further, consecutive diabetic patients attending general medical OPD for first time were examined, their previous investigations were carefully scrutinized and recorded. Urine for albuminuria and serum creatinine were tested every month over a period of one year.

Results: In Delhi diabetic-CKD was observed in 68.4% and the same was 56.2% in BBSR giving a combined figure of 62.3 percent. On close analysis of past record primary hypertension was observed in 75.4% who subsequently developed diabetes and CKD. Frequency of association between diabetic-CKD and HT were 88.2% and 69.3% in two cities respectively, combined frequency being 78.7 percent. Association of diabetic-CKD and obesity was 55.1 % and 55.9% in two cities respectively with combined frequency of 55.5 percent. In contrast obesity in non-diabetic-CKD patients in Delhi and BBSR was found in 43.1% and 18.5% respectively, combined frequency being 30.8%. Fifty four percent of diabetic patients who attended medical OPD for the first time were found to have proteinuria and elevated serum creatinine. However, they were not earlier tested for those parameters. Hence, they were unaware of CKD.

Conclusion: Diabetes was found to be a bigger cause (62.3%) of CKD than what has been reported thus far in India. At presentation association of diabetic-CKD with HT was recorded higher (78.7%) in India. Hence use of the syndrome “DHKD”, (complex of diabetes, hypertension and kidney disease) is justifiable. Our study shows 54.4% of diabetic patients attending medical OPD were uninvestigated by either physician or GP for CKD because urine albumin and serum creatinine tests were lacking. Thus, progression to CKD in many patients went unnoticed. Syndromic diagnosis of “DHKD” therefore in our view is important to create general awareness for early detection and effective treatment of diabetic nephropathy.

Introduction

Diabetes and Hypertension two major causes of CKD are spreading like silent epidemic in India and other developing countries. It has reduced quality man days and has already put huge financial burden on families and government exchequer. ICNR study reported in 2011 revealed 64.4 and 77.2 million people had diabetes and prediabetes respectively. It is predicted that by 2030 India’s diabetic population would be nearly 87 million. Similarly, incidence of hypertension has been progressively rising at alarming rate. According to 2010 WHO report on global status of non-communicable diseases, prevalence of HT has increased from 16% in 2004 to 32.6% in 2008. Further more Jaipur heart watch study on urban Indians also revealed incidence of HT increased from 30% in 1994 to 51% in 2003 both in male and female population. An earlier study has shown several fold increase in incidence of hypertension among rural “Oraon” tribal people when they migrated to urban areas.

Aims and Objective

However, there is no clear data on (i) how frequently diabetes is complicated by chronic kidney disease (ii) What is the frequency of association between diabetic-CKD and hypertension. (iii) What percentage of Indian diabetic patients in the society are aware of associated renal dysfunction (iv) What...
is the correlation between obesity and kidney disease. To find answers to above questions we prospectively studied consecutive diabetic patients attending renal clinic in two major referral hospitals in two different geographic regions and followed them over a period of 10 and 6 years respectively. The study also aimed at identifying frequency of renal dysfunction in diabetic patients attending medicine OPD for first time.

**Material and Methods**

Consecutive adult patients attending nephrology clinic of the author from 1994 -2003 in a premier teaching hospital of Delhi and 2006-2012 in an Eastern India referral Hospital in Bhubaneswar (BBSR) constituted subjects of this study. Patients, who gave informed consent to participate, were included. Most patients were admitted to indoor in order to complete the investigations.

Patients with unreliable history and serious complications were excluded. Similarly, those who had evidence of acute kidney injury were also excluded from the study. Detail history and physical examination, prior records of HT, DM and renal function tests were analysed. Blood Pressure was measured by sphygmomanometer and 14 cm Cuff by the same observer throughout the study. After giving 5 minutes rest three readings were taken in supine position. Mean figure of three readings was taken as the actual blood pressure. From analysis of history and record primary hypertension was defined as elevated blood pressure of ≥140/90 mmHg detected earlier than onset of diabetes or both detected at the same time in the absence of CKD. CKD was defined for this study as serum creatinine ≥ of 1.7 mg/dL (as per our lab standard) and or proteinuria > 0.3 gm. Serum creatinine was measured on more than 3 occasions in 3 months (after correction of acute kidney injury factors if any). Body Mass Index was calculated from equation, 

\[ \text{Body weight in Kg} \times \frac{100}{(\text{Height in meter})^2} \]

for correlation. After overnight fasting, morning blood sample was taken for serum lipid profile, uric acid, blood glucose, glycosylated hemoglobin (HbA1C). Twenty-four hour urine protein estimation was done at the institute laboratories. ECG, chest X-ray and ocular fundi examination were conducted as part of routine protocol for all CKD patients. They were followed in renal clinics at 2-3 months interval for assessment and treatment. Consecutive non-diabetic CKD patients during 5 years at Delhi and 9 years at BBSR were examined for assessment of past or present hypertension. Author in collaboration with medicine consultant conducted simple tests like urine for albuminuria and serum creatinine in consecutive diabetic patients attending medicine OPD for first time over a period of one year.

**Results**

A total 6175 consecutive patients attending two nephrology units constituted our study population. There were 3050 subjects (Male=62 %, Female=38%) in Delhi group and 3125 subjects (Male=73%, Female=27%) in BBSR group. In them CKD was associated with diabetes in 68.4% among Delhi patients and 56.2% among BBSR patients (Tables I and 2). Among 2087 Delhi patients with diabetic-CKD, 14% had stage-I and II (proteinuria only) where as more advanced stage-III, IV, V were seen in 38.8 %, 30.2% and 16.7% respectively (Table 1). The same were seen in 21.2%, 27.7%, 26.7% and 24.4% in BBSR respectively (Table 2).

Frequency of association between diabetic-CKD and HT was seen in 88.2% (Delhi) and in 69.3% (BBSR) respectively. In contrast those figures in non-diabetic CKD in Delhi and BBSR were 56.8% and 53.8% respectively (Table 3). Frequency of association between diabetic-CKD and obesity was 55.1% (Delhi) and 55.9% (BBSR) respectively. In contrast those figures in nondiabetic-CKD were 43.2%, 18.5% respectively (Table 4).

It was revealed that as high as 54% of diabetic patients attending general medicine OPD were positive for heavy proteinuria and or abnormal serum creatinine unknown to them as their renal function was never tested before. In both centers, CKD associated with hypertension was observed in higher percentage in diabetics compared to non diabetics. Similarly diabetic CKD patients were more frequently associated with obesity than non diabetics. This was true in all patients studied at different time period of study and were statistically significant.

**Discussion**

Higher rate of diabetic renal disease is reported among Indo-Asians in UK, African-American, Mexican-Americans in USA and Pima Indians. These ethnic groups have shown not only higher incidence of Type-2 diabetes but also high incidence of hypertension suggesting genetic predisposition to hypertension. It is well known that combination of diabetes and hypertension leads to higher incidence of nephropathy. The same has been shown by current study. Hypertension, diabetes and hyperlipidemia are risk factors for life-threatening complications like CKD and CVD (Cardio Vascular Disease) which put huge financial burden on patients and on state exchequer for treatment.

Current study observed significant higher association between diabetes and CKD (62.3% mean value in two hospitals). This is much higher than incidences 22.3% - 30.3% reported in literature 11 years ago. Despite a possible bias factor as patients were seen in nephrology clinic, findings were relevant. Similarly, it revealed a much higher incidence of hypertension among diabetic-CKD patients (combined value 79.5%) compared to nondiabetic CKD; (55.0%) respectively (Table 3). Furthermore higher association of obesity was observed among diabetic-CKD patients than non diabetic-CKD, combined value of 55.6% against 25.5% respectively (Table 4).

Regarding association of CKD and hypertension, Bivariate analysis (Table 3) showed CKD due to diabetes was associated with higher incidence of hypertension (88.2%) and nondiabetic CKD associated with lower incidence (56.8%) at Delhi. At Bhubaneswar those figures were 69.3 percent and 53.8 percent respectively. These associations were statistically highly significant. Diabetes and hypertension have been co-prevalent in patients as high as 62%. Almost one- third of patients with hypertension developed diabetes later. Present study also confirm to the earlier observation, because when associated with hypertension incidence of DN rose to 79.5 percent.

In the present study fifty four percent of CKD was detected among
Table 1: Frequency of association between CKD and DM at AllIMS, New Delhi (year 1994-2003)

<table>
<thead>
<tr>
<th>Year</th>
<th>Total no. of CKD cases</th>
<th>Total no. of CKD cases with DM</th>
<th>Proteinuria</th>
<th>S. Cr ≤ 1.7 mg/dl</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>CKD III</td>
<td>CKD IV</td>
</tr>
<tr>
<td>1995</td>
<td>282</td>
<td>192</td>
<td>28</td>
<td>78</td>
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<td>1996</td>
<td>316</td>
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<td>245</td>
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</tr>
<tr>
<td>2004</td>
<td>2050</td>
<td>1335</td>
<td>925</td>
<td>811</td>
</tr>
</tbody>
</table>

(68.4%) (14.1%) (38.8%) (30.2%) (16.7%)

Table 2: Frequency of association between CKD and DM at renal clinic, KIMS, Bhubaneswar (year 2006-2012)

<table>
<thead>
<tr>
<th>Year</th>
<th>Total no. of CKD</th>
<th>Total no. of CKD cases with DM</th>
<th>Proteinuria</th>
<th>S. Cr ≤ 1.7 mg/dl</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>CKD III</td>
<td>CKD IV</td>
</tr>
<tr>
<td>2006</td>
<td>378</td>
<td>235</td>
<td>125</td>
<td>54</td>
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<tr>
<td>2015</td>
<td>429</td>
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<td>372</td>
<td>487</td>
</tr>
</tbody>
</table>

(56.2%) (21.2%) (27.7%) (26.7%) (24.4%)

Table 3: Bivariate analysis showing association between diabetic CKD and hypertension

<table>
<thead>
<tr>
<th>Hypertension (HT) no. (%)</th>
<th>No HT no. (%)</th>
<th>Total</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>A. AllIMS New Delhi (Year 1994-2003)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetic CKD</td>
<td>1804 (88.2)</td>
<td>247 (11.8)</td>
<td>2087</td>
</tr>
<tr>
<td>Primary HT 565 (30.7)</td>
<td>Secondary HT 1275 (69.3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-diabetic CKD</td>
<td>547 (56.8)</td>
<td>416 (43.2)</td>
<td>963</td>
</tr>
<tr>
<td>B. KIMS, Bhubaneswar (Year 2006-2012)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetic CKD</td>
<td>1218 (69.3)</td>
<td>540 (30.7)</td>
<td>1758</td>
</tr>
<tr>
<td>Primary HT 354 (29.06)</td>
<td>Secondary HT 864 (70.94)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-diabetic CKD</td>
<td>736 (53.8)</td>
<td>631 (46.2)</td>
<td>1367</td>
</tr>
</tbody>
</table>

Table 4: Bivariate analysis showing association between diabetic CKD and obesity

<table>
<thead>
<tr>
<th>Obesity number no. (%)</th>
<th>No obesity number no. (%)</th>
<th>Total</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>A. AllIMS New Delhi (Year 1994-2003)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetic CKD</td>
<td>629 (55.1)</td>
<td>512 (44.9)</td>
<td>1141</td>
</tr>
<tr>
<td>Non-diabetic CKD</td>
<td>234 (43.2)</td>
<td>308 (56.8)</td>
<td>542</td>
</tr>
<tr>
<td>B. KIMS, Bhubaneswar (Year 2006-2012)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetic CKD</td>
<td>983 (55.9)</td>
<td>775 (44.1)</td>
<td>1758</td>
</tr>
<tr>
<td>Non-diabetic CKD</td>
<td>253 (18.5)</td>
<td>1114 (81.5)</td>
<td>1367</td>
</tr>
</tbody>
</table>

diabetic patients attending medicine OPD. It was revealed that they were unaware of presence of CKD in them. Moreover, what was observed in medical OPD was at a point of time. Those patients primarily attended for diabetes. Given longer time on longer follow up patients likely to develop proteinuria and or raised serum creatinine. Thus, it is clear that CKD occurs in higher proportion among Indian diabetic population.

Pathophysiologically, CKD produces hypertension by several mechanisms such as salt and water retention, ischemic damage to renal medulla (producing less secretion of prostaglandin secretion). Several studies have suggested a genetic link between diabetes and hypertension. Interesting to note that 75.4% of our patients had primary hypertension before their serum creatinine was elevated or other parameters of CKD detected. Co-existence of HT and hyperglycemia dramatically and synergistically increase risk of microvascular diseases like renal retinal microangiopathy. Several studies have suggested sensitizing effect of hyperglycemia on vascular system leading to complication of HT. What then is the relation between hypertension and diabetes? Prediabetics frequently have HT as one of the feature of metabolic syndrome.

Genetic link: (i) Angiotensinogen: Among many candidate genes linking HT to DM/DN, genes of renin-angiotensin system have been of most interest. Pro-renin, renin, ACE and angiotensin level are elevated in diabetic nephropathy. (ii) Furthermore studies have implicated genes of renin-angiotensin system to be determinants for both hypertension and diabetic kidney damage as well as cardiovascular disease. (iii) Linkage of the M235T polymorphism gene has been demonstrated in essential hypertension. (iv) Although there are conflicting reports one study has clearly shown association TT genotype with elevated blood pressure in patients with diabetic nephropathy.

Conclusion

Present study provides ample evidence confirming high association between diabetes, hypertension and kidney disease is like a nexus. More than 50% of diabetic patients of our country are unaware of existence of renal damage prior to presentation due to lack of simple urine albumin test and or serum creatinine estimation. Thus CKD at the crucial early stage go unnoticed leading to more advanced stages. This is a serious mistake and therefore it is necessary to use the term “Diabetic Hypertension-Kidney Disease (DHKD) Syndrome” for creating awareness among patients and doctors for early detection of DN, at a stage when it can be effectively treated.

References

8. Dash SC, Sundaram KR, Swain PK. Blood Pressure profile, obesity number (%)
9. Cowie CC, Port FK, Wolfe RA, et al. Disparities in incidence of diabetic end stage renal disease according to race and


Prevalence of Chronic Liver Disease Among the Patients of Celiac Disease and Effect of Gluten-Free Diet on Outcome of Liver Disease: A Prospective Study

Aniket Mule¹, Parmendra Sirohi², Nimba Ram¹

Abstract

Objectives: Descriptive reports of liver involvement in celiac disease (CD) are sparse, and the effect of a strict gluten-free diet (GFD) on the course of liver injury is also poorly understood. We conducted a study on 94 adult patients with CD and found that 39 of them were having chronic liver disease as well. We further followed patients of CD with CLD with strict Gluten-free diet (GFD) for six months.

Methods: We screened 94 patients of CD for CLD and found 39 patients to have CLD as well. We further followed these 39 patients of CD with CLD for six month with strict gluten-free diet. Follow up was done in terms of Child Pugh score. We recorded their clinical as well as laboratory findings after 1 month, 3 months and 6 months and compared them with those at the time of recruitment.

Results: The liver involvement was found in 39(41.5%) out of 94 patients celiac disease.

Mean Child-Pugh score on admission was 10.22±1.09 and on first follow-up mean Child-Pugh score was 7.38±1.47 was found to be statistically highly significant (p <0.001)

Mean Child-Pugh score on admission was 10.15±1.09 and on second follow-up 7.33±1.33 respectively and was statistically highly significant (p <0.001)

Mean Child-Pugh score on admission was 10.12±1.09 and on third follow-up mean Child-Pugh score was 6.31±0.93 respectively was statistically highly significant (p <0.001)

Material and Method

This study was a prospective study, conducted in the Department of Medicine in collaboration with Department of Gastroenterology, Sardar Patel Medical College & Associated Group of Hospitals, Bikaner (Rajasthan) from September 2013 to October 2014.

Inclusion criteria

1. Patients > 15 years of age
2. Proven cases of ‘celiac disease’ (CD) based on aforementioned criteria
3. Patients who have given written informed consent
4. Patients who were well motivated to follow strict GFD.

Exclusion criteria

1. Patients having known cause of liver disease
2. Terminally ill patients.

Among these 94 patients, we identified 39 cases who also had liver dysfunction. Diagnosis of CLD was based on the demonstration of splenomegaly, ascites and other signs of portal hypertension clinically and/or abdominal ultrasonography (USG), the presence of varices in upper GI endoscopy together with the presence of portal hypertension on upper GI endoscopy.

Introduction

Prevalence of liver involvement in celiac disease is not much studied in India partly because of lack of awareness, investigation facilities and expertise in the field of gastroenterology. Liver involvement in CD has a wide spectrum of manifestations ranging from an asymptomatic isolated elevation of hepatic transaminases to severe liver insults like the chronic liver disease, cirrhosis, acute liver failure and even end-stage liver disease.¹ CD is an important cause of hypertransaminasemia. Indeed, it has been reported in about 40% of adults and in 54% of children with a classical presentation of CD at the time of diagnosis.²³ Conversely, CD is present in about 9% of patients with chronic unexplained hyper-transaminasemia.⁴⁻⁹

A GFD leads to normalization of serum transaminases in 75% to 95% of patients with CD especially with isolated hypertransaminasemia, usually within a few months of good adherence to the diet. Even a severe liver failure is also potentially treatable by a gluten-free diet, even in the patients who are listed for liver transplantation.²⁻⁵,¹⁰,¹¹
of at least one of the four of the following features.\textsuperscript{13}

1. Hypoalbuminemia (serum albumin < 3.0gm/dL) with reversal of albumin: globulin ratio.
2. Persistent elevation of prothrombin time (>5 sec. above control), which is not correctable by parenteral vitamin K.
3. One or more episodes of hepatic encephalopathy.
4. The presence of clinical stigmata of CLD like palmar erythema, parotid swelling, finger clubbing, gynecomastia, spider naevi.
5. Supportive evidence of CLD in the abdominal sonography included the presence of coarse echogenic liver pattern with dilated portal and splenic vein, and splenomegaly.\textsuperscript{14}

We excluded all other known causes of liver disease like alcohol, viral, autoimmune, toxic, iron and copper overload related liver disease by detailed history, thorough physical examination and appropriate investigations like CBC, Slit Lamp Examination, HBsAg, Anti-HCV, IgM Anti HCV Antibody, Autoimmune markers (ANA, ASMA, Anti LKM-1), Serum ceruloplasmin level, Serum α-1 antitrypsin level, once diagnosis of celiac disease associated CLD was made and these cases were included for further study.

Then, we followed these patients with strict gluten-free diet (GFD) for six months. The follow-up was done in terms of Child-Pugh score, which is the prognostic indicator of severity of CLD and is a constellation of 5 features namely encephalopathy, ascites, serum bilirubin, prothrombin time (INR) and serum albumin.\textsuperscript{14}

We observed their symptoms and signs, routine blood investigations, liver biochemical test results, including alanine transaminase, aspartate transaminase, alkaline phosphatase, and bilirubin levels, on every follow up after one month, after three months and after six months and compared them to those at time of diagnosis.

Data was analyzed by statistics package for social sciences (SPSS, Chicago-10) statistical software. Before comparing the groups studied, each variable was tested for normality distribution. The mean values of discrete variables were calculated along with their 95% confidence interval or percentages. Then, data was processed using the Chi-square test, Student’s t-test.

### Results

The liver involvement was found in 39(41.5%) patients with CD. All the patients had elevated liver biochemical test results (aspartate transaminase, alanine transaminase, bilirubin, and/or alkaline phosphatase) at the time recruitment.

Mean SGOT on admission was 140.77±30.03 IU/L and on first follow-up 47.83±36.02 respectively, and the difference was statistically highly significant (p <0.001). Mean SGPT on admission was 134.19±30.08 IU/L and on first follow-up 53.00±31.44 respectively. Mean SAP on admission was 348.69±100.71 and on first follow-up 264.41±116.34 respectively. Mean total bilirubin on admission was 3.23±0.70 and on first follow-up 1.33±0.35 respectively. Mean direct bilirubin on admission was 1.33±0.36 and on first follow-up 0.43±0.24 respectively. Mean indirect bilirubin on admission was 1.93±0.50 and on first follow-up 0.87±0.48 respectively. Mean total protein on admission was 3.80±0.47 and on first follow-up 4.98±0.81 respectively. Mean serum albumin on admission was 2.29±0.27 and on first follow-up 3.26±0.62 respectively. Mean prothrombin time on admission was 26.11±5.32 and on first follow up 17.63±3.06 respectively. Mean INR on admission was 2.02±0.40 and on first follow-up 1.38±0.22 respectively (Table 1).

Mean Child-Pugh score on admission was 10.15±1.09 and on second follow-up mean Child-Pugh score was 7.33±1.33 and we observed that all the differences were statistically highly significant (p <0.001) (Table 1).

Mean SGOT on admission was 143.06±30.95 IU/L and on third follow-up 39.43±25.26 respectively. Mean SGPT on admission was 135.25±31.23 IU/L and on third follow-up 50.62±23.36 respectively. Mean SAP on admission was 349.43±103.16 and on third follow-up 244.39±116.04 respectively. Mean total bilirubin on admission was 3.21±0.73 and on third follow-up 1.06±0.27 respectively. Mean direct bilirubin on admission was 1.30±0.32 and on third follow-up 0.36±0.25 respectively. Mean indirect bilirubin on admission was 1.94±0.53 and on third follow-up 0.70±0.16 respectively. Mean total protein on admission was 3.81±0.49 and on third follow-up 5.24±0.55 respectively. Mean serum albumin on admission was 2.29±0.27 and on third follow-up 3.26±0.62 respectively. Mean prothrombin time on admission was 26.36±5.49 and on second follow up 17.42±2.91 respectively. Mean INR on admission was 2.02±0.42 and on second follow-up, 1.36±0.21 respectively (Table 1).

Mean Child-Pugh score on admission was 10.15±1.09 and on third follow-up mean Child-Pugh score was 6.31±0.93. We observed that all the differences were statistically highly significant (p <0.001) (Table 1).

### Discussion

Despite the large body of literature documenting CD-associated liver disease, descriptive studies in this setting are sparse. The effect of a
Almost similar results on GFD were also observed in a study done by Volta et al in 1998 as well as by Bardella et al in 1999. In 2002, Kaukinen et al done a study on 185 Finnish patients and found that dietary treatment may prevent progression to hepatic failure, even in cases considered for liver transplantation.

In another study by Barbero Villares, et al in 2008 and showed that 40-85% cases of celiac disease had improvement in their disease and liver disease was resolved after strict GFD for variable duration.

### Conclusion

In conclusion, chronic liver involvement in CD is an underestimated and potentially treatable cause of liver failure affecting 40-50% cases. We strongly recommend screening of CLD in every cases of CD because early diagnosis and treatment with gluten-free diet (GFD) not only delay or stop the progression of liver damage in these cases but also can improve already damaged the liver, even in cases of the end stage liver disease.

### References

NovoMix™ 30
(biphasic insulin aspart I.P.)
The Simple Insulin

**Significant reduction in PPG**
**Improved safety vs Human Insulin**
**Better quality of life after shifting from OADs**
**One insulin in one device even as needs change**

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The Influence of Metformin on Serum Carbohydrate Antigen 19-9 (CA 19-9) Levels in Type 2 Diabetes Mellitus Patients

BS Ankit¹, Ritvik Agrawal², Ajeet Gadhwal¹, Chitresh Chahar¹, RP Agrawal³*

Abstract

Objective: Diabetes mellitus has been claimed to be a risk factor for the development of pancreatic carcinoma. CA 19-9 has a great sensitivity in detection of pancreatic adenocarcinoma. Metformin exhibits a strong and consistent antiproliferative action on several cancer cell lines including pancreatic cancer. We aim to determine the influence of metformin on CA 19-9 levels in type 2 diabetes mellitus patients.

Methods: Total 193 patients with type 2 diabetes mellitus were registered for a single centre, cross-sectional study. On the basis of treatment modalities, patients were divided into metformin group (93 patients) and non-metformin group (100 patients). Detailed history, clinical examination, anthropometric measurements, serum CA 19-9 level, glucose and lipid metabolic profiles were determined. Results were presented as mean±SD. Association between CA 19-9 level and other variables were assessed with Pearson correlation and multiple stepwise regression analysis.

Results: Mean CA 19-9 level was 18.99±4.30 U/ml in the metformin group as compared to 30.49±5.61 U/ml in non-metformin group (p<0.001). Mean value of CA 19-9 was found highest among all i.e. 37.05±4.94 U/ml in patients taking insulin. Patients having lifestyle modification for the management of diabetes had their mean CA 19-9 level of 21.39±5.62 U/ml. CA 19-9 level is positively correlated with age, duration of diabetes, BMI, 2-hour Plasma Glucose level, HbA 1C, VLDL cholesterol, triglyceride, total cholesterol, LDL cholesterol (p<0.005) and negatively correlated with HDL cholesterol (p<0.001).

Conclusion: Metformin is associated with lower level of CA 19-9 in type 2 diabetes mellitus patients. It may have a protective role in preventing pancreatic damage and pancreatic cancer in diabetic individuals. CA 19-9 level could be an effective indicator of glycemic control, disease progression and lipid metabolism in patients with type 2 diabetes mellitus.

Introduction

Diabetes has been recognized as a key factor contributing to the development of solid organ malignancies including liver, pancreas, colorectal, breast, endometrial, uterine, and bladder.¹,² The hepatic¹ and pancreatic carcinoma¹ shows the strongest association with type 2 diabetes mellitus. Insulin resistance, hyperinsulinemia, oxidative stress, and proinflammation have been suggested as the potential mechanisms¹. Potential risk factors (modifiable and non-modifiable) common to both cancer and diabetes include aging, sex, obesity, physical activity, diet, alcohol, and smoking.

Carbohydrate antigen 19-9 (CA 19-9) was originally isolated from a human colorectal cancer cell line as a mucin like product by Koprowski and colleagues in 1979. The antigen is found in the normal epithelial cells of the gall bladder, biliary ducts, pancreas and stomach.³ While elevations in serum CA 19-9 appear to be useful in the diagnosis of adenocarcinoma of the upper gastrointestinal tract and in the monitoring of colonic carcinoma, its greatest sensitivity is in the detection of pancreatic adenocarcinoma.³ CA 19-9 is the only US Food and Drug Administration (FDA) approved biomarker for the diagnosis of pancreatic cancer. CA 19-9 level also increases in inflammatory conditions of the hepatobiliary system and in thyroid diseases as well as in pancreatic tissue damage that might be caused by diabetes.⁷

Metformin belongs to the biguanide class of oral hypoglycemic agents and is a widely used antidiabetic drug now prescribed to almost 120 million people in the world for the treatment of type II diabetes. Metformin exhibits a strong and consistent antiproliferative action on several cancer cell lines, including breast, colon, ovarian, pancreatic, lung and prostate cancer cells.⁵

Metformin exerts both indirect (insulin dependent) and direct (insulin independent) actions at the cellular level.⁶,⁷ Its direct effect is mediated via AMPK activation and reduction of mTOR signaling pathway, which leads to inhibition of gluconeogenesis in the liver, protein synthesis and cell proliferation in cancer cells. The indirect effects of metformin are mediated through its blood glucose lowering ability and subsequent reduction of the circulating insulin level.

Various studies have shown the antineoplastic effect of metformin. However, very few data are available regarding the correlation between metformin and CA 19-9 levels. Therefore, we planned this study to determine the influence of metformin on CA 19-9 levels in type 2 diabetes mellitus patients.

³ Sr. Registrar, ¹ Jr. Registrar, ² Professor & Head, Department of Medicine, S.P. Medical College, Bikaner, Rajasthan; ³ Corresponding Author

Received: 20.04.2016; Accepted: 21.12.2017
Aims and Objectives

We are aimed to determine serum carbohydrate antigen 19-9 (ca 19-9) levels in
1. Type 2 diabetes patients taking metformin.
2. Type 2 diabetes patients on life style modification only.
3. Type 2 diabetes patients with different treatment modality viz insulin, Sulphonylurea, Thiazolidinediones etc.

Material and Methods

Study design

Total 193 patients with type 2 diabetes mellitus were registered for a single centre, cross-sectional study. The study was conducted in department of medicine and diabetic care and research centre, S.P. medical college & associated group of P.B.M. hospitals, Bikaner during the period of October 2014 to September 2015. On the basis of treatment modalities, patients were divided into two groups; Patients taking metformin for more than 2 years were taken in the metformin group (93 patients) and patient taking treatment other than metformin were labeled as non-metformin group (100 patients).

Inclusion criteria:

- Known case of diabetes mellitus type 2
- Taking treatment for more than 2 years

Exclusion criteria:

1. Patients with type 1 diabetes mellitus
2. Patients with history of smoking and alcoholism
3. Patients with history of hypertension
4. Patients with history of liver and kidney disease
5. Patients with history of infectious disease and malignancy
6. Patients with history of acute and chronic pancreatitis
7. Patients with history of bronchial asthma and chronic allergic condition, Buerger’s disease, systemic sclerosis, Raynaud’s disease and other connective tissue disorders
8. Patients with history of hormonal replacement therapy

9. Patients with history of thyroid disorders
10. Patients with history of AIDS, hepatitis B and hepatitis C

Detailed history, clinical examination, anthropometric measurements, biochemical indices were assessed for all the selected patients.

Routine investigations performed were CBC, ESR, renal function test, blood sugar (fasting and postprandial), HbA1C, liver function test, lipid profile, urine complete and microscopy and ECG.

Ca 19-9 Levels

Approximately 2ml of venous blood sample was withdrawn in a microtitre well after an overnight fasting. Samples were stored at 2° to 8°C. CA 19-9 level was measured from serum by commercially available CA 19-9 ELISA kit by complete automatic chemistry auto analyzer (ARK diagnostics private limited).

Statistical analysis

Statistical analysis was performed with SPSS software. Distributions of patients between case and control groups were tested for significance using χ2 test. Results are presented as mean±SD. Unpaired student’s t-test was used to compare case and control group. To compare different treatment modality in type 2 diabetic patients, ANOVA test was used. Association between CA 19-9 level and other variables were assessed with Pearson correlation and multiple stepwise regression analysis. Multifactorial ANOVA (analysis of variance) test was used to study the independent effect of different variables on CA 19-9. p value less than 0.05 was considered significant.

Observations

The number of patients were more with CA 19-9 level in the range of 21-30 U/ml. There were 32 patients in metformin group and 43 patients in non-metformin group in the same range. Number of patients with level <10 U/ml of CA 19-9 level were 2 in metformin group and 1 in non-metformin group. The patients with CA 19-9 level in the range of 11-20 U/ml were 58 in patients taking metformin as compared to no patient in non-metformin group. 53 patients were reported with CA 19-9 level of 31-40 U/ml in non-metformin group as compared to only 1 patient in metformin group. Minimal cases were reported with the level of CA 19-9 level >40 U/ml i.e. 3 cases were found in non-metformin group and none was reported in metformin group. This difference was found to be highly significant (p<0.001) (Table 1, Figure 1).

In the present study, the mean value of CA 19-9 in the metformin group was found to be 18.99±4.30 U/ml that was less than that found in non-metformin group i.e. 30.49±5.61 U/ml. This difference was also found to be highly significant (p<0.001).

Mean value of CA 19-9 in patients taking metformin was 18.99±4.30 U/ml, while who only had life style modification had a value of 21.39±5.62 U/ml. Patients taking sulfonylurea had a mean CA 19-9 value of 29.59±3.40 U/ml and in patients taking insulin it was found to be highest of all i.e. 37.05±9.44 U/ml. In patients taking both thiazolidinedione and sulfonylurea, mean CA 19-9 level was found to be 28.96±4.31 U/ml, whereas in patients having a combination of sulfonylurea and alpha-glucosidase inhibitor it was 32.04±4.50 U/ml, in patients taking insulin+sulfonylurea it was 32.25±2.0 U/ml while in patients treated with insulin + DDP-4 inhibitor mean value of CA 19-9 level was 36.40±4.39 U/ml. The highest levels were reported in patients taking insulin only whereas lower levels of CA 19-9 were found in patients who took metformin and this difference was found to be highly significant statistically (p<0.001) (Table 2).

Correlation of CA 19-9 level with different variables shows that age, duration of diabetes, BMI, 2-hour Plasma Glucose level, HbA1C, VLDL cholesterol, triglyceride, total cholesterol (p<0.001) and LDL cholesterol (p<0.005) was positively correlated while HDL cholesterol was negatively correlated with CA 19-9 level (p<0.001) (Table 3, Figure 2).

When we applied multiple stepwise regression analysis for different variables on CA 19-9 level, age had a significant correlation and when we added the duration of diabetes, BMI, HbA1C, HDL cholesterol, LDL, cholesterol and triglyceride, significance level had a higher range (p<0.001) (Table 4, Figure 3).
Table 1: Distribution of cases according to CA 19-9 level (U/ml) in both groups

<table>
<thead>
<tr>
<th>CA 19-9 (U/ml)</th>
<th>Metformin</th>
<th>Non-Metformin</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. (%)</td>
<td>No. (%)</td>
<td>No. (%)</td>
<td></td>
</tr>
<tr>
<td>&lt;10</td>
<td>2 (2.15)</td>
<td>1 (1)</td>
<td>3 (1.55)</td>
</tr>
<tr>
<td>11-20</td>
<td>58 (62.37)</td>
<td>0</td>
<td>58 (30.05)</td>
</tr>
<tr>
<td>21-30</td>
<td>32 (34.40)</td>
<td>43 (43)</td>
<td>75 (38.86)</td>
</tr>
<tr>
<td>31-40</td>
<td>1 (1.07)</td>
<td>53 (53)</td>
<td>54 (27.97)</td>
</tr>
<tr>
<td>&gt;40</td>
<td>0</td>
<td>3 (3)</td>
<td>3 (1.55)</td>
</tr>
<tr>
<td>Total</td>
<td>93</td>
<td>100</td>
<td>193</td>
</tr>
</tbody>
</table>

\[ \chi^2 = 112.9 \]

\[ p < 0.001 \]

Table 2: Mean CA 19-9 level (U/ml) in different treatment modalities

<table>
<thead>
<tr>
<th>Individual Group</th>
<th>No. of cases</th>
<th>Mean ± SD (U/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metformin</td>
<td>93 (48.2)</td>
<td>18.99 ± 4.30</td>
</tr>
<tr>
<td>Lifestyle</td>
<td>9 (4.7)</td>
<td>21.39 ± 5.62</td>
</tr>
<tr>
<td>Sulfonylurea</td>
<td>36 (18.7)</td>
<td>29.59 ± 3.40</td>
</tr>
<tr>
<td>Insulin</td>
<td>13 (6.7)</td>
<td>37.05 ± 4.94</td>
</tr>
<tr>
<td>Thiazolidinedione</td>
<td>18 (9.3)</td>
<td>28.96 ± 4.31</td>
</tr>
<tr>
<td>Sulfonylurea+Alpha-glucosidase inhibitor</td>
<td>10 (5.2)</td>
<td>32.04 ± 4.50</td>
</tr>
<tr>
<td>Sulfonylurea</td>
<td>10 (5.2)</td>
<td>32.25 ± 2.03</td>
</tr>
<tr>
<td>Insulin + DDP-4</td>
<td>4 (2.1)</td>
<td>36.40 ± 4.39</td>
</tr>
<tr>
<td>Total</td>
<td>193</td>
<td>64.68</td>
</tr>
</tbody>
</table>

\[ p < 0.001 \]

Discussion

CA 19-9 is typically used as a screening tool to diagnose pancreatic cancer and as a marker of pancreatic damage that might be caused by diabetes. Limited numbers of studies showed that diabetic patients have increased CA 19-9 levels as compared with control group. Antineoplastic effect of metformin on pancreatic cancer has been demonstrated in various preclinical studies. In the present study, we observed the influence of metformin on serum carbohydrate antigen 19-9 (CA 19-9) levels in type 2 diabetes mellitus patients.

In our study, both the groups were comparable in terms of age, duration of diabetes, BMI, 2 h plasma glucose, HbA1C, HDL cholesterol, VLDL cholesterol, LDL cholesterol, triglyceride, total cholesterol.

The mean value of CA 19-9 for the metformin group was much lower i.e. 18.99±4.30 U/ml as compared to 30.49±5.61 U/ml in non-metformin group. This difference was highly significant (p<0.001). In non-metformin group, the patients were subjected to different modes of treatment. Mean CA 19-9 level was found highest among all i.e. 37.05±4.94 U/ml in patients taking insulin. Patients who took sulfonylureas had mean CA 19-9 level of 29.59±3.40 U/ml while patients having lifestyle modification for the management of diabetes had their mean CA 19-9 of 21.39±5.62 U/ml. Patients taking combination therapy for treatment also had their mean CA 19-9 level more than metformin group patients. The difference in the mean value of CA 19-9 in different treatment modalities was found to be statistically highly significant (p<0.001).

In a study, Zhang et al11 (2015) showed that incidence of elevated CA 19-9 level in diabetes mellitus patients was more in non-metformin group than in short-term and long-term metformin group patients. After a 1-year follow-up, the decrease in CA 19-9 level was highest in long-term metformin group than short-term metformin and non-metformin group patients.

In diabetic patients, hyperglycemia with endogenous hyperinsulinemia is associated with increased cancer incidence and progression by over activation of insulin receptor and IGF-1 receptor (INSR/ IGF-1R) signaling pathways.12 Hyperinsulinemia has been indicated as a possible factor for pancreatic cancer. CA19-9 is a tumor marker mainly used for the diagnosis of pancreatic cancer.16 This possibly explains our finding in the present study that lower level of CA 19-9 was found in metformin group while patients taking insulin have a higher CA 19-9 level.

In our study, CA 19-9 level is positively correlated with age, duration of diabetes, BMI, 2-hour Plasma Glucose level, HbA1C, VLDL cholesterol, triglyceride, total cholesterol, LDL cholesterol (p<0.005) and negatively correlated with HDL cholesterol (p<0.001).

In the year 1986, Nakamura N et al17 found that CA 19-9 level was positively correlated with fasting plasma glucose level and HbA1C. They concluded that even though diabetes mellitus is not a malignant disease, serum CA19-9 levels were increased in diabetic patients.

Benhamou et al18 in 1991 found a significant correlation between CA 19-9, fasting blood glucose, serum creatinine, bicarbonate level and HbA1C. They concluded that CA 19-9 in diabetic patients is positively correlated with blood glucose concentration and raised acute metabolic situations.

In the year 2011, Gul K et al19 found that median CA 19-9 level in diabetes was significantly higher with diabetes patients than non-diabetic controls. CA 19-9 level was positively correlated with age, duration of diabetes, HbA1C and number of complications.

In a study, Huang Y et al20 (2012) observed that CA 19-9 levels were positively and significantly associated with fasting plasma glucose, 2 hour post-load plasma glucose, and HbA1C.

In a study by Haoyong Yu et al21 (2012) noted that mean CA 19-9 level in type 1 and type 2 diabetes mellitus patients was higher than non-diabetic...
individuals. They showed that CA 19-9 was positively correlated with fasting plasma glucose, 2-hour plasma glucose, HbA1C, total cholesterol and negatively correlated with LDL cholesterol.

Esteghamati A et al22 in 2014 showed that CA 19-9 level was significantly higher in diabetic patients. Fasting plasma glucose, postprandial plasma glucose, HbA1C insulin resistance and β-cell function were directly correlated with CA 19-9 levels.

In another study, Yinfang Tu et al23 (2014) showed significant positive correlation of CA 19-9 with fasting plasma glucose, 2-hour post-challenge plasma glucose levels, glycated hemoglobin levels, glycated albumin levels, total cholesterol, insulin resistance and β-cell function.

Limitations of study

There were few limitations to our study. This was a single centre study. It was cross-sectional in design and therefore, a cause and effect relationship determination was not possible. The sample size (n=193) in this study was relatively small.

Conclusions

- Metformin is associated with lower level of CA 19-9 in type 2 diabetes mellitus patients. It may have a protective role in preventing pancreatic damage and pancreatic cancer in diabetic individuals.
  - CA 19-9 level was higher in patients taking insulin or insulin secretagogues. Insulin, because of its known mitogenic effects, may increase the incidence of pancreatic cancer in diabetes mellitus patients.
  - CA 19-9 level has a positive correlation with duration of diabetes, 2-hour plasma glucose, HbA1C, body mass index and lipid profile. Hence, it could be an effective indicator of glycemic control, disease progression and lipid metabolism in patients with type 2 diabetes mellitus.

References

Coexistent Pituitary Adenoma with Rathke’s Cleft Cyst: A Case Series

Varsha S Jagtap1*, Anurag R Lila2, Vijaya Sarathi3, Amol P Bukan1, Tushar R Bandgar2, Nalini S Shah4

Abstract

Objective: Coexistent pituitary adenoma and Rathke’s cleft cyst (RCC) is a rare entity. Purpose of this study is to describe the clinical presentation, imaging findings, and management of patients with this combination.

Methods: Retrospective review of records from a single tertiary care center for a period of three years (2009-2012).

Results: Out of the total 284 pituitary adenoma patients in the study period, there were four patients one each of Cushing’s disease, acromegaly, prolactinoma and non-secretory pituitary adenoma with coexisting RCC in all. Three of these were diagnosed to have coexisting RCC in preoperative MRI. All of them underwent transphenoidal excision of the lesions. Histopathology confirmed the collision sellar lesions in all four.

Conclusions: It is difficult to diagnose coexisting RCC preoperatively due to variable size, position and signal intensity. However when a nonenhancing cyst is incidentally detected by MRI in a patient with pituitary adenoma, the possibility of a coexisting RCC should be considered.

Introduction

Collision sellar lesions represent an uncommon entity. It comprises of combination of neoplastic, inflammatory, vascular or congenital lesions.1 Majority of these cases are missed preoperatively but get diagnosed postoperatively on histopathology.

Rathke’s cleft cysts (RCC) are commonly believed to be cysts derived from remnants of the Rathke’s pouch. RCCs are cystic sellar and supra-or parasellar lesions. Although small asymptomatic RCCs are seen at autopsy in 13–22% of normal pituitary glands, symptomatic examples are relatively rare (2). RCC with pituitary adenoma is a rare combination with around 42 cases described in literature (2-8). The pituitary adenomas associated with RCC are mainly prolactinoma followed by acromegaly, non-secretory, corticotropinoma and TSHoma.1

Methods

Retrospective review of the records of all pituitary adenoma patients attending the outpatient services of endocrinology department of a tertiary care center in India was carried out for a period of three years (Jan 2009-Dec 2012). The histopathology reports of patients were studied and those patients with coexisting pituitary adenoma and RCC were included in the study. The clinical features, hormonal investigations, MRI characteristics and management offered were noted. All hormonal measurements were carried out by chemiluminescence assay (Immulite 1000, Siemens, Los Angeles USA). Intra-assay and interassay coefficients of variation were less than 8% and 10%, respectively, for all hormonal evaluation. MRI scans were performed in a 1.5 Tesla unit using T1-weighted sagittal and coronal scans using gadolinium contrast.

Results

Total 284 patients with pituitary adenoma (193 secretory and 91 nonsecretory) attended the outpatient services in the span of three year study period. On evaluation of the histopathology reports of operated patients, four were found to have coexisting RCC with pituitary adenoma. Herein we describe these four patients with coexisting RCC and Cushing’s disease, acromegaly, prolactinoma and non-secretory pituitary adenoma. Three of the four patients were diagnosed to have coexisting RCC on preoperative radiology. In all patients histopathology was positive for pituitary adenoma and RCC.

Case 1

Fifty five year old postmenopausal housewife presented with chief complaint of weight gain, mooning of face, bilateral edema feet and proximal muscle weakness of two year duration (Figures 1a, 1b). She was found to be diabetic and hypertensive. Her evaluation revealed ACTH dependent endogenous hypercortisolism. MRI pituitary revealed a 13*16*11 mm macroadenoma with 8* 10*10 mm suprasellar cyst (T1 isointense and T2 hyperintense with no enhancement with thick wall) (Figures 1c, 1d). She underwent transphenoidal excision of the adenoma and the cystic structure. Histopathology showed an adenoma with occasional cysts lined by pseudostratified columnar epithelium containing mucin (Figure 2). Cholesterol clefts and foamy histiocytes were also seen. The final histopathology report was pituitary adenoma with RCC. Unfortunately the patient died due to ventilatory complications on third post-operative day.

Case 2

Thirty three year old female presented with headache, progressive
acral enlargement, oligomenorrhea and diminution of left eye vision since two years. She was found to have GH excess state with impaired fasting glucose. Her MRI revealed a 32*25*20 mm pituitary macroadenoma with suprasellar and right parasellar extension. It also revealed a cystic cleft within the adenoma (Figure 3). She underwent transsphenoidal excision of the adenoma. Histopathology revealed an adenoma with small cyst lined by pseudostratified ciliated columnar epithelium with intraluminal mucinous material. It was diagnostic of pituitary macroadenoma with RCC. Post operative evaluation revealed a residual macroadenoma with mainly parasellar component. There was no recurrence of RCC on MRI done 1.5 years later. The patient was subjected to fractional stereotactic conventional radiotherapy.

Case 3

28 year old female comes with complaints of amenorrhea, galactorrhea and bitemporal hemianopia. Hormonal evaluation was diagnostic of hyperprolactinemia (Prolactin: 594 ng/ml). Her MRI revealed a giant 48*37*29 mm adenoma with suprasellar, sphenoidal and bilateral parasellar extension (Figure 4). The macroadenoma had cystic changes. She was started on cabergoline 1mg/week. The dose was gradually increased over the next three years to 5 mg/week due to the consistently elevated prolactin values. The patient then started having CSF rhinorrhea. She was subjected to transphenoidal surgery and postoperatively cabergoline was restarted on low dose. The histopathology report was suggestive of atypical pituitary adenoma with RCC. The adenoma was composed of polyhedral cells with pleomorphic nuclei, focal squamous metaplasia, occasional mitosis, bony infiltration and small foci of psammomatoid calcification. Post operatively followup is available for 6 months; she has residual adenoma and requires cabergoline for hyperprolactinemia. There has been no recurrence of RCC.

Case 4

Forty-eight year old male comes with the complaints of visual disturbances. On evaluation he had bitemporal hemianopia. Hormonal evaluation was suggestive of secondary
RCCs are remnants of Rathke’s pouch. The relationship between pituitary adenomas and RCCs is controversial. Associations between these lesions have been reported to be only occasional and purely coincidental. In contrast other theory states that as pituitary adenomas also originate by clonal proliferation from anterior pituitary (derivative of Rathke’s pouch), they have shared embryonic origin. Kepes considered that this collision lesion was derived from ‘transitional’ cells between the lining of Rathke’s cleft and the glandular cells of the anterior pituitary, and coined the term ‘transitional cell tumour of the pituitary gland’ for this lesion. However, electron microscopy and immunohistochemistry proved that the cyst within the pituitary adenoma differs from cysts found in the embryonic stage of the pituitary gland. Therefore this theory that the tumour originated from the epithelium of an RCC in the early developmental stage was rejected. Inspite of this shared embryonic origin, RCC and adenoma have a rare coexistence.

RCCs were associated with 1.4% of pituitary adenomas in our series. RCCs were associated with 1.7% of pituitary adenomas in a large study series involving 464 patients. In another recent study of 782 adenomas, 4 also had RCC (0.51%). The clinical features can be due to pituitary adenoma or due to mass effect of the RCC.

Preoperative diagnosis of these collision lesions based on MRI findings is difficult. Although RCCs are rarely associated with pituitary adenomas; their presence may be overlooked in patients with pituitary adenomas. The differential diagnosis of incidental cysts in this region includes other lesions like cystic craniopharyngioma, cystic or haemorrhagic pituitary adenoma and arachnoid cyst. RCC show variable position, size and signal intensity. MR intensities of RCCs vary considerably depending on the cystic contents. High T1-weighted image intensity has been interpreted to indicate a high content of protein and mucopolysaccharide or the rare occurrence of haemorrhage. The cystic content of high- and iso-intensity RCCs on T1-weighted images is usually indicative of mucous with varying viscosity. By contrast, RCCs with low intensity on T1-weighted images usually contain CSF like transparent fluid with low viscosity. Some studies have reported the presence of intracystic nodules as characteristic for RCC but it was not observed in any of our cases.

Out of 42 patients reported in literature, in 16 cases preoperative...
In all four patients histopathology was positive for pituitary adenoma and RCC. Complex sellar lesions consisting of pituitary adenoma admixed with RCC and metaplastic squamous epithelium have also been reported as was seen in case 3. Whether these tumors are true “transitional” neoplasms or simply examples of an intimate collision of adenoma and cyst is unclear.11

The rate of recurrence for RCC varies from 0 to 33% due to variable signal intensity on MRI (Table 1).5,6 Three of our four patients were suspected to have coexisting RCC on preoperative radiology.

In this paper we describe three patients with unusual combination of pituitary adenoma with RCC. It is difficult to differentiate between them preoperatively due to variable size, position and signal intensity. However when a nonenhancing cyst is incidentally detected by MRI in a patient with pituitary adenoma, the possibility of a coexisting RCC should be considered. Careful analysis of preoperative imaging could prevent incomplete resection of this rare condition.

**Table 1: Review of literature showing cases with coexisting RCC and pituitary adenoma**

<table>
<thead>
<tr>
<th>Author (year, ref)</th>
<th>No. of cases</th>
<th>Pre-operative radiological diagnosis</th>
<th>Histopathological confirmation</th>
<th>Followup (mths)</th>
<th>Recurrence Type of adenoma</th>
</tr>
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<tbody>
<tr>
<td>Shuangshoti S (1970, 20)</td>
<td>1</td>
<td>N</td>
<td>Y</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Trokoudes KM (1978, 21)</td>
<td>1</td>
<td>N</td>
<td>Y</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Keppes JJ (1978, 11)</td>
<td>1</td>
<td>N</td>
<td>Y</td>
<td>NA</td>
<td>NA</td>
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<tr>
<td>Kurisaka M (1982, 22)</td>
<td>2</td>
<td>N</td>
<td>Y</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Swanson SE (1985, 23)</td>
<td>1</td>
<td>N</td>
<td>Y</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Hiyama H (1986, 24)</td>
<td>1</td>
<td>Y</td>
<td>Y</td>
<td>NA</td>
<td>NA</td>
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<td>Ikeda H (1987, 25)</td>
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<td>Y</td>
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<td>NA</td>
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<tr>
<td>Matsumori K (1987, 26)</td>
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<td>N</td>
<td>Y</td>
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<td>NA</td>
</tr>
<tr>
<td>Nishio S (1987, 13)</td>
<td>9</td>
<td>N</td>
<td>Y</td>
<td>2 to 60</td>
<td>N</td>
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<tr>
<td>Nakasu S (1989, 27)</td>
<td>1</td>
<td>N</td>
<td>Y</td>
<td>NA</td>
<td>GH + Prolactinoma</td>
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<tr>
<td>Ikeda H (1992, 12)</td>
<td>1</td>
<td>Y</td>
<td>Y</td>
<td>NA</td>
<td>NA</td>
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<td>Miyagi A (1993, 28)</td>
<td>1</td>
<td>Y</td>
<td>Y</td>
<td>1</td>
<td>NA</td>
</tr>
<tr>
<td>Nishio S (1995, 29)</td>
<td>2</td>
<td>Y</td>
<td>Y</td>
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<tr>
<td>Sumida M (2001, 14)</td>
<td>8</td>
<td>Y</td>
<td>Y-2</td>
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<td>1</td>
<td>Y</td>
<td>Y</td>
<td>3</td>
<td>N</td>
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<td>Kaku S (2005, 30)</td>
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<td>Y</td>
<td>NA</td>
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<td>Vancura RW (2006, 31)</td>
<td>1</td>
<td>N</td>
<td>Y</td>
<td>NA</td>
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<td>Geller JL (2006, 32)</td>
<td>1</td>
<td>N</td>
<td>Y</td>
<td>NA</td>
<td>NA</td>
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<tr>
<td>Noh SJ (2007, 3)</td>
<td>1</td>
<td>Y</td>
<td>Y</td>
<td>6</td>
<td>N</td>
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<tr>
<td>Koutourousiou M (2010, 1)</td>
<td>2</td>
<td>N</td>
<td>Y</td>
<td>27 to 55</td>
<td>N</td>
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<td>Radhakrishnan N (2011, 9)</td>
<td>1</td>
<td>N</td>
<td>Y</td>
<td>NA</td>
<td>NA</td>
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<tr>
<td>You C (2012, 6)</td>
<td>1</td>
<td>N</td>
<td>Y</td>
<td>NA</td>
<td>NA</td>
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<tr>
<td>Gupta V (2012, 5)</td>
<td>1</td>
<td>N</td>
<td>Y</td>
<td>3</td>
<td>N</td>
</tr>
<tr>
<td>Wang K (2012, 4)</td>
<td>1</td>
<td>N</td>
<td>Y</td>
<td>6</td>
<td>N</td>
</tr>
<tr>
<td>Our series</td>
<td>4</td>
<td>Y-3</td>
<td>Y</td>
<td>0 to 18</td>
<td>N</td>
</tr>
</tbody>
</table>


**Conclusion**

In this paper we describe three patients with unusual combination of pituitary adenoma with RCC. It is difficult to differentiate between them preoperatively due to variable size, position and signal intensity. However when a nonenhancing cyst is incidentally detected by MRI in a patient with pituitary adenoma, the possibility of a coexisting RCC should be considered. Careful analysis of preoperative imaging could prevent incomplete resection of this rare condition.

**References**


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Glycomet<sub>2</sub>/0.3
Metformin HCl 850 mg + Gliclazide 2 mg + Glycerol 6.5 mg

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Clinical Profile, Hepatic Dysfunctions, and Outcome of Dengue Patients in a Tertiary Care Hospital of Eastern India

Divendu Bhushan1*, Ramesh Kumar2

Abstract

**Background:** Dengue is one of the commonest tropical infections in India. This study was aimed to evaluate clinical profile, magnitude and spectrum of hepatic dysfunctions, outcome and clinical predictors of mortality in patients with dengue.

**Methods:** In an observational study, data of 183 consecutive admitted dengue patients were prospectively collected. The magnitude of hepatitis and its association with outcome were studied.

**Results:** The transaminases elevation was seen in 156 (85%) patients, with 21 (11.4%) patients had levels above 10 times the upper normal limit (UNL). Aspartate aminotransferase (AST) showed greater elevation as compared to Alanine aminotransferase (ALT) in 136 (87%) patients. Patients who died (n=8), compared with those who survived (n=175) had higher mean serum bilirubin (3.4 vs. 0.7 mg/dl, p = 0.01), median AST (8791 vs. 138 IU/L, p = 0.02), median ALT (2692 vs 81 IU/L, p = 0.02), median serum creatinine (2.0 vs 1.0 mg/dl, p = 0.007), mean International normalized ratio (3.5 vs 1.1, p = 0.04), and lower median platelet count (20000 vs 60000/mm³, p < 0.001). Among patients who died 87.5% (n = 7) had AST levels greater than 100 times UNL while among patients who survived 93% (n = 162) had AST levels lower than 10 times UNL. In a multivariate analysis, serum bilirubin (≥2.2 mg/dl, OR 4.8) and creatinine (≥1.65 mg/dl, OR 2.8) were found to be independent predictors of mortality.

**Conclusions:** Hepatitis is very frequent in patients with dengue. AST elevation is usually more than ALT elevation. Presence of jaundice and renal dysfunction at presentation are ominous signs in predicting mortality.

Introduction

Dengue is an important arboviral disease in tropical countries. It is one of the commonest mosquito-transmitted diseases, second only to malaria, and it is spread by bite of Aedes mosquito (Aedes aegypti). Globally Dengue is an epidemic in tropical and subtropical areas, affecting around 50 million persons; of this 0.5 million develop dengue hemorrhagic fever and around 20,000 deaths occur every year. The loss to the economy is 264 disability-adjusted life years (DALY) per million of population.

Dengue virus has profound effect on multiple organ systems, the commonest being the liver. A wide spectrum of hepatic manifestations has been described, ranging from mild elevation of serum transaminases to acute liver failure. Despite being one of the commonest tropical infections in India, published data on clinical profile, spectrum of liver involvement, and outcome is still scant in the English literature. Therefore, this study was conducted to evaluate the clinical profile, magnitude and spectrum of hepatic dysfunctions, outcome and clinical predictors of mortality in patients with dengue.

Material and Method

The study was conducted at Paras-HMRI hospital Patna, a tertiary care hospital in eastern India, between July 2015 July to December 2015. During this period, 183 consecutive patients with dengue who required hospitalization were included in this study. Patients with mild uncomplicated dengue fever who did not require hospitalization were excluded from study. The diagnosis of dengue was made on the basis of clinical feature along with positive NS1 antigen and/or positive IgM antibody against dengue virus. The severity of dengue was defined using modified categorization of WHO in 2012 which included dengue with or without warning signs or severe dengue. The consent for including data for the purpose of study was obtained from each patient at the time of enrollment.

A thorough clinical history and examinations were done in all patients at the initial visit. The blood sample were collected for a complete blood count and biochemical investigations including a liver function test, kidney function tests, coagulation profiles, blood glucose, and other test as and when needed. A uniform management protocol was followed which included antibiotics, stress ulcer prophylaxis, monitoring and correction of blood sugar levels, maintenance of mean arterial pressure >60 mm Hg and other supportive treatment. The microbiological surveillance was done to detect infection. Renal replacement therapy was used when required.

Statistical Analysis

Normally distributed continuous variables were expressed as mean (± SD), and the continuous variables with skewed distribution were expressed as median (range). Categorical data were presented as proportion. Comparisons were done using t test for continuous variables and the Chi square (x²) test.
or Fishers exact test for discrete variables, wherever applicable. The baseline variables that independently predicted deaths were identified using multiple regression analysis. The variables with significance p≤0.10 in the univariate analysis were taken in the multivariable analysis. A receiver operating characteristic (ROC) curve technique was used to identify an appropriate cut-off value of predictive variable. Data were analyzed by using GNU PSPP Statistical analysis software.

Results

The baseline characteristics laboratory parameters and outcome of all dengue patients in all are summarized in Table 1. Majorities of all dengue patients in all are expressed as median (range). Categorical data are normally distributed continuous variables are expressed as mean (SD) and the continuous variables with skewed distribution were expressed as median (range).  

Table 1: Baseline characteristics of all patients (N=183)

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Total N=183</th>
</tr>
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<tbody>
<tr>
<td>Age, median (range) (years)</td>
<td>35 (13-78)</td>
</tr>
<tr>
<td>Male: Female</td>
<td>141:42</td>
</tr>
<tr>
<td>Bilirubin, median (range) mg/dl</td>
<td>0.7 (0.1- 9.02)</td>
</tr>
<tr>
<td>Aspartate transaminase (AST), median (range) IU/L</td>
<td>144 (11-45176)</td>
</tr>
<tr>
<td>Alanine transaminase (ALT), median (range) IU/L</td>
<td>86 (12-12260)</td>
</tr>
<tr>
<td>Transaminases Not elevated</td>
<td>27 (15%)</td>
</tr>
<tr>
<td>Transaminases elevated</td>
<td>75 (41%)</td>
</tr>
<tr>
<td>AST/ALT ratio ≥1</td>
<td>136 (77%)</td>
</tr>
<tr>
<td>AST/ALT ratio &lt;1</td>
<td>20 (13%)</td>
</tr>
<tr>
<td>Albumin, mean±SD g/dl</td>
<td>3.4 ± 0.5</td>
</tr>
<tr>
<td>Sodium, mean±SD meq/dl</td>
<td>133 ± 7.6</td>
</tr>
<tr>
<td>Potassium, mean±SD meq/dl</td>
<td>4.6 ± 0.9</td>
</tr>
<tr>
<td>Serum creatinine, median (range) (mg/dl)</td>
<td>1.0 (0.4-3.2)</td>
</tr>
<tr>
<td>Hb, mean±SD gm/dl</td>
<td>13.3 ± 1.9</td>
</tr>
<tr>
<td>PCV mean±SD</td>
<td>41.4 ± 6.4</td>
</tr>
<tr>
<td>TLC, median (range) /mm3</td>
<td>4980 (1620-35430)</td>
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<tr>
<td>Platelet count, median (range) /mm3</td>
<td>60000 (4000-325000)</td>
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<td>INR, median (range)</td>
<td>1.2 (0.9-5.5)</td>
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<tr>
<td>Outcome, n (%)</td>
<td>127 (69)</td>
</tr>
<tr>
<td>Died</td>
<td>88 (48)</td>
</tr>
<tr>
<td>Survived</td>
<td>39 (21)</td>
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</table>

Table 2: Comparison of variables between died and survived patients (univariate analysis)

<table>
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<th>Died N=08</th>
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<td>35 (13-78)</td>
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<tr>
<td>Male: Female</td>
<td>136:39</td>
<td>0.05</td>
<td>0.28</td>
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<tr>
<td>Dengue shock Syndrome (n %)</td>
<td>0</td>
<td>4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Bilirubin, median (range) mg/dl</td>
<td>0.7 (0.1- 6.7)</td>
<td>0.7 (0.1- 6.7)</td>
<td>0.01</td>
</tr>
<tr>
<td>Aspartate transaminase, median (range) IU/L</td>
<td>138 (11-37919)</td>
<td>138 (11-37919)</td>
<td>0.24</td>
</tr>
<tr>
<td>Alanine transaminase, median (range) IU/L</td>
<td>81 (12-932)</td>
<td>81 (12-932)</td>
<td>0.026</td>
</tr>
<tr>
<td>Transaminases levels Within normal limit</td>
<td>27 (15%)</td>
<td>0</td>
<td>0.001</td>
</tr>
<tr>
<td>Transaminases elevation</td>
<td>75 (41%)</td>
<td>0</td>
<td>0.001</td>
</tr>
<tr>
<td>AST/ALT ratio ≥1</td>
<td>136 (77%)</td>
<td>0</td>
<td>0.001</td>
</tr>
<tr>
<td>AST/ALT ratio &lt;1</td>
<td>20 (13%)</td>
<td>0</td>
<td>0.001</td>
</tr>
<tr>
<td>Albumin, mean±SD g/dl</td>
<td>3.8 ± 0.5</td>
<td>3.8 ± 0.5</td>
<td>0.27</td>
</tr>
<tr>
<td>Sodium, mean±SD meq/dl</td>
<td>135 ± 4.0</td>
<td>135 ± 4.0</td>
<td>0.09</td>
</tr>
<tr>
<td>Potassium, mean±SD meq/dl</td>
<td>4.2 ± 0.7</td>
<td>4.2 ± 0.7</td>
<td>0.09</td>
</tr>
<tr>
<td>Serum creatinine, median (range) (mg/dl)</td>
<td>1.0 (0.4-3.2)</td>
<td>1.0 (0.4-3.2)</td>
<td>0.09</td>
</tr>
<tr>
<td>Hb, mean±SD gm/dl</td>
<td>13.3 ± 1.9</td>
<td>13.3 ± 1.9</td>
<td>0.09</td>
</tr>
<tr>
<td>PCV mean±SD</td>
<td>41.3 ± 6.4</td>
<td>41.3 ± 6.4</td>
<td>0.43</td>
</tr>
<tr>
<td>TLC, median (range) /mm3</td>
<td>4900 (1620-35430)</td>
<td>4900 (1620-35430)</td>
<td>0.062</td>
</tr>
<tr>
<td>Platelet count, median (range) /mm3</td>
<td>60000 (4000-325000)</td>
<td>60000 (4000-325000)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>INR, median (range)</td>
<td>1.1 (0.9 - 1.4)</td>
<td>1.1 (0.9 - 1.4)</td>
<td>0.04</td>
</tr>
</tbody>
</table>

Discussion

Dengue is an endemic mosquito transmitted arboviral disease threatening 3.6 billion persons and affecting around 50 million people in 128 tropical and subtropical countries around world annually.4 Near about 75% of exposed people live in Asia pacific region. In India the first case was reported in 1780 in madras (Chennai). Since 1970, several epidemics of dengue
fever (DF) have occurred in different parts of country. Dengue can present as mild self-limiting illness DF, or as dengue hemorrhagic fever (DHF) and dengue shock syndrome (DSS). Though, dengue has been traditionally classified into DF, DHF, and DSS (WHO 1997 Classification), the modified categorization of WHO in 2009 and 2012 include dengue with or without warning sign and severe dengue. The warning signs include abdominal pain or tenderness, persistent vomiting, fluid accumulation like effusions and ascites, bleeding, lassitude, hepatomegaly, or rise in hematocrit (≥ 20%) with rapid reduction in platelet count (< 5000/mm³). The severe dengue which includes DHF and DSS has evidence of severe plasma leakage, bleeding and organ impairment.

Dengue was initially believed to be a disease of childhood but now nearly similar incidences has been seen in older age group. In our study, patients’ age varied from 13-78 years with median age being 35 years. Many studies from south-east Asia suggest that males are more affected than females in DF/ DHF inpatients which may be linked to a gender bias in health seeking behavior. In our study also, 77% of patients were male. Studies in India by Shekhar et al; and in Malaysia by Kabra et al; have reported a higher mortality rates in females which could be due to different pathogenesis and immune response. In our study, the mortality rates in female was 7.1% (03/42) compared to 3.5% (05/141) among male patients. The case fatality due to dengue has declined from 3.3% in 1996 to 0.3% in 2013. In our study, the mortality rate was 4.4%. This higher figure is not only because of referral bias, but also because of the fact that we selectively excluded uncomplicated patients from the study.

The course of illness involves 3 phases-febrile, critical and recovery. Febrile phase last for 2-7 days and is characterized by fever, retro orbital pain, headache, myalgia, arthralgia, nausea, and vomiting. Critical period starts after 3-5 days of fever subsides and patient developed capillary leak, hepatitis, and may leads to DHF. Clinical deterioration often occur in this phase. The DHF is characterised by haemoconcentration, thrombocytopenia and coagulation abnormalities. The DSS which is accompanied by narrow pulse pressure or hypotension has grave prognosis. In our study none of the survived patients had DSS at admission whereas 50% died patients had it at admission.

The prominent gastrohepatic manifestation in dengue involves acute abdomen due to hepatitis, acalculus cholecystitis, shock and pancreatitis. Abdominal pain is an early sign of plasma leakage and become more severe as hypovolemia progresses. The commonest involvement of liver is asymptomatic elevation of transaminases but acute liver failure can also occur in severe DF. In our study, transaminases elevation was seen in 85% patients. Interestingly and contrary to what is seen in viral hepatitis, AST elevation was higher than ALT, and AST/ALT ratio was >1 in 87% of patients. This could be due to extrahepatic release of AST. The AST has various sources such as the liver, heart, muscle, erythrocytes, whilst ALT primarily is hepatic in origin. Similar findings were reported by Chung et al in a large series of patients, and it was attributed to be due to release of AST from damaged monocytes. All patients who did not survive had massive elevation of transaminases, 85% had levels >100 times UNL, and the median serum AST level was 8791 IU/L which was much higher than the median AST levels in survived patients (138 IU/L). The thrombocytopenia was more severe in patients who died than who survived (table 2). However, neither transaminases nor platelet count at presentation had independent role in predicting mortality. In multivariate analysis only serum bilirubin and serum creatinine were found to be independent predictors of mortality. The best discriminatory cut-off values for serum bilirubin and serum creatinine between died and survived patients were 2.2 mg/dl, and 1.65 mg/dl, respectively. When both poor prognostic markers were present at admission, the mortality rate was 83% with sensitivity of 62%, specificity of 99.4%, PPV 83%, and NPV 98%. Therefore, the presence of jaundice and renal dysfunctions at presentation are ominous signs in patients with dengue.

In conclusion, our study found a high prevalence of hepatitis in hospitalized patients with dengue. AST elevation was greater than ALT elevation. The mortality in our study cohort was 4.4%, and the presence of jaundice and renal dysfunctions at presentation predicted mortality independently. An obvious limitation of our study is the hospital based observational study, small sample size and restrictive selection of variables predicting mortality. A confirmatory study using larger sample is needed.

References

Snake Bite Envenomation in a Tertiary Care Centre

Rupal Padhiyar1, Swati Chavan2*, Swapnil Dhampalwar3, Trupti Trivedi1, Nivedita Moulick4

Abstract

Background: In India, it is estimated that up to 20,000 people die annually from snake bites. The present study was carried to out to estimate the snake bite related epidemiology, predictors of severity, relationship between type of snake, clinical severity, complications, outcome and usage pattern of polyvalent anti snake venom (ASV) in a tertiary care center.

Methods: All indoor patients admitted in our institute with definitive history of bite by a snake, with or without presence of fang marks, Evidence of cellulitis, acute onset of neurotoxicity or bleeding diathesis were serially recruited in the study.

Results: The majority of cases were in the range of 21- 40 years (54.7%). There were 82.8% males (53/64), 17.2% females (11/64) and 60.9% (39/64) bites were during day time. Upper limb bites were seen in 34% (22/64) of the patients and lower limb bites in 54% (35/64), and axial body bites in 6%. There were 43.8% (28/64) vasculotoxic bites, 34.4% (22/64) neurotoxic bites and 20.3% (14/64) non-poisonous bites. Viper was the most common (9%) identified snake, followed by krait (5%). References from Rural Health Centers were 57.8% (57/64), 11% were from Primary health centers and rest from private sector. Anti snake venom (ASV) was received by 68.75% (44/64) patients before reaching tertiary care. Local swelling was present in 90.6% (58/64) patients, Systemic bleeding was seen in 35.9% (23/64), and Neuromuscular weakness in 35.9% (23/64) patients. Complications like Respiratory paralysis developed in 18.75% (12/64), Acute kidney injury in 12% (8/64), DIC in 9% (6/64), and hepatic involvement in 7% (5/64) of snake bite patients. Blood transfusion was required in 20.3% (13/64) p<0.001, 18.75% (12/64) required Mechanical ventilation (p=0.001), 4 received hemodialysis and 4 required ionotropic support (p=0.001). Improvement was seen in 57.8% (37/64), morbidity during hospital stay was seen in 39% (25/64) and 2 patients expired (3%). ASV was received within 4 hours in 67% (42/64) patients, 22.5% (14/64) received ASV between 4 to 24 hours and remaining after 24 hours (p=0.016). Total ASV requierment was 24.05 vials in patients who improved and 34.4vials in patients in Morbid group and 29.0 vials in mortality group (p>0.05). The SSS score amongst improved was 4.76 ± 2.46 whereas among morbid, it was 8.48 ± 1.75 and amongst expired, it was 8.5 ± 0.707 (p<0.05).

Conclusions: Patients requiring various supportive treatments like blood transfusion, Inotropes, Haemodialysis and Mechanical ventilation, had a statistically significant correlation with poor outcome. Early administration of ASV that is within 4 hours was, associated with better outcome. The total amount of ASV (in vials) had no a significant correlation with outcome. Snakebite Severity Score correlates significantly with early recovery in vasculotoxic snake bites (p=0.03).

Introduction

Fear of snakes is a powerful, primordial and possibly innate human emotion.1,2 More than 2,00,000 cases of snake bite are reported in India each year. Reports from Maharashtra state in India disclose that an estimated 10000 annual venomous snake bites account for 2000 deaths.3 Morbidity is also significant and there has been little improvement in reducing the fatalities over the years in spite of now having good supplies of polyvalent anti-snake venom (ASV) available. The major reason for high mortality rate is the delay in getting the victim to a well-equipped casualty treatment facility fast enough. Romulus Whitaker, pointed out that, the Indian cobra (Naja naja), the common krait (Bungarus caeruleus), the Russell’s viper (Daboia russelii) and the saw scaled viper (Echis carinatus) are basically four venomous snakes found in India.4,5 In 2009, Snake bite was recognized for the first time by WHO as a tropical neglected disease.6 To make more meaningful use of resources such as anti-venom, mechanical ventilation and renal support systems in patients with snake bite, it is important that the healthcare providers aptly identify those at high risk of potentially fatal complications. Simple demographic and clinical characteristics could be used to help doctors distinguish between high-risk and low-risk patients. The predictors like snake bite severity score are simple, accurate and clinically credible.

The present study was carried to out to estimate the snake bite related demography, clinical characteristics, severity and outcome. An attempt was made to evaluate the predictors of severity, relationship between type of snake, clinical severity, complications, outcome and usage pattern of polyvalent anti snake venom (ASV) in a tertiary care centre in West India.

Methods

This was a prospective, cross sectional study where 64 indoor patients admitted during the study period, were studied with following

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### Aims

1. To study demographic and clinical profile of snake bite patients including first aid received. 2. To study laboratory parameters for assessment of renal and hepatic function and hemorrhology at admission and during in-hospital stay. 3. To evaluate independent predictors of early improvement, assessing the role of ASV administration (early vs. late), in impacting early recovery.

### Inclusion Criteria

Presence of any one of the following qualified the patient for entry into this study.

- Definitive history of bite by a snake, with or without presence of fang marks and with or without local inflammatory signs (i.e. local cellulitis).
- Evidence of swelling, cellulitis, bleeding at local site, but no definitive history of witnessing the snake and fang marks.
- Evidence of acute onset neurotoxicity or bleeding diathesis but no definitive history of witnessing the snake and fang marks. The study was approved by the ethical committee of our hospital.

The demographic characters like age and sex were collected. Age was divided into four subgroups for statistical analysis viz. 0-20, 21-40, 41-60 and more than 60 years. Place of bite in terms of indoor or outdoor bites were recorded. Day time was defined as 7 am to 7 pm and night time from 7 pm to 7 am. Type of Bite: The snakebites with predominant Neur muscular weakness as suggested by ptosis, diplopia, dysphagia were classified as neurotoxic bites. The bites with bleeding and/or coagulation abnormalities were classified as vasculotoxic snakebites.

Snakes were also identified if brought to hospital. First aid received: This was the treatment received, if any, by patients before coming to our hospital like injection tetanus toxoid (TT), anti-snake venom (ASV), neostigmine. Loading dose of ASV given was noted. Patients were referred by private hospitals or by primary health centers (PHC), Rural health centres (RH). Early recovery assessment: In neurotoxic snake bites, early recovery was defined as those which do not require mechanical ventilation and those who required for less than 48 hrs. In vasculotoxic snake bites, early recovery was defined as those not requiring transfusion support and those requiring less than 8 Fresh Frozen Plasma units. Severity assessment: The severity of envenomation is assessed using to the modified snakebite severity score (SSS) according to Dart et al, 1996 and Nualong et al7,8 (Annexure). SSS is a validated tool for assessing Crotalinae snake envenomation. SSS is a composite measure of severity that correlates well with the clinical condition of the patient.

Total score ranges from 0 – 20. Mild envenomation: 0 – 3 points, Moderate envenomation: 4 -7 points, Severe envenomation: 8 – 20 points. The factors that affect SSS like pre-hospitalization period, demographical variables, type of snakebite and the outcome were evaluated. Renal functions, liver functions and coagulation profile for each patient was done. The clinical outcomes were sorted out using three variables, namely improved, morbid state or fatal outcome. The variable ‘improved status’ was defined as state of complete recovery without any supportive management. ‘Morbidity state’ was defined as a state requiring supportive management during hospital stay. The treatment provided was assessed in terms of the quantity of polyvalent anti snake venom vials (ASV) administered during the hospitalization and compared with the severity and outcome. The time lapsed was compared to assess its role in predicting severity and outcome.

### Results

64 indoor patients admitted during the study period, were evaluated. Our study had 82.8% (53/64) male patients and 17.2% (11/64) female patients. The age group of 0-20 years had 21.9% (14/64) patients, 21-40 years had 54.7% (35/64), 41-60 had 20.3% (21/64) and 2 patients above 60 years. Male to Female ratio was 4.81:1. 57.8% (37 out of 64) of our patients were referred from Rural Health Centers, 10.9% from PHC, and 10.9% from private sector. There was predominance of vasculotoxic bites 43.8% (29/64), followed by neurotoxic snakebites 34.4% (22/64), and non-poisonous bite 20.3% (13/64). In identified snakes, viper was the most common implicated, 9% (6/64) followed by Krait 7% and 80% of the snakes were unidentifed. We had 54.6% (35/64) patients with lower limb bites, 34.3% (22/64) patients with upper limb bites, and 4 axial bites. Of the lower limb bites 68.6% (24/35) were vasculotoxic and 40.9% (9 out of 22) bites on upper limbs were neurotoxic. All 4 axial bites were of neurotoxic. Regarding circumstantial and epidemiological factors, bites were more common at night 60.9% (39/64), at outdoor places 64.1% (41/64) and were unprovoked 64.1% (41/64) In our study 62.5% (40/64) patients had received ASV before they were referred to tertiary care centre, 51.6% (33/64) had received Injection Tetanus Toxoid, and 45.3% (29/64) had a tourniquet tied at or above the site of bite. Majority of the patients 90.6% (58/64) had local symptoms (Figure 1) at presentation. Systemic bleeding was present in 35.9% (23/64) of patients, Neuromuscular weakness was also seen in 35.9% (23/64) patients, Oliguria was present in 12.5% (8/64) and Respiratory distress was seen in 21.9% (14/64) patients at presentation.

The mean pulse on presentation was 92/min (58-130/min), Respiratory Rate was 20/min and Blood Pressure was 116/76 mm of Hg. Laboratory parameters on presentation were as shown in Table 1. Whole Blood Clotting

### Table 1: Laboratory parameters on presentation

<table>
<thead>
<tr>
<th>Statistics</th>
<th>Sr Fibrinogen</th>
<th>Hb (gm/dl)</th>
<th>TLC (cumm)</th>
<th>PLT (cumm)</th>
<th>BUN (mg/dL)</th>
<th>Creat (mg/dl)</th>
<th>S. Bili (mg/dl)</th>
<th>RBS (mg/dl)</th>
</tr>
</thead>
<tbody>
<tr>
<td>N Valid</td>
<td>64</td>
<td>64</td>
<td>64</td>
<td>64</td>
<td>64</td>
<td>64</td>
<td>64</td>
<td>64</td>
</tr>
<tr>
<td>Mean</td>
<td>182.22</td>
<td>13.325</td>
<td>12715.62</td>
<td>549.3366</td>
<td>19.02</td>
<td>1.39</td>
<td>1.172</td>
<td>132.08</td>
</tr>
<tr>
<td>SD</td>
<td>40.586</td>
<td>2.5421</td>
<td>5762.96</td>
<td>3421.8924</td>
<td>23.483</td>
<td>1.497</td>
<td>1.1736</td>
<td>48.621</td>
</tr>
<tr>
<td>Minimum</td>
<td>100</td>
<td>1.7</td>
<td>1500</td>
<td>.27</td>
<td>6</td>
<td>0</td>
<td>.6</td>
<td>48</td>
</tr>
<tr>
<td>Maximum</td>
<td>350</td>
<td>18.2</td>
<td>37600</td>
<td>26000.00</td>
<td>155</td>
<td>8</td>
<td>6.9</td>
<td>374</td>
</tr>
</tbody>
</table>

Fig. 1: Blistering and early tissue necrosis following cobra bite
Time (WBCT) >20 minutes was seen in 34.3% (22/64) patients and INR >2 minutes was seen in 23.4% (15/64) patients. Respiratory paralysis was seen in 12 patients (p=0.001), 8 patients had Acute kidney injury (p<0.001), 6 patients went into DIC (p<0.001), and 5 had hepatic complications as shown in Table 2. Respiratory paralysis, AKI, and DIC statistically correlate with outcome. 8 vasculotoxic and 15 neurotoxic snake bite patients required Intensive care. There was no statistically significant difference in ICU stay in vasculotoxic versus neurotoxic snake bites. In terms of supportive management 13 patients required platelet transfusions (p=0.001), 12 patients required Mechanical Ventilation (p=0.001), 4 required ionotropic support (p=0.001), and 4 patients required dialysis (p=0.005). Requirement of supportive treatment had a statistically significant correlation with poor outcome (Table 3). In our study 57.8 (37/64) patients improved, 39% (25/64) had some morbidity during hospital stay and 2 patients expired.

In our study 62.5% (40/64) patients had received ASV before they were referred to tertiary care centre. First dose of ASV was received within 4 hours in 68.75% (44/64) patients, between 4 to 24 hours in 22.5% (14/64) and remaining patients received after 24 hours (Table 4). Timing of first dose of ASV, less than 4 hours correlated significantly with better final outcome (P value 0.016). Total ASV duration among Improved group (N=37) was 1.83 ± 0.8 days whereas among Morbid group (N=25) it was 2.96 ± 1.2 days and among expired group (N=2) it was 3.5 ± 2.1 days. This difference was statistically significant (P < 0.001). Total ASV requirement among Improved group (N=37) was 24.05 ± 19.9 whereas among Morbid group (N=25) it was 34.44 ± 23.7 and among expired group (N=2) it was 29.0 ± 4.23. This difference was not statistically significant (P > 0.05).

The Snakebite Severity score amongst improved patients was 4.76 ± 2.46 whereas in morbid, it was 8.48 ± 1.75 and amongst expired, it was 8.5 ± 0.707. This difference was statistically significant (P < 0.005). The Snakebite Severity score in non-poisonous snake group (14/64) was 2.15 ± 0.37 whereas among vasculotoxic, it was 7.71 ± 2.25 and in neurotoxic bites it was 7.18 ± 1.79. This difference was statistically significant (P < 0.05). A comparison of clinical features of various types of snakes was studied. Maximum cases of ptosis (3/5) were observed among krait bites. Respiratory paralysis was observed among cobra (2/2) and krait (2/5) envenomation. INR derangement on presentation was seen maximally in viper (4/6) envenomations. Acute kidney injury and 20WBCT did not have significant association with individual envenomations.

**Discussion**

The present study was carried to out to estimate the snake bite related epidemiology, clinical characteristics, severity and outcome. An attempt was made to evaluate the predictors of severity, relationship between type of snake, clinical severity, complications, outcome and usage pattern of polyvalent anti snake venom (ASV) in a tertiary care centre in West India. The demographic factors of our study are as follows.

Majority of patients in our study were in age group of 21 – 40 years (54.7%). Mean age was 31.72±12.41 years. Most of the Indian studies like Kularatne et al. Sanjib et al. and in Rojnuckarin et al’s study, the mean age was 31 –32 years. Our study had 82.8% male patients; most of them were in young age group. Similarly there was female clustering seen in age group of 21 to 40 years. Male to Female ratio in our study was 4.81:1. Rojnuckarin et al had majority of male patients (59%). While Sharma et al had a male to female ratio of 4.25:1. This difference is explained by the fact that in age group of 21 to 40 years, where most of clustering of case in both genders seen, it would be expected that these people belong to a working group.

Two fatalities seen in our study belong to age group 21 to 40 and 41 to 60 years each. The difference was statistically not significant when compared with outcome among different age groups when analysed by Chi square test (p=0.211) and One way ANOVA test (p=0.694). Although older people might be expected to have comorbid conditions leading to higher mortality, in cases of acute event like snakebite related mortality which usually occurs in a short period after snakebite, these factors are unlikely to influence it.

57.8% of our patients were referred from Rural Health Centers; 17.2% were self referred, and rest from PHC and Private Hospitals. Referral to our center was made only in case if patient’s condition merited ICU care, with or without ventilator. Kalantri et al reported 37% referral rate in their study, all from PHCs..2 patients who expired were referred from peripheral centres. The higher mortality among referred peripheral cases likely reflects their overall poor general status and hence need for referral. However, there was no statistical significant correlation (p=0.346) of locality with outcome.

Our study shows predominance of vasculotoxic bites (43.8%), followed by neurotoxic (34.4%) and non-
poisonous (20.3%). We also report a case of Myotoxic snakebite with Total CPK elevation and pseudo-infarction pattern on ECG. Sanjib et al.13 had 72% neurotoxic bites in their study. Their study was conducted in Nepal, 27% of the bites being non-poisonous in their study. Sharma14 et al had majority of neurotoxic snake bites (60.6%), their study area being north India. Kalantri et al15 who based their study in rural Maharshtra (in Sevagram); found the incidence of vasculotoxic bite to be 84.27%. Bawaskar et al.16 found 68.45% snakebites to be vasculotoxic in their study done in Mahad in Western Maharshtra. Studies from this part of India have higher incidence of vasculotoxic bites with significant coagulopathy, than neurotoxic bites. In identified snakes, viper was the most common one. Bawaskar et al also found Russell’s viper as the most common snake responsible for snake bites in Western Maharshtra.

This reflects natural habitat of snakes, the predominant snake identified being Russell’s viper, in Maharashtra region. 34% of our patients were bitten on upper limb, 54% on lower limb and 6% had bite on axial body. The site of bite had significant statistical correlation (p<0.001) with the type of bite. 68.6% bites on lower limbs were vasculotoxic. 40.9% bites on upper limbs were neurotoxic followed by non-poisonous bites. All 4 axial bites were of neurotoxic snakes. Upper limb bites, occurred in farmers, while bending over and working or while manually picking crops.13 14 Axial body bites occurred during sleep. This probably reflects the diurnal and bite pattern of different snakes.17 However, the site of bite has no statistically significant correlation (p=0.569) with outcome. Sharma et al12 reported 38% bites on lower limbs; upper limb bites in 47% and 14% axial bites. Kalantri et al.15 noted that 66% bites were on lower limbs, rest being on upper limbs; no axial bites were reported in their study. In our study, majority of bites were in night time (60.9%) as defined from 7 pm to 7 am. Krait bites generally occur at night, whereas viper and cobra bites mostly occur during daytime.17 There was no statistically significant correlation of time of bite with outcome in our study (p=0.159).

62.5% patients received first dose of anti-snake venom (ASV) prior to arrival. 51.6% of our patients received injection tetanus toxoid (TT) prior to arrival at our hospital. 45.3% of our patients arrived with tourniquet in place. In our study, pre-hospital did not have significant correlation with outcome (p=0.170) when compared collectively as shown in Table 16. Kalantri et al13 reported anti-venom use as a first aid in 18% of their patients; 37% had used tourniquets. Sanjib et al10 reported tourniquet use in 88% of their patients.

90.6% patients had local complaints in form of either swelling, pain or bleeding from bite place. Majority of our patients had either systemic bleeding (35.9%) or neuromuscular weakness (35.9%); and oliguria on presentation (12.5%). 14 patients had respiratory distress (21.9%) on presentation. In their study, Kularatne et al12 studied only neurotoxic snake bites; among them ptosis was seen in 70%, diplopia in 54% of cases (n=190). Bawaskar et al.10 reported local swelling (72%) and external ophthalmoplegia (49%) as presenting complaints in vasculotoxic and neurotoxic bites respectively. In our study mean systolic blood pressure (SBP) was 115.09±19.08. Minimum SBP was 76 mmHg and maximum of 170 mmHg. Mean respiratory rate was 19/min±3.4 with a minimum rate of 12/min and maximum of 28/min. Low SBP on presentation was associated with poor outcome. Mean platelet count was 5.4±0.34 lac/cumm with a minimum count of 26,000/cumm. Mean Blood urea nitrogen was 19.02 mg/dl with a maximum value of 155 mg/dl and mean creatinine was 1.39 mg/dl with a maximum being 8 mg/dl.

Mean Serum bilirubin was 1.172 mg/dl with a maximum value of 6.9 mg/dl (Table1). Renal involvement had a statistically significant correlation with poor outcome (p<0.05).

We studied coagulation abnormalities in our patients. Presence of DIC was studied using 20 minutes whole blood clotting time (20WBCCT), prothrombin time (PT) and INR. Serum Fibrinogen level, D-dimer and fibrin degradation products (FDP) levels were not available uniformly and hence not included in our analysis. In our study, prolonged 20WBCCT and INR did not have statistically significant correlation with outcome (p value 0.080 and 0.616 respectively). The non-correlation of prolonged clotting and prothrombin time might be explained by the fact that anti-venom is usually administered promptly in these patients. Rojnuckarin et al11 noted that prolonged clotting time and low platelet count correlated with worse outcome.

On correlating individual organ involvement with outcome (Table 2) neurotoxicity in form of respiratory paralysis, presence of acute kidney injury (AKI) and vasculotoxicity in form of Disseminated intravascular coagulation (DIC) seem to be significantly associated with outcome (p values<0.001). Kalantri et al13 noted the correlation of neurotoxicity and renal involvement as predictors of poor outcome. Kulratne et al noted presence of acute respiratory distress syndrome (ARDS) as predictor of mortality in their study on neurotoxic snake bite. In our study, 13 patients required transfusion (p<0.001), 4 patients required inotropic support (p<0.001), 4 required hemodialysis (p=0.005) and 12 mechanical ventilation (p=0.001). The 2 patients that expired, required all 4 modalities of supportive treatments. They had a statistically significant correlation with poor outcome.

In our study total ASV requirement among Improved group (N=37) was 24.05 ± 19.9 whereas among Morbid group (N=25) it was 34.44 ± 23.7 and among expired group (N=2) it was 29.0 ± 4.23. This difference was not statistically significant. (P > 0.05). Total ASV duration among Improved group (N=36) was 1.83 ± 0.8 days whereas among Morbid group (N=25) it was 2.96 ± 1.2 days and among expired group (N=2) it was 3.5 ± 2.1 days. This difference was statistically significant. (P < 0.001). There is no evidence that shows that low dose strategies,18-20 and initial high dosage loading regimens21 have any validity in India.

The correlation of timing of receiving 1st dose of ASV with outcome is shown in Table 4. In the improved group 65.9% (29/45) patients, 60% (15/25) in morbid group had received ASV within first 4 hours. Both the expired patients received ASV after 4 hours and within 24 hours. In our study early administration of ASV was significantly associated with better outcome (p=0.016). Narvencar K et al22 found a significant difference between early and late administration of Anti-snake venom in terms of mortality benefit. SSS score was calculated for...
SSS was significantly associated with early recovery in vasculotoxic snake bite \((p=0.03)\). Table 5 correlates SSS score with different types of bites. The SSS score amongst non-poisonous snake group was \(2.15 \pm 0.37\) whereas among vasculotoxic, it was \(7.71 \pm 2.25\) and in neurotoxic, it was \(7.18 \pm 1.79\). This difference was statistically significant \((P<0.05)\). The SSS score amongst improved was 4.76 \(\pm 2.46\) whereas among morbid, it was 8.48 \(\pm 1.75\) and amongst expired, it was \(8.5 \pm 0.707\). This difference was statistically significant \((P<0.05)\). Thus SSS can be used to predict outcome. A comparison of clinical features of various types of snakes was studied. A significant association between the type of snake and the occurrence of ptosis without respiratory paralysis, respiratory paralysis and INR is seen \((p<0.05)\). Maximum cases of ptosis were observed among krait bites. Maximum cases of respiratory paralysis were observed among cobra and krait envenomation.\(^{23,24}\) INR derangement on presentation was seen maximally in viper envenomation.\(^{25,26}\) Acute kidney injury and 20WBCT did not have significant association with individual envenomation.

**Limitations of the study**

As this study was conducted at a tertiary care reference center, it does not reflect the true incidence of snakebite in the community. In fact, the study is skewed towards the more severe cases as the latter are predominantly referred to this tertiary care reference center.

**Annexure: Snakebite Severity Score**

<table>
<thead>
<tr>
<th>Date</th>
<th>Time</th>
<th>Pulmonary symptoms</th>
<th>Cardiovascular system</th>
<th>Local wound</th>
<th>Gastrointestinal system</th>
<th>Hematologic symptoms</th>
<th>Central nervous system</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>No signs/symptoms</td>
<td>HR 100-125 BPM, palpitations, generalized weakness, benign dysphasia, or hypotension</td>
<td>No signs/symptoms</td>
<td>No signs/symptoms</td>
<td>No signs/symptoms</td>
<td>No signs/symptoms</td>
</tr>
<tr>
<td></td>
<td></td>
<td>HR 126-175 BPM, or hypotension with SBP &gt;100 mmHg</td>
<td>HR &gt;175 BPM, or hypotension with SBP &lt;100 mmHg</td>
<td>Pain, swelling, or ecchymosis within 5-7.5 cm from bite site</td>
<td>Pain, swelling, or ecchymosis involving less than half the extremity (7.5-50 cm from site)</td>
<td>Pain, swelling, or ecchymosis involving less than half the extremity (50-100 cm from site)</td>
<td>Pain, swelling, or ecchymosis involving more than half the extremity (more than 100 cm from site)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Moderate respiratory distress, 26-40 bpm</td>
<td>Severe respiratory distress, &gt;75 bpm</td>
<td>Pain, swelling, or ecchymosis involving more than half the extremity (more than 100 cm from site)</td>
<td>Pain, swelling, or ecchymosis involving more than half the extremity (more than 100 cm from site)</td>
<td>Pain, swelling, or ecchymosis involving more than half the extremity (more than 100 cm from site)</td>
<td>Pain, swelling, or ecchymosis involving more than half the extremity (more than 100 cm from site)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cynosis, air hunger, extreme tachypnea, or respiratory insufficiency/failure</td>
<td>Coagulation parameters slightly abnormal: PT &gt;20 secs, PTT &gt;50 secs, platelets 50-100 K/mL, or fibrinogen 100-150 mcg/mL</td>
<td>Coagulation parameters abnormal: PT &lt;20-25 sec, PTT &lt;50-75 sec, platelets 50-100 K/mL, or fibrinogen 100-150 mcg/mL</td>
<td>Coagulation parameters abnormal: PT &lt;20-25 sec, PTT &lt;50-75 sec, platelets 50-100 K/mL, or fibrinogen 100-150 mcg/mL</td>
<td>Coagulation parameters abnormal: PT &lt;20-25 sec, PTT &lt;50-75 sec, platelets 50-100 K/mL, or fibrinogen 100-150 mcg/mL</td>
<td>Coagulation parameters slightly abnormal: PT &gt;20-25 sec, PTT &gt;50-75 sec, platelets 50-100 K/mL, or fibrinogen 100-150 mcg/mL</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Dyspnea, minimal chest tightness, mild/</td>
<td>Dyspnea, minimal chest tightness, mild/</td>
<td>Dyspnea, minimal chest tightness, mild/</td>
<td>Dyspnea, minimal chest tightness, mild/</td>
<td>Dyspnea, minimal chest tightness, mild/</td>
<td>Dyspnea, minimal chest tightness, mild/</td>
</tr>
</tbody>
</table>

**References**

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Metformin in Prevention of Type 2 Diabetes

Chamukuttan Snehalatha¹, Susairaj Priscilla¹, Arun Nanditha¹, Raghavan Arun¹, Krishnamoorothy Satheesh¹, Ambady Ramachandran¹

Abstract
Identification and treatment of individuals with prediabetes is crucial. Effective interventional strategies are key to reducing the diabetes risk at the population level. Lifestyle intervention is found to be more effective but more expensive. Evidence of potential benefits from pharmacotherapy is accumulating. The choice of a pharmacologic intervention to reduce the progression of type 2 diabetes (T2DM) in high risk individuals must consider the balance between the benefit to risk ratio. A meta-analysis of the results of the three important studies has shown that metformin used for up to three years decrease the likelihood of progression to diabetes. Metformin showed greater beneficial effect in people with higher baseline Body Mass Index (BMI) and higher Fasting Plasma Glucose (FPG) than in leaner prediabetic counterparts with low FPG concentrations. Besides diabetes risk reduction, the drug has also proved to be cancer and cardio-protective. The National Institute for Clinical Excellence, UK has recommended the use of metformin in prevention of T2DM in adults at high risk on failure to adhere to lifestyle changes. In view of the long standing safety and tolerability, metformin could be prescribed to people who are unable to comply with lifestyle advice.

Introduction
The increasing prevalence of type 2 diabetes (T2DM) constitutes a leading global public health concern. It is estimated that there are more than 318 million people with prediabetes worldwide.¹ According to the American Diabetes Association (ADA) expert panel; up to 70% of individuals with prediabetes will eventually develop diabetes. An interaction of genetic and environmental risk factors causes T2DM and dysglycaemia. Insulin resistance and β-cell dysfunction are genetically determined, and weight gain and physical inactivity aggravate these inherited metabolic abnormalities. Current evidence explains a two-step development of T2DM.² Primarily in normal glucose tolerant (NGT) individuals, development of insulin resistance causes impaired glucose tolerance (IGT). At this stage, plasma insulin levels are elevated but β-cell compensatory hyperinsulinemia occurs due to β-cell insufficiency. Consequently, IGT advances to T2DM because of a progressive decline in β-cell function and insulin sensitivity increases further (Figure 1). The progressive decline in insulin sensitivity and β-cell function in prediabetes should be arrested or reversed. Persons with prediabetes are also at a high risk of damage to the micro and macrovasculature.

Persons with IGT characterized by postprandial (2 hr plasma glucose 140 mg to ≤199 mg/dl) and fasting (110 mg/dl to ≤125 mg/dl) hyperglycaemia are at increased risk for the development of diabetes and are the target population for interventions which prevent or delay the onset of T2DM. Lifestyle modifications involving healthy dietary habits, regular physical activity have been shown to aid in prevention of diabetes. But the long-term adherence is often difficult, limiting their effectiveness. Pharmacotherapy has also shown the benefit with respect to diabetes prevention.

A few pharmacological agents such as metformin, thiazolidinediones, acarbose, drugs for weight loss and basal insulin have also proven to be effective in preventing the progression to diabetes in high risk subjects. They are likely to act through a number of mechanisms, in addition to weight control or reduction.³ This review revisits the utility of metformin in diabetes risk reduction and metabolic disorders and the safety profile of the drug.

Metformin is a biguanide that has been in use for decades to treat diabetes. Efficacy and safety of metformin in the management of T2DM is well established.³ It has the advantage that it is rarely associated with hypoglycaemia unless used in conjunction with insulin secretagogues such as sulphonylureas or insulin. Metformin has beneficial effects on body mass index (BMI) and lipid concentrations and has been proven to be safe showing no serious adverse effects.⁴ Besides acting as an oral hypoglycaemic agent, it has been used with diet and physical activity to prevent diabetes in people at high risk. It is also used in treating polycystic ovarian syndrome and gestational diabetes in women.

Metformin reduces plasma glucose level by several different mechanisms, in particular through non-pancreatic mechanisms without increasing insulin secretion. It sensitizes the effects of insulin; hence, termed “insulin sensitizer”. Metformin also suppresses the endogenous glucose production by the liver, which is mainly due to a reduction in the rate of gluconeogenesis and a small effect on glycogenolysis.

Moreover, metformin activates the enzyme adenosine monophosphate kinase (AMPK) resulting in the inhibition of key enzymes involved in gluconeogenesis and glycogen synthesis in the liver while stimulating insulin signaling and glucose transport in muscles. AMPK regulates the cellular and organ metabolism and

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Any decrease in hepatic energy, leads to the activation of AMPK. Furthermore, metformin increases the peripheral glucose disposal that arises largely through increased non-oxidative glucose disposal into skeletal muscle.\(^8\)

The major side-effect of metformin is gastrointestinal irritations which can be minimized by smaller doses or by using prolonged–released formulations.\(^9\) The risk of lactic acidosis is extremely rare. Vitamin B12 deficiency, if occurs can be reduced with supplementation of the vitamin.

Metformin is first line recommended therapy for T2DM according to the International Diabetes Federation Global Guidelines for T2DM, in agreement with similar guidelines from the ADA, as well as the European Association for the Study of Diabetes (EASD).\(^9,10\) The ADA Consensus Conference also recommended that high-risk individuals (Hba1c ≥ 6.0%; body mass index ≥ 30 kg/m\(^2\); age ≤ 60 years) with IGT or Impaired Fasting Glucose (IFG) be treated with metformin.\(^11\)

**Studies in Primary Prevention using Metformin**

Several drugs have been successfully used in the prevention of T2DM; among them metformin has been studied extensively in different populations for prevention of diabetes.

The BIGPRO (BIGuanides and the Prevention of the Risk of Obesity) study was one of the earlier studies designed to investigate whether metformin, used in combination with lifestyle modification, could modify the metabolic abnormalities associated with insulin resistance in persons without diabetes but with central adiposity (high waist-to-hip ratio).\(^12\) Compared with placebo, this combination produced significant weight loss, better maintenance of fasting blood glucose, total and LDL cholesterol levels, and a greater decrease of fasting plasma insulin concentration. This was an early observation that suggested metformin would be a suitable candidate for long-term intervention treatment for the prevention of diabetes.

In the US Diabetes Prevention Programme (DPP) use of metformin (1700 mg/day) resulted in a 31% relative risk reduction (RRR) in the incidence of T2DM in subjects with IGT during a median follow-up period of 2.8 years.\(^13\) Its effectiveness was lower compared to that of intensive lifestyle modification (LSM) (58%). The effectiveness of intervention was largely attributable to weight reduction as subjects recruited were largely overweight or obese. In the LSM group nearly 5% developed diabetes per year compared to 7.8% metformin and 11% in the placebo group. During the extended follow-up; Diabetes Prevention Program Outcomes Study (DPPOS),\(^14\) both metformin and lifestyle intervention showed long-term beneficial effects, but did not reduce microvascular complications (Table 1).

The Indian Diabetes Prevention Programme-1 (IDPP-1) conducted in subjects with IGT compared the effectiveness of moderate but consistent LSM and treatment with metformin in smaller doses (500 mg/day) vs a control group.\(^15\) A combination of LSM and metformin was also used. This study in comparatively non-obese, Asian Indian subjects showed that all three modalities of intervention had approximately 28% RRR in relation to the control group in the incidence of diabetes in a period of 3 years. Thus, metformin was found to be equally effective as LSM in reducing the incidence of diabetes among subjects with IGT (Table 1).

The Chinese DPP, evaluated the effects of diet and exercise, acarbose and metformin on the incidence of T2DM in 321 subjects with IGT.\(^16\) During the mean study period of 3 years, glycaemic level deteriorated in the control group. In the LSM group, the fasting plasma glucose increased slightly with beneficial changes in postprandial plasma glucose; and in the drug treated group, both the glycaemic indices showed significant reduction. Beneficial changes were seen with acarbose and metformin in reducing the risk of diabetes. The RRR with metformin (750 mg/day) was 77%, while it was 88% in the group treated with acarbose (Table 1).

A study in 631 subjects with IFG using acarbose and metformin compared to placebo showed that metformin was more effective at 3 years than acarbose in reducing the incidence of diabetes vs placebo (8%,37% RRR respectively).\(^17\) At a 6 year followup, there was a significant risk reduction with acarbose (0.66) but not with metformin (1.09) for subjects with IGT at baseline. Probably, there could be difference in the effectiveness of therapy in subjects with IFG/IGT.

A meta-analysis of randomized trials of at least 8 weeks of metformin use compared with placebo or no treatment in non-diabetic persons was performed.\(^18\) The analysis of 31 trials with 4570 participants followed for 8267 person-years showed that incidence of diabetes was reduced by 40% with an absolute risk reduction of 6%. During the mean trial duration of 1.8 years, significant improvement in body weight, lipid profile, insulin resistance and benefit on incidence of diabetes were noted.

**Results of the Canadian Normoglycemic Outcomes Evaluation (CANOE)\(^19\)** trial in 207 subjects with IGT, randomly assigned to receive a combination of 2 mg rosiglitazone and 500 mg metformin twice daily or matching placebo for a median of 3.9 years showed that the combination was highly effective in preventing type 2 diabetes (Table 1).

Observational studies in insulin resistant adults have shown metformin use can reduce the incidence of diabetes with reduced fasting glucose and atherogenic lipid fractions.\(^20\)

**Prevention of T2DM in Women with Gestational Diabetes Mellitus (GDM)**

Metformin has been found to be effective and safe for the treatment of GDM, particularly in overweight and obese women. Recently, the Endocrine Society has confirmed the use of metformin during pregnancy and also recommended it as a first-line treatment of cutaneous manifestations, for prevention of pregnancy complications, and for the treatment of obesity.\(^21\) In the DPPOS, women with a history of GDM assigned to the placebo group had a 48% higher risk of progressing to T2DM.
than women without a history of GDM. The study specifically examined 350 women with a history of GDM and 1416 women with previous live births but no GDM. Among those who had GDM, both intensive lifestyle intervention and metformin reduced progression to diabetes compared with placebo by 35% and 40% respectively. However, among women with no prior GDM, metformin had no impact while intensive lifestyle intervention reduced progression to diabetes by 30%.

### Weight Loss

Obesity is the most important causal factor for progression of IGT to diabetes and is primarily responsible for the rising trend in T2DM. Weight loss achieved via lifestyle modification or pharmacologic intervention enhances insulin sensitivity thereby improving glucose tolerance in IGT individuals. Metformin reduces insulin resistance which is the underlying cause of both obesity and PCOS in non-diabetic persons. Improving insulin sensitivity may account for weight reduction under metformin therapy. Effect of metformin on weight loss has been reported in several trials. Results of the studies by the Diabetes Prevention Program Research Group found metformin most effective in obese participants (baseline BMI > 35 kg/m²), with a 53% reduction in the incidence of diabetes, and in participants <45 years of age, with a 44% reduction. Metformin had little benefit for older individuals who were 60–85 years of age at baseline. The effectiveness of metformin was attributed in part to weight loss, which averaged 1.7 kg and accounted for 64% of the beneficial effect of metformin. Importantly, after an average of 10 years of follow-up, the metformin group had maintained an average weight loss of 2.5 kg, and diabetes risk was reduced by 18% compared to the former placebo group. The mean weight change at 1 year was 22.7 kg in the metformin group and 20.4 kg in the placebo group. However, adherence to metformin did not impact the waist circumference during the first two years.

Studies conducted in India and China reported similar reductions in diabetes risk. In a study comparing metformin, exercise (about 190 minutes per week), and the combination of the two in persons with impaired glucose tolerance, metformin and metformin plus exercise decreased body weight more than exercise alone.

### Cost Effectiveness

T2DM causes increased mortality and morbidity at a younger age than in the normal population. Management of the disease is costly and being a chronic disorder it requires constant medical care. In 2012, the ADA estimated that the cost incurred due to diabetes was $306 billion as direct medical costs and $680 billion as indirect costs. In the UK Prospective Diabetes Study, metformin was found to produce decreased risk of myocardial infarction compared to other intensive therapy in overweight persons (hazard ratio (HR) 0.61, 95%-CI 0.51–0.81; p = 0.001). The risk reduction for myocardial infarction persisted in the metformin group during 10 years of post-trial observational follow-up (HR 0.67, 95%-CI 0.51–0.89; p = 0.005), despite an early loss of glycated haemoglobin (HbA1c) differences between treatment groups, suggesting a legacy effect of early intensive glucose-lowering therapy with metformin for obese patients. However, a cardioprotective effect of metformin in excess of that conferred by its glucose-lowering ability have not been confirmed based on meta-analyses from large and small trials. To date, prospective cardiovascular outcome trials with metformin are sparse.

Epidemiologic evidence from large cohort metformin studies suggests benefit for several types of cancers. A meta-analysis of 11 observational studies showed a 31% reduced risk of cancer in those taking metformin compared to other antidiabetic drugs. Preclinical studies have shown that metformin can inhibit the growth of cancer cells in vitro and in vivo and provide evidence for a direct, insulin-independent anti-tumour effect. Metformin has shown strong antiproliferative effects on colon, pancreatic, breast, ovarian, prostate and lung cancer cells. Preclinical studies have also shown reliable anti-tumoral effects in different animal models. A clinical trial has demonstrated beneficial effect in colon and breast cancers.

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**Table 1: Randomized trials on primary prevention using metformin**

<table>
<thead>
<tr>
<th>Study (year)</th>
<th>Population patients in each group</th>
<th>Medication (mg)</th>
<th>Duration (Years)</th>
<th>Cumulative incidence in control (%)</th>
<th>Relative risk reduction % (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>DPPOS (2009)</td>
<td>Multi ethnic (910:924)</td>
<td>Metformin: 850/twice daily</td>
<td>8</td>
<td>Metformin 4.9-100 person years (4.2-5.7)</td>
<td>18 (7-28)</td>
</tr>
<tr>
<td>CANOE (2011)</td>
<td>Multi ethnic (103:104)</td>
<td>Rosiglitazone: 4/day and metformin: 1000/day</td>
<td>3.9</td>
<td>39</td>
<td>66 (41-80)</td>
</tr>
</tbody>
</table>

NR: Not reported
Controversies on the use of Metformin

Despite the several studies on the efficacy of metformin in reducing the incidence of diabetes there has been an active debate as to the rationale and benefit for using metformin as a pharmacological agent to delay or prevent diabetes progression. The American Diabetes Association in its “Standards for Medical Care in Diabetes” guidelines, 2013 has recommended metformin for use in diabetes prevention for those at very high risk, under the age of 60, are severely obese, or have a history of gestational diabetes.31 However, according to a study conducted between 2010 and 2012, metformin is still a rarely prescribed drug for prediabetes. Data obtained from a retrospective study conducted in a large private insuring company in the US found that among 17,352 adults aged 19 to 58 with pre-diabetes, metformin was prescribed for only 3.7% of individuals with prediabetes for over three years. Among those with a BMI ≥ 35 kg/m² or gestational diabetes the prevalence of metformin prescription was 7.8%.32

The major argument that drugs such as metformin could merely mask hyperglycaemia by reducing the blood glucose levels remains a matter for debate. More evidence on improved long-term outcomes in metformin – treated prediabetic persons is required.

Major international guidelines from expert groups in the US, Europe and the International Diabetes Federation favour the use of metformin as the second line intervention. The 2015 Position Statement from the American Diabetes Association recommends that metformin has the strongest evidence base of pharmacological agents for diabetes prevention.33

The reasons for the limitations in the use of metformin are still unclear. A possibility could be that the outcome of the evidence based trials is not fully realized in practicality by the caregivers. Also, metformin is not approved by the US Food and Drug Administration (FDA) for prediabetes, which may increase hesitancy to prescribe it “off label” in this context.

Conclusions

In the primary prevention of diabetes, use of metformin is proven to be effective and safe. Several long-term studies such as the DPPOS have shown the long-term effectiveness of the drug. The possible side-effects are minimal compared to other pharmacological agents used in prevention of diabetes. The major action of the drug is by improving insulin sensitivity and also partially by reduction in weight. On account of the relative safety and efficacy, expert groups such as the ADA, International Diabetes Foundation, EASD and the National Institute for Clinical Excellence, UK have recommended the use of metformin as the second-line intervention for individuals at high risk of developing diabetes.

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Amlodipine in the Era of New Generation Calcium Channel Blockers

Mangesh Tiwaskar¹, Amit Langote², Resham Kashyap³, Archana Toppo⁴

Abstract
Amlodipine is a classical drug with varied properties extending from control of blood pressure to as an antianginal and anti atherosclerotic agent. Amlodipine is a longer acting dihydropyridine calcium channel blocker, effective for 24 hours BP control and cause no BP variability. It is a powerful, well-tolerated, and safe antihypertensive agents that is widely used either alone or as a key component of combination therapy for hypertension. Its effective BP reduction has shown proven benefits in cardiovascular event reduction that is supported with strong evidences from large randomised controlled trials. Combination therapies of amlodipine with other agents eliciting renin-angiotensin-aldosterone system blockade (angiotensin II receptor blockers or renin inhibitors) have shown effective blood pressure lowering strategies in CV risk reduction and progression of renal disease. Novel type of calcium channel blockers have been developed which have additional properties of blocking T and N subtypes of calcium channels and apart from their class effects they exerts specific action on heart rate and renin aldosterone system. They are considered to be more renoprotective due to this additional properties. Amlodipine is most potent and longer acting agent compared to the newer CCBs, its effectiveness in BP lowering still makes it the agent of choice among all the CCBs.

Hypertension a universal public health hazard, a leading cause of mortality and ranked third as a cause for disability-adjusted life years.¹ It affects approximately 26% of the population worldwide, nearly 45% of deaths by heart disease and 51% of deaths by stroke are due to hypertension; accounting for 9.4 million deaths worldwide every year.² ³ In India, its prevalence varies from 20-40% in urban to 12-17% in rural areas. It is estimated that the prevalence of hypertension might rise to 214 million by 2025.⁴ For the management of hypertension various classes of antihypertensive drugs are available such as diuretics, β-blockers (BB), α blockers, calcium channel blockers (CCBs), angiotensin converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) that can be used as monotherapy or in combination.⁵ Dihydropyridine calcium channel blockers are a class of powerful, well-tolerated, and safe drugs widely used is in the management of elevated blood pressure (BP) as a monotherapy or as a key component of combination therapy for hypertension. The initial indication, besides hypertension, also includes angina and peripheral vascular disease.⁶⁷ Amlodipine was introduced in early 90’s has many unique qualities that set it apart from other agents in this class. It is a third generation Dihydropyridine (DHP) calcium antagonist, with high selectivity for vascular smooth muscle, has minimal impact upon heart rate, and no negative inotropic effects or electrophysiological disturbances.⁸ It is an extensively studied classical drug with varied properties extending from control of blood pressure to as an antianginal and anti atherosclerotic agent. The newer generation DHP's block L/N type calcium channel of which cilnidipine is considered more renoprotective. Amlodipine, despite of the new generation CCBs, it still remains one of the top global pharmaceutical products. Its effectiveness in lowering blood pressure in addition to high tolerability and minimal side effects have made it an agent of choice in both single and combination drug treatment for reducing the burden of cardiovascular disease across the globe.⁹ The aim of the review is to assess the potential advantages of amlodipine above the new DHPs with a focus of its benefits in varied cardio vascular diseases.

Pharmacodynamics and Pharmacokinetics
Calcium channels (Ca²⁺) are classified into at least six subtypes; namely, L-, N-, P-, Q-, R-, and T-type, based on electrophysiological and pharmacological evidence. L-type of voltage-gated calcium channel blockers (CCBs) are potent vasodilators and often used as a first or second line drug in management of hypertension. Amlodipine, is a longer acting DHP, no longer considered as L-type-specific Ca²⁺ channel blockers (Figure 1). Studies have shown, that amlodipine and cilnidipine blocked N-type Ca²⁺ channels as well.¹⁰¹² Amlodipine along with benidipine, cilnidipine, nicardipine, and barnidipine significantly blocked N-type and P/Q-type Ca²⁺ channels. Amlodipine profoundly blocks the N-type Ca(2+) channels with high affinity[(3)H]amlodipine (K(d), 3.08nM and high potency (IC(50), 2.7 microM at -60mV.¹³

Amlodipine inhibits the transmembrane influx of calcium ions into vascular smooth muscle cells and myocardial cells. It is a peripheral arterial vasodilator that acts directly on vascular smooth muscles

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Amlodipine has a gradual onset of action and hence no significant reflex activation of the sympathetic nervous system. Amlodipine has the longest half-life of all DHPs with a plasma elimination half-life of 35-40 h, longest among all CCBs. It is usually dosed on a once daily basis which is favourable for patient compliance.

A starting dose of 5 mg is usually recommended with a maximum daily dose of 10 mg. In the elderly population and those with hepatic failure, a starting dose of 2.5 mg is recommended. Amlodipine has a gradual onset of action and hence no significant reflex neuroendocrine activation. Activating reflex mechanisms, such as increased peripheral vascular resistance and elevated heart rate, can cause negative effects on lipid and carbohydrate metabolism. These notable adverse effects are commonly seen with other agents including the first generation β-blockers (BBs; such as atenolol and metoprolol) and earlier generation DHPs. Amlodipine has a high bioavailability, ranging from 60% to 80%; it undergoes hepatic metabolism and shows some impaired elimination in the setting of liver cirrhosis but no accumulation with renal failure. Amlodipine also has a slow rate of elimination over 40–60h. If amlodipine is discontinued, BP generally returns to baseline over 1 week without any dangerous rebound elevations in BP (unlike clonidine). Novel type of CCBs have been developed which have additional properties of blocking T and N subtypes of calcium channels and apart from their class effects they exerts specific action on heart rate and renin aldosterone system. Cilnidipine through its dual L/N-type calcium channel blocker property presumed to effectively suppress neurohumoral regulation of cardiovascular system by inhibition of sympathetic over-activity and modulation of the renin-angiotensin-aldosterone system. In addition to blood pressure lowering effects these novel drugs are anticipated to provide organ protection in management of hypertension.

### 24 Hours BP Control

Both the magnitude of BP reductions and the control of BP variability may be important in the prevention of Cardiovascular and cerebrovascular events. Ambulatory blood pressure monitoring (ABPM) provides an opportunity to obtain measurements of BP throughout the 24 h period during an individual’s normal daily routine. Amlodipine has the longest elimination half-life and slow receptor dissociation kinetic, it shows a gradual and prolonged reduction in BP. A high trough to peak concentration (T:P =0.85) and high smoothness index (SI) indicates that amlodipine is consistent in BP reduction throughout 24 hours. In a meta-analysis of 5188 patients in 11RCTs, amlodipine 5mg and telmisartan 80mg had similar SI which was higher than all ARBs. Across the CCBs, the 24h SI value for amlodipine 5mg was higher than those of manidipine, lercanidipine, nifedipine felodipine and diltiazem.

### Blood Pressure Variability

BP variability (BPV) is independent risk factor for CVD events and target organ damage. A 3 year follow up study by Sander et al has shown that greater than 15-mm Hg s.d. of daytime SBP increases the risk of development of early atherosclerosis and CV events. Early morning BP surges (EMBPS) a transient increase in both Systolic BP (SBP) and diastolic BP (DBP) during the morning hours around the time of rising, is one pattern of variability linked with target organ damage and cerebrovascular events. A 10-mm Hg increase in the EMBPS has been shown to increase stroke risk by 22%, independent of age and average 24 h BP. Also a long-term increase in average BP values is risk factor for endothelial dysfunction leading to atherosclerosis, and a relatively short term exaggerated BPV may trigger an atherothrombotic CVD event.

According to Anglo Scandinavian Cardiac Outcomes Trial - Blood Pressure Lowering Arm (ASCOT-BPLA) trial a good control of mean BP but greater residual SBP had a 5 times higher risk of stroke than those with lower variability values hence Visit-visit variability (VVV) is a key predictor of the long-term risk of stroke after transient ischemia. ASCOTBPLA compared Amlodipine-based regimens with Atenolol-based regimens in 19,257 patients with hypertension and other vascular risk factors. It was found that within-visit, VVV and ABPM BPV were all reduced by amlodipine irrespective of its effect on mean BP, whereas BPV increased with Atenolol-based regimen. A significant reduction in CV event, mortality and stroke was observed in amlodipine group compared to atenolol. Similarly in the XCELLENT trial Amlodipine significantly decreased daytime, night-time and 24-hrs SBP; whereas Indapamide SR significantly decreased SBP in the daytime and 24 hours. Amlodipine was efficacious across all time-frames even after adjustment for mean BP reduction.

Antihypertensive and Lipid Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) showed that even after...
adjusting for mean BP, Amlodipine and Chlorthalidone reduced VVV BPV to a greater extent than Lisinopril. A pooled analysis of five studies (47,558 BPV-evaluable patients, duration varied from 4 months to 6 years) showed that BPV with amlodipine was significantly (P < .0001) lower compared to atenolol, lisinopril, enalapril. Treatment difference (standard error) was −1.23 (0.46; P = .008) mm Hg for amlodipine vs all active comparators. These findings suggest that amlodipine is effective for minimizing BPV.

**Side Effect Profile**

The most commonly reported adverse effect hindering compliance with amlodipine is peripheral oedema. However, this adverse effect can be minimised if the agent is given at bedtime, and lower doses (2.5 or 5 mg/day) are used. Other reported side effects include dizziness, fatigue, headache, palpitations and nausea, although these are generally not bothersome enough to cause discontinuation of the drug. Also, its vasodilatory effect can lead to decreased cardiac output in the setting of aortic stenosis.

Angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) cause post capillary dilation and normalize hydrostatic pressure, and are thus ideally suited for prevention/reversal of CCB-induced oedema. ARB/CCB and ACEI/CCB combination therapy is also more effective than CCB monotherapy in controlling blood pressure. These combinations represent an important advance in the management of hypertension. Although the incidence of oedema recorded in the CCB monotherapy groups varies widely (range, 4.9–34.4%), the data are consistent in showing lower rates of this side effect in the patients who receive ACEI/CCB or ARB/CCB combination therapy. For example addition of olmesartan medoxomil 40 mg to amlodipine 10 mg reduced the placebo-subtracted rate of oedema by more than 50%. In an additional study, the incidence rate of peripheral oedema was lower with valsartan and amlodipine in combination (5.4%) than with amlodipine monotherapy (8.7%).

**Amlodipine in Diabetes with Microalbuminuria**

Endothelial dysfunction alters the structural and functional effects on the target vessel. Endothelial dysfunction within the glomerular basement membrane may modify glomerular barrier permeability, thus leading to the excretion of albumin to the urine. In diabetic patients presence of microalbuminuria helps in early diagnosis of incipient diabetic nephropathy. Microalbuminuria is considered as an independent risk factor for renal impairment, cardiovascular disease and premature mortality. An early intervention may retard the progression to end-stage renal disease (ESRD). CCBs are not always able to protect against kidney injury, as was shown in the Renoprotection in Patients with Nondiabetic Chronic Renal Disease (REIN)-2. And, in Gauging Albuminuria Reduction with Lotrel in Diabetic Patients with Hypertension (GUARD) trials, the antialbuminuric effect of CCB was weaker than that of diuretics in RAS inhibitor-treated hypertensive patients with type 2 diabetic nephropathy. The uncertain renoprotective effects of L-type CCBs may be due to the presence of L-type calcium channels at the afferent but not efferent arterioles. L-type CCBs cause afferent arteriole-specific vasodilatation, which increases the glomerular pressure. This adverse action of L-type CCBs in the glomerular microcirculation counteracts their ability to attenuate glomerular hypertension through the systemic decrease in BP. Thus, the use of L-type CCBs is not always beneficial in patients with renal dysfunction. In contrast, L/ N -type CCBs are able to inhibit renal sympathetic nerve activity and cause efferent arteriolar vasodilation. Thus, protect the glomeruli through the attenuation of glomerular hypertension. Since, L-type calcium channels do not express glomerular hyperfiltration (which may underlie the initiation and progression of DN) are by increases in the levels of hormones, such as insulin-like growth factor 1, atrial natriuretic peptide, intracellular accumulation of sorbitol and protein glycosylation, and activated tubuloglomerular feedback, which are caused by increased tubular sodium reabsorption through hyperinsulinemia and hyperglycemia. Sympathetic nerve activation is not thought to be a major mechanism of glomerular hyperfiltration in DN. The lack of a clear difference in the antialbuminuric effects of cilnidipine and amlodipine in the present study may be due to the marginal contribution of sympathetic nerve activation to the progression of DN.

**Amlodipine and Atherosclerosis**

Amlodipine has a potential benefit in atherosclerosis. It prevents the formation of free radicals thus averting the oxidative damage to the lipid bilayer. Zhang and Hintze in preclinical study found that amlodipine increased NO production in canine coronary microvasculature, which could be another plausible antiatherosclerotic effect. Additionally,
Amlodipine has been shown to up regulate the expression of interleukins, which may also have antiproliferative effects, and to have favourable effects on extracellular matrix remodelling.

The PREVENT trial was a placebo controlled prospective randomized trial to study the effect of amlodipine upon atherosclerotic progression in patient with established CAD. Amlodipine reduced the progression of atherosclerosis in the carotid arteries as assessed with B-mode ultrasonography. Amlodipine had a significant effect in slowing the 36-month progression of carotid artery atherosclerosis: the placebo group experienced a 0.033-mm increase in Intima Media Thickness. Amlodipine also reduced coronary revascularizations (53 versus 86, HR 0.57 [0.41 to 0.81]) regardless of the use of β-blocker, nitrates, or lipid-lowering therapy. Fewer events in the amlodipine group compared to placebo (86 versus 116, HR 0.69 [0.52 to 0.92]), mostly attributable to a difference in unstable angina and revascularization. These beneficial effects were not seen in previous angiographic trials with nifedipine or nicardipine in patients with stable coronary artery disease even though with proved antianginal effects, suggestive of fact that amlodipine may have an additional effects.

The Comparison of Amlodipine vs Enalapril to Limit Occurrences of Thrombosis (CAMELOT) study compared amlodipine and enalapril, with placebo in normotensive patients with CAD. Amlodipine group vs placebo (P=0.12), showed a trend towards less progression of atherosclerosis which was significant in patients with higher systolic blood pressure.

In the randomised trial Coronary Angioplasty Amlodipine Restenosis Study (CAPARES), patients had a reduced incidence of repeat percutaneous transluminal coronary angioplasty when treated with amlodipine.

### Amlodipine and Angina

Antianginal efficacy of amlodipine, is mediated by the amlodipine-induced dilation of coronary arteries and reduction in total peripheral resistance, decreasing the occurrence of symptomatic angina, and silent MI.

In the PREVENT trial wherein 68% of participants had history of angina, amlodipine showed a significant reduction in hospitalization for unstable angina compared to placebo (HR: 0.67, 95% CI: 0.48–0.93). In ASCOT-BPLA, amlodipine vs atenolol significantly reduced unstable angina (HR: 0.68, 95% CI 0.51–0.92; P <0.015) but had no significant effect on chronic stable angina (HR: 0.98, 95% CI: 0.81–1.19).

### Table 1: Cardiovascular event and outcome with amlodipine in landmark trials

<table>
<thead>
<tr>
<th>Trials</th>
<th>Intervention</th>
<th>No. of patients</th>
<th>No. of events</th>
<th>Odds ratio 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>AML vs ACEi</td>
<td>AASK45</td>
<td>Ramipril</td>
<td>436</td>
<td>23</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Amlodipine</td>
<td>217</td>
<td>5</td>
</tr>
<tr>
<td>ALLHAT46</td>
<td>Lisinopril</td>
<td>9054</td>
<td>457</td>
<td>796</td>
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<tr>
<td></td>
<td></td>
<td>Amlodipine</td>
<td>9048</td>
<td>377</td>
</tr>
<tr>
<td>AML vs ARBs</td>
<td>VALUE47</td>
<td>Amlodipine</td>
<td>796</td>
<td>281</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Valsartan</td>
<td>7649</td>
<td>322</td>
</tr>
<tr>
<td>IDNT48</td>
<td>Irbesartan</td>
<td>567</td>
<td>15</td>
<td>27</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Lisinopril</td>
<td>579</td>
<td>28</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Amlodipine</td>
<td>2349</td>
<td>47</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Candesartan</td>
<td>2354</td>
<td>60</td>
</tr>
<tr>
<td>AML vs Diuretic</td>
<td>ALLHAT49</td>
<td>Chlorthalidone</td>
<td>15255</td>
<td>675</td>
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<tr>
<td></td>
<td></td>
<td>Amlodipine</td>
<td>9048</td>
<td>397</td>
</tr>
<tr>
<td>ACCOM-PLISH50</td>
<td>Amlodipine</td>
<td>5744</td>
<td>112</td>
<td>125</td>
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<td></td>
<td></td>
<td>HCTZ</td>
<td>5762</td>
<td>133</td>
</tr>
<tr>
<td>AML vs BB</td>
<td>ASCOT-BPLA51</td>
<td>Amlodipine</td>
<td>9639</td>
<td>327</td>
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<tr>
<td></td>
<td></td>
<td>Atenolol</td>
<td>9618</td>
<td>422</td>
</tr>
</tbody>
</table>

Adapted from Seung-Ah Lee et al. Korean J Intern Med 2014;29:315-324; AASK The African American Study of Kidney Disease and Hypertension; ALLHAT Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial; IDNT Irbesartan diabetic nephropathy trial; ASCOT Anglo-Scandinavian Cardiac Outcomes Trial; VALUE Valsartan Antihypertensive Long-Term Use Evaluation; CASE J Candesartan Antihypertensive Survival Evaluation in Japan; ACCOMPLISH The Avoiding Cardiovascular Events in Combination Therapy in Patients Living with Systolic Hypertension trial; AML amlodipine, RAM Ramipril, MET Metoprolol, CT chlorthalidone, LIS lisinopril, ATN atenolol, VAL valsartan, HCTZ hydrochlorothiazide.
Amlodipine and Cardiovascular Outcomes

Amlodipine has been most widely and extensively studied CCB. Its effect on cardiovascular outcomes in hypertensive patient are evaluated in many outcome trials.40 A data of around 87,000 patients who were enrolled in different trials for a duration of 3–6 years has been shared in Table 1.

A significant reduction in cardiovascular events and total mortality was observed with amlodipine compared to other antihypertensive agents. Risk of MI was significantly decreased with amlodipine compared to other antihypertensives. Also amlodipine showed better results in stroke prevention. CHF incidence seemed to be increased with amlodipine compared with ACE inhibitors or ARBs, but was comparable to that with ß-blockers and diuretics. Amlodipine can be safely used in high-risk cardiac patients and is associated with benefits for all major cardiovascular endpoints as well as total mortality. 41,42,43 Newer CCBs like Cilnidipine have been introduced shortly and clinical data on long term cardiovascular outcomes trials are still lacking. Few animal studies are available in support of cardio protective benefits of Cilnidipine. In a preclinical study for MI, Cilnidipine showed a decrease in the myocardial interstitial norepinephrine levels during ischemia and reperfusion periods, leading to reduction of the myocardial infarct size and occurrence of ventricular premature beats.44 Likewise, in vivo experimental data have stated that cilnidipine shows antianginal effects in the experimental model of vasopressin-induced angina and improvement of the ventricular repolarization in the canine model of long QT syndrome.50,51 Large multicentric trials in support of the above findings are still the need of hour. Whereas amlodipine is backed with sufficient evidences to support the above findings.

Amlodipine and Renal Outcomes

Hypertension is a major cause of end stage renal disease (ESRD), and blood pressure levels have been shown to be correlated with renal disease progression. A strict BP control is the mainstay of treatment to prevent renal progression and to reduce cardiovascular risk in hypertensive patients with chronic kidney disease (CKD).52 ALLHAT found no significant differences between amlodipine vs diuretic in the development of ESRD or renal disease progression (by estimated glomerular filtration rate [eGFR]) in high risk hypertensive patients.53 CASE-J also noted no significant difference in rates of renal events between candesartan- and amlodipine-treated high-risk hypertensive patients (HR: 0.70, 95% CI: 0.59–1.26; P = 0.23).54 Considerable clinical evidences suggest that an inhibitor of the renin–angiotensin system (RAS), such as an angiotensin-converting enzyme (ACE) inhibitor and an angiotensin II type 1 receptor blocker (ARB), has an apparent renoprotective effect. Adequate BP levels are seldom achieved with only one RAS inhibitor. A combination of two to three antihypertensive drugs is required to decrease BP to target levels, especially in patients with kidney disease.55 ACCOMPLISH found that using the progression of chronic kidney disease endpoint comprised of doubling of serum creatinine, ESRD, and dialysis, treatment with an ACE-inhibitor (benazepril) plus amlodipine was associated with significantly reduced risk of kidney disease progression compared to treatment with ACE inhibitor plus a diuretic (hydrochlorothiazide) (HR: 0.52, 95% CI: 0.41–0.65; P = 0.0001). In elderly patients >65 years age amlodipine group showed 70% RRR in progressing to dialysis compared to HCTZ group (p = 0.053, for the difference). In the intention-to-treat population, the amlodipine group had a 48% RRR for chronic kidney disease (CKD) progression, defined as doubling of serum creatinine, estimated glomerular filtration rate (eGFR) <15 mL/min, or dialysis compared with the HCTZ group.46

Conclusion

Amlodipine is a superior option in the HTN armamentarium, not only for controlling BP but also for safely improving patient outcomes (Table 2). There has been a vast clinical experience with its use both as monotherapy or combination in varied condition. It has proven benefits in angina with lesser hospitalization and fewer revascularization rates. Its unique mechanism and property has shown benefits in reduction of progression of atherosclerosis. Amlodipine unlike newer CCBs, has shown robust reduction in cardiovascular endpoints particularly stroke. Even in renal impaired patients, amlodipine with effective BP control over 24hrs reduces the progression of ESRD. Hence, compared to all the CCBs, amlodipine still stands the test of time.
Rosuvastatin: Role in Secondary Prevention of Cardiovascular Disease

Gurpreet S Wander¹, Mohammed Yunus Khan Hukkeri², Sachin Yalagudri³, Bharti Mahajan⁴, Archana Toppo Panda⁵

Abstract
Cardiovascular (CV) diseases are a major cause of premature death and disability. Non-communicable diseases (NCD) are responsible for 52% of mortality amongst Indians, of these CV diseases are responsible for 66% of NCD mortality in India. We not only need widespread primary preventive strategy but also need effective secondary prevention protocols to reduce this.

Secondary prevention in patients who already had myocardial infarction (MI) or revascularization is of utmost importance to reduce mortality, cardiac events and improve quality of life. Lifestyle changes and medical therapy have a very important role in secondary prevention of CVD.

Optimal control of hypertension, diabetes mellitus and dyslipidemia plays a critical role in secondary prevention. Statins are one of the most commonly used drugs in secondary prevention as a part of medical therapy. Effective LDL reduction, more patients achieving LDL goals, reduction in intima thickness, improvement in endothelial dysfunction, reduction in inflammatory markers are considered to be surrogate markers of reduced risk with statins.

Rosuvastatin is one of the two most commonly used statins. It is a potent, effective and safe HMG-CoA reductase inhibitor. Data related to secondary prevention is limited with rosuvastatin. Most of the clinical evidences with rosuvastatin have shown more effective LDL reduction than other statins. More number of patients achieve LDL goals and reduction in intima thickness. This article attempts to explore data on role of rosuvastatin for secondary prevention.

Introduction
Cardiovascular diseases are the major cause of premature death and disability in Western countries. This trend is becoming more common in developing countries. In developing countries like India, CV events are associated with huge economic burden and health problems, so efforts are being put to reduce the incidence of CV events. CV disease occurs a decade earlier in Indians when compared to Europeans. In India, almost 66% of NCD mortality is attributed to CVD related condition.

Rosuvastatin is a HMG-CoA reductase (HMG-CoA reductase) inhibitors i.e. Statins, lower cholesterol effectively and are used to prevent CV events. It has been shown in several large clinical trials that use of statins has reduced cardiovascular event rates.

Given the fact that low density lipoprotein-cholesterol (LDL-C) levels have been used to monitor the lipido-lowering response to treatments in almost all trials, it remains the primary target in the management of dyslipidemias. The benefits with statins can be seen across LDL cholesterol range. There is no exact lower value of LDL for the benefits. The ability to reduce LDL levels and raise high density lipoproteins (HDL) levels differs with different statins.

The aim of this paper is to evaluate evidence base that exists on the role of rosuvastatin in secondary prevention of CVD.

Secondary Prevention
Lifestyle measures and drug therapy for optimal control of hypertension, diabetes mellitus and dyslipidemia plays a critical role in secondary prevention. Many studies have shown that reduction of cholesterol levels decreases recurrence of coronary events at all levels of baseline cholesterol. The Adult Treatment Panel III (ATP III) and American Heart Association (AHA) recommended the LDL goals of < 70 mg/dL for secondary prevention. The recent ACC/AHA guidelines recommend high intensity statin therapy for secondary prevention of all patients with atherosclerotic cardiovascular disease (ASCVD) irrespective of the baseline LDL levels. Statins are the initial choice of drugs for lowering LDL levels and one can consider additional agents if LDL goals are not reached.

Many studies have now shown that as compared to standard therapy, intensive statin therapy helps in reducing all cause mortality in patients with acute coronary syndrome (ACS). With statin therapy for every 2 mg/dL LDL cholesterol reduction it has shown to reduce stroke, coronary events and coronary revascularization by one percent. Different statins are used routinely which help in reducing LDL, triglycerides (TGs) and increase HDL levels (Table 1).

Rosuvastatin
Rosuvastatin is a HMG-CoA reductase inhibitor that is used for the treatment of elevated blood cholesterol and triglyceride levels.

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Rodubstatin has high hepatocyte synthesis of apolipoprotein B (APO B) and reduces production of very low density lipoprotein (VLDL), resulting in enhanced synthesis of LDL receptors and hence more LDL is being taken from circulation into liver. This inhibition leads to decreased hepatic cholesterol, resulting in decreased sterol synthesis and hence decreased total cholesterol (TC) concentration and low systemic availability.13,14 Roduvastatin also reduces production of very low density lipoprotein-cholesterol (VLDL-C) and triglycerides (TGs) by reducing synthesis of apolipoprotein B (APO B).15 Roduvastatin has high hepatocyte concentration and low systemic concentration and this is because of high affinity of roduvastatin to organic anion transporting polypeptide-1B1 (OATP-1B1) present in basolateral membrane of hepatocyte. It also has pleiotropic effects. It has shown to improve endothelial dysfunction by increasing production of nitric oxide. It has also shown anti-inflammatory effects which is due to reduction in high sensitivity C reactive protein. The antithrombotic effects of roduvastatin are because of its ability to reduce platelet aggregation.16

**Clinical Pharmacokinetics**

**Absorption**

Ruduvastatin has oral bioavailability of 20% with peak plasma levels achieved in 5 hours.

Food does not affect absorption and can be taken with or without food.

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**Table 1: Comparative effectiveness of routinely used statins**

<table>
<thead>
<tr>
<th>Statin and dose</th>
<th>Rosuvastatin 10 mg</th>
<th>Atorvastatin 10 mg</th>
<th>Simvastatin 10 mg</th>
<th>Fluvastatin 20 mg</th>
<th>Pravastatin 10 mg</th>
<th>Lovastatin 10 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>HDL increase %</td>
<td>8 %</td>
<td>6 %</td>
<td>5 %</td>
<td>1 %</td>
<td>3 %</td>
<td>7 %</td>
</tr>
<tr>
<td>LDL reduction %</td>
<td>46 %</td>
<td>37 %</td>
<td>28 %</td>
<td>17 %</td>
<td>20 %</td>
<td>29 %</td>
</tr>
<tr>
<td>TG reduction %</td>
<td>20 %</td>
<td>20 %</td>
<td>12 %</td>
<td>5 %</td>
<td>8 %</td>
<td>12 %</td>
</tr>
</tbody>
</table>

**Table 2: Comparative pharmacokinetics of statins**

<table>
<thead>
<tr>
<th>Statin</th>
<th>Solubility</th>
<th>Bioavailability %</th>
<th>Protein binding %</th>
<th>Active metabolites</th>
<th>CYP 450 metabolism and iso enzyme</th>
<th>Elimination half-life (h)</th>
<th>Renal excretion %</th>
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</thead>
<tbody>
<tr>
<td>Rosuvastatin</td>
<td>Hydrophilic</td>
<td>20</td>
<td>90</td>
<td>Minor</td>
<td>Limited</td>
<td>19</td>
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<tr>
<td>Atorvastatin</td>
<td>Lipophilic</td>
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<td>Yes 3A4</td>
<td>14</td>
<td>&lt;5</td>
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<tr>
<td>Simvastatin</td>
<td>Lipophilic</td>
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<td>95-98</td>
<td>Yes</td>
<td>Yes 3A4</td>
<td>2</td>
<td>13</td>
</tr>
<tr>
<td>Fluvastatin</td>
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<td>24</td>
<td>&gt;98</td>
<td>No</td>
<td>Yes 2C9</td>
<td>1.2</td>
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<tr>
<td>Pravastatin</td>
<td>Hydrophilic</td>
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<td>50</td>
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<td>No</td>
<td>1.8</td>
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<tr>
<td>Lovastatin</td>
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<td>5</td>
<td>&gt;95</td>
<td>Yes</td>
<td>Yes 3A4</td>
<td>3</td>
<td>10</td>
</tr>
</tbody>
</table>

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**Distribution**

Roduvastatin is 88% plasma protein bound with volume of distribution being 134 litres.

The ability of statins to passively diffuse into extrahepatic tissues depends on their lipophilicity. This can have implications on their extrahepatic side effects. The more lipophilic the statin the more chance it has to diffuse into extrahepatic tissues. When compared to other statins like atorvastatin and simvastatin, roduvastatin is less lipophilic14 (Table 2).

**Metabolism**

Roduvastatin is a poor substrate for metabolism by hepatic cytochrome P-450 (CYP3A4) enzymes. It is mainly metabolised by CYP 2C9 to a less potent metabolite N-desmethyl rosvustatin. It shows minimal drug-drug interactions and plasma half life of rosvustatin is 19 hours.

**Elimination**

Approximately 90% of rosvustatin is eliminated in faeces with 10% being eliminated in urine.

**Markers of atherosclerosis**

Many efforts are being made to identify markers of atherosclerosis.

**Biomarkers:** It has been shown that there is a relation between increased risk and increased levels of cytokines, the cell adhesion molecules P-selectin and E-selectin; and acute-phase reactants such as high sensitive C-reactive protein (hsCRP), serum amyloid A and fibrinogen. Many efforts are also towards identifying factors which affect plaque stability and CAD which is not stable like myeloperoxidase, soluble CD40 ligand, placental growth factor, free fatty acids and pregnancy-associated plasma protein A. There are also markers to identify endothelial dysfunction.20

Intima media thickness: There is a strong co-relation between carotid intima media thickness (IMT) and atherosclerosis extent and end-organ damage. Determination of markers of preclinical atherosclerosis could influence clinician’s decision to intervene with medication and to use more aggressive treatment of risk factors in primary prevention and in patients with atherosclerotic disease. Measuring IMT in large superficial arteries using ultrasonography helps to assess the deterioration in arterial wall and also to assess cardiovascular risk. Carotid IMT is influenced by age, lifestyle, cholesterol level, hypertension, smoking and lipoprotein-a. Carotid IMT mirrors burden of atherosclerosis and help predict subsequent events. Now there is growing interest to use carotid IMT clinically and identify atherosclerosis and subjects at high risk.21

**Rosuvastatin in Secondary Prevention**

The 4S trial with simvastatin (Scandinavian Simvastatin Survival Study) was one of the first secondary prevention trial which showed significant reduction in overall mortality, major coronary events and coronary death in post MI patients or patients with ischaemic heart disease.22 Similarly, the LIPID study (Long term intervention with pravastatin in ischemic disease) with pravastatin showed reduction in cardiovascular events and mortality in post MI patients or patients with unstable angina.23 There are clinical evidences with rosvustatin which shows improvement in surrogate markers.

**Clinical Evidence with Rosuvastatin**

We have many studies with use of rosvustatin. The characteristics and salient findings of these trials are being analysed below (Table 3).

**Statin therapies for elevated lipid levels** compared across doses to Rosuvastatin trial (STELLAR) was a multicentre randomised trial. At the conclusion of the trial it was shown that rosvustatin reduced non-HDL-C by 42.0% to 50.9% compared with...
34.4% to 48.1% with atorvastatin, 26.0% to 41.8% with simvastatin, and 18.6% to 27.4% with pravastatin. Adult Treatment Panel III LDL cholesterol goals were achieved by 82% to 89% of patients treated with rosuvastatin 10 to 40 mg compared with 69% to 85% of patients treated with atorvastatin 10 to 80 mg; rosuvastatin reduced apo B by 36.7% to 45.3% compared with pravastatin. Increase in apo A-I (8.8%) was highest in the rosuvastatin 20 mg group, and this change was seen in plaque volume, but not much improvement of lipid ratios and apolipoprotein A-1 levels was better than rosuvastin 10 mg as compared to atorvastin 20 mg. The study also found rosuvastin to be cost effective and was well tolerated and there were no incidences of liver insufficiency, renal insufficiency or rhabdomyolysis.25

A Study to Evaluate the Effect of Rosuvastatin on Intravascular Ultrasound-Derived Coronary Atheroma Burden (ASTEROID trial): It is a multicentric prospective, open label trial. 507 patients were randomised in the trial and 349 completed the trial. The assessments were done by intravascular ultrasound (IVUS) imaging at baseline and at end of 24 months. At the end of trial it was found that the LDL-C reduction was 53.2% (statistically significant p<0.001) from the baseline, there was 14.7% (statistically significant p<0.001) increase in HDL levels.

There was also significant reduction in endpoints of regression of atherosclerosis which were measured by IVUS imaging. Common carotid artery sites showed –0.0039 mm/y change in maximum carotid intima media thickness (CIMT). Carotid bulb sites showed −0.0040 mm/y change in maximum CIMT and Internal carotid artery showed −0.0039 mm/y change in maximum CIMT.

Compared to placebo, rosuvastatin reduced rate of progression of maximum CIMT and the results were statistically significant. The study showed rosuvastatin caused very few adverse effects and it was well tolerated.26

Coronary Atherosclerosis Study Measuring Effects of Rosuvastatin Using Intravascular Ultrasound in...
Rosuvastatin has been studied in different ethnic groups and it is well tolerated. The risk of myopathy was comparable or slightly less than other available statins. The incidence of myopathy was 0.1% in placebo controlled trials with 40 mg rosuvastatin. Rosuvastatin does not have adverse effect on renal function.43,44 40,600 patients were analysed retrospectively and the results showed that rosuvastatin does not increase risk of renal failure or renal impairment. In all the studies of rosuvastatin in secondary prevention of CVD and discovery group of studies, it was well tolerated and found to be safe.

### Conclusion
Rosuvastatin reduces LDL-C, increases HDL-C more effectively and helps more patients achieve lipid goals than other statins. In addition, rosuvastatin showed improvement in markers of atherosclerosis like reduction in lipid rich necrotic core, reduced rate of progression of maximum CIMT, reduction in plaque volume and decreasing apo B/apo A-1 ratio. These studies have shown that rosuvastatin has a role in regression of coronary atherosclerosis and is beneficial in patients for secondary prevention.

### References


Thyro-weight: Unlocking the Link between Thyroid Disorders and Weight

Shashank R Joshi

Abstract
Thyroid hormone is an important determinant of energy expenditure and contributes to appetite regulation, while hormones and cytokines from the adipose tissue act on the CNS to inform on the quantity of energy stores. A continuous interaction between the thyroid hormone and regulatory mechanisms localized in adipose tissue and brain is important for human body weight control and maintenance of optimal energy balance. Direct effects on ATP utilization are a result of thyroid hormone's actions on metabolic cycles and increased cell membrane ion permeability. However, the majority of thyroid hormone induced energy expenditure is thought to be a result of indirect effects, which, in turn, increase capacity for energy expenditure. This review discusses the direct actions of thyroid hormone on energy expenditure, and places special emphasis on the indirect actions of thyroid hormone, which include mitochondrial biogenesis and reduced metabolic efficiency through mitochondrial uncoupling mechanisms.

Introduction
It is well defined that Thyroid Hormone regulates energy balance, body weight, lipid metabolism and cardiovascular function. Excessive thyroid hormone levels (hyperthyroidism) lead to hypermetabolic state characterized by increased energy expenditure and weight loss despite increased appetite. Decreased thyroid hormone levels (hypothyroidism), by contrast, is associated with decreased metabolic rate and weight gain. Most of these effects are due to the direct action of thyroid hormones on target tissues, such as liver, white and brown adipose tissues (WAT and BAT, respectively), heart and skeletal muscle via modulation of adrenergic nervous system and direct actions on genes expression. However, there is increasing body of evidence for a direct central action of thyroid hormone modulating metabolic processes and energy expenditure.

Thyroid Hormone and Energy Expenditure
Thyroid hormone plays a role in the determination of energy expenditure in humans. Thyroid hormone has been demonstrated to modulate the behaviour of many metabolic pathways potentially relevant for the basal metabolic rate (BMR) and REE. Major mechanisms include uncoupling of cellular metabolism from adenosine triphosphate (ATP) synthesis, or changes in the efficiency of metabolic processes downstream from the mitochondria. The latter category includes “futile cycles,” which occur when single reversible steps in metabolism proceed simultaneously, or “substrate cycles” such as when opposing energy-requiring pathways of metabolism proceed simultaneously, for example, glycolysis simultaneous with gluconeogenesis (Figure 1). The critical role of thyroid hormone in energy expenditure modulation has been known for more than a century, starting with the ground-breaking work of Magnus-Levy in 1895. However, each specific mechanism, and in particular their regulatory systems, have yet to be fully elucidated.

Direct Effects
Direct effects refer to TH actions that inherently cause an increase in ATP utilization. In general, these actions can be further classified into those that are related to metabolic cycles, and those that are related to ion leaks.

Metabolic Cycles
Metabolic cycles, also referred to as substrate or futile cycles, are the combination of two or more reactions which act in a cyclical manner; for a two reaction cycle, the reactions operate in reverse under the control of separate enzymes. Broadly then, futile cycles include such processes as glycolysis/gluconeogenesis, lipolysis.

Fig. 1: Glycolysis simultaneous with gluconeogenesis
Fig. 2: Mechanisms by which thyroid hormone modulates energy expenditure on the cellular level. Adapted from: Vaitkus JA et al. Thyroid Hormone Mediated Modulation of Energy Expenditure. Int J Mol Sci. 2015 Jul 16;16(7):16158-75.

(also referred to as fatty acid oxidation)/lipogenesis, and protein turnover, among others. Thyroid hormone action promotes substrate cycling. Interestingly, Grant and colleagues demonstrated that this increase in cycling results in a reduction in reactive oxygen species (ROS) formation in states of over nutrition. Therefore, thyroid hormones, by promoting “futile” cycles, play an important role as an antioxidant in addition to increasing energy expenditure.

Ion Leaks

A similar yet distinct target of thyroid hormone activity is an increase in ion leakage, resulting from thyroid hormone-induced increased cellular membrane permeability to ions. Consequently, a new ion gradient is established, and cells act to re-establish the desired ion concentrations across the membrane of interest at the cost of increased ATP utilization. Two of the most widely studied and understood ion leaks which are induced by thyroid hormone and lead to futile ion cycling are the Na+/K+ ATPase and the sarco/endoplasmic reticulum Ca2+ ATPase (SERCA) (Figure 2). TH action increases both Na+ influx and K+ efflux into/out of cell plasma membranes, which not only results in increased Na+/K+ ATPase activity but also increased expression and insertion of these Na+/K+ ATPases into the plasma membrane. TH also mediates leakage of Ca2+ from the sarcoplasmic/endoplasmic reticulum (SR/ER) into the cytosol, and induces increased expression of ryanodine receptors, which in turn further increase Ca2+ efflux out of the SR/ER into the cytosol. Since Ca2+ is an extremely important signaling ion and second messenger used by cells, its leakage has the potential to undermine cell survival. In order to restore homeostasis, the cell compensates by increasing Ca2+ influx back into the SR/ER via TH-induced expression of SERCA.

Indirect Effects

Thermogenic effect

While direct effects have been demonstrated to be important in thyroid hormone-induced energy expenditure, the majority of the thermogenesis induced by thyroid hormone can be attributed to indirect effects. Indirect effects result in an increased capacity for EE through non-genomic pathways and mitochondrial biogenesis, and also a reduction in metabolic efficiency at the stage of ATP production, by activating uncoupling mechanisms.

Non-Genomic Pathways

thyroid hormone participates in diverse non-genomic actions which can be initiated at the plasma membrane, in the cytoplasm, or in the mitochondria. These recently discovered non-genomic actions of TH are important for the coordination of normal growth and metabolism, and include regulation of ion channels and oxidative phosphorylation. The principal mediators of non-genomic thyroid hormone actions on metabolism are the protein kinase signalling cascades.

Mitochondrial Biogenesis Thyroid hormone exerts some of its thermogenic effects by stimulating mitochondrial biogenesis, which has substantial energy expenditure implications. Of note, the elevated oxidative capacity due to an increase in the number of mitochondria is not synonymous with an increase in baseline energy expenditure, but rather reflects the
potential for expansion of respiration in response to an increased demand (such as muscle contraction or adaptive thermogenic response activation). 14

THD-dependent mitochondrial biogenesis occurs via three mechanisms:
1. action on nuclear thyroid hormone receptors;
2. activation of mitochondrial transcription; and
3. expression and activation of intermediate factors that span both the nucleus and the mitochondria

Alternatively, changes in ion fluxes linked to ATP utilization or kinase activities may lead to increased metabolic inefficiency and heat generation, as could increases in protein turnover and perhaps bone turnover. Data exist to support the concept that thyroid hormone acts in each of these ways, at least in pathologic states of thyroid hormone excess or deficiency, but it still remains to be determined which are most physiologically relevant in euthyroid subjects. The example of thyroid hormone–dependent thermogenesis is not strictly related to the basal metabolic rate, but rather adaptive thermogenesis, with uncoupling of oxidative phosphorylation in cold-exposed brown adipose tissue (BAT) being dependent on locally generated thyroid hormone. In small mammals, sympathetic adrenergic stimulation of BAT induces uncoupling protein-1 (UCP-1), a protein that uncouples the mitochondrial proton gradient from ATP production promoting the generation of heat. A critical element in this pathway is the type 2 deiodinase (D2), which increases local, intracellular T3 production from T4 to such an extent that thyroid hormone receptor (TR) saturation increases from 70% to near 100% upon cold exposure, while serum T3 levels do not appear to be affected. 15 The increased cyclic adenosine monophosphate (cAMP)-synergistically combines with the increased, locally produced T3 such that UCP-1 is upregulated. This mechanism also illustrates the molecular links between the adrenergic signalling cascade/sympathetic innervation and thyroid hormone action, a relationship that has been shown to be important for both thermogenic and nonthermogenic roles of thyroid hormone. 9–16

The modulation of thyroid hormone’s actions is critical in the delivery of time and tissue specific signalling. The effects of thyroid hormone in increasing energy expenditure via modulation of the adaptive thermogenesis response, coupled with the ability of increasing respiratory capacity by regulating mitochondrial biogenesis, are augmented by the increase in thyroid hormone’s non-mitochondrial effects on futile cycles and ion transport. 17

Thyroid Function in Obese Patients

TSH levels are at the upper limit of the normal range or slightly increased in obese children, adolescents, and adults and are positively correlated with BMI. 18 Low fT4 with a moderate increase in T3 or free T3 (fT3) levels has been reported in obese subjects. 19 Progressive fat accumulation was associated with a parallel increase in TSH, and fT3 levels irrespective of insulin sensitivity and metabolic parameters and a positive association has been reported between the fT3 to fT4 ratio and both waist circumference and BMI in obese patients. 20

The causes underlying these alterations in thyroid functions are not known. One theory suggests an increased deiodinase activity leading to a high conversion rate of T4 to T3. This is interpreted as a defense mechanism in obese subjects capable of counteracting the accumulation of fat by increasing energy expenditure. 21 Another probable mechanism is the compensatory increase in secretion of TSH and fT3 in an attempt to overcome decreased tissue responsiveness to circulating thyroid hormones due to the reduced expressions of both TSH and thyroid hormones in adipocytes of obese subjects. 22 High levels of leptin, found in obese subjects, is another potential cause. The main action of leptin is to report centrally the amount of fat, leading to a decrease in appetite and food intake. Leptin has also been shown to stimulate centrally the transcription of pro-thyrotropin-releasing hormone (TRH) and consequently also that of TRH and TSH. Leptin also enhances the activity of deiodinases. Further explanation is that inflammatory cytokines secreted from adipose tissue such as tumor necrosis factor alpha, interleukin (IL)-1 and IL-6, inhibit sodium/iodide symporter mRNA expression and iodide uptake activity.

Hypothyroidism and Weight Gain

Thyroid hormones and body fat appear to be closely related. In humans, overt hypothyroidism is associated with variable degrees of weight gain of 3 to 6 kg. 23 Thyroid hormones play an important role in regulating basal metabolism, thermogenesis and play an important role in various metabolic processes like lipid and glucose metabolism, food intake and fat oxidation. 24 Thyroid dysfunction undoubtedly is associated with changes in body weight and composition, body temperature and total and resting energy expenditure (REE) independent of physical activity.

Hypothyroidism is associated with decreased thermogenesis, decreased metabolic rate, and has also been shown to correlate with a higher body mass index (BMI) and a higher prevalence of obesity. 25 There is clinical evidence suggesting that even mild thyroid dysfunction in the form of subclinical hypothyroidism is linked to significant changes in body weight and represents a risk factor for overweight and obesity.

In humans, overt hypothyroidism is associated with variable degrees of weight gain. While being a frequent complaint (weight excess was reported in 54% patients with overt hypothyroidism), weight gain is usually of limited extent. In line with this concept, the BMI was not found to be greater in elderly women with subclinical hypothyroidism compared with euthyroid controls. 26 The alterations in body weight associated with hypothyroidism may reflect both the accumulation of body fat, due to decreased REE and reduced physical activity, and the increased water content of the body, consequent to a reduced capacity of excreting free water. Hypothyroid subjects also have increased amounts of glycosaminoglycans that are responsible for the greater water-binding capacity, a condition that results in the typical ‘myxedema’ of hypothyroidism. 27

From a clinical perspective, obesity and mild thyroid failure are common diseases and frequently coexist. An Indian study showed that among the obese, 33% had overt, and 11%
had subclinical hypothyroidism. It further showed that obesity was more common (46% vs. 34%) in overt than in subclinical hypothyroidism.30

**Hyperthyroidism and Weight Loss**

Despite increased appetite, hyperthyroidism is usually associated with a variable decrease in body weight, due to a decline in both lean and fat mass, associated with an increase in total energy expenditure.31,32 The latter phenomenon results from a reduced thermodynamic efficiency of the biologic machine with increased heat production.33 As a consequence, accelerated protein catabolism and skeletal muscle atrophy has been observed in experimental thyrotoxicosis.34 Furthermore, hyperthyroidism causes a negative calcium balance and reduced bone mineral density.35 The extent of these phenomena depends on the severity of the thyrotoxic state and the length of exposure. Occasionally, a paradoxical weight gain is observed in some thyrotoxic patients because, due to a greatly increased appetite, their caloric intake exceeds the augmented energy expenditure.

**Pearls for Clinical practice**

Clinicians should be particularly alert to the possibility of thyroid dysfunction in obese patients. The problem lies in identifying obese subjects who are affected by mild thyroid hormone deficiency. On one hand, raised TSH may be a just a functional consequence of obesity. On the other hand, thyroid failure, especially the subclinical form, may go undiagnosed in obese patients. These patients will continue to increase in weight and will develop a deranged lipid profile, thereby bringing the thyroid/obesity and cardiovascular link association to a full circle. The question that emerges is whether an obese patient should be diagnosed as having subclinical hypothyroidism based on an elevated serum TSH level alone. Data suggest that just an elevated serum TSH might not be enough for diagnosing subclinical hypothyroidism in patients with morbid obesity. Thus, it would seem reasonable to measure circulating plasma levels of thyroid hormones and thyroid autoantibodies in these patients to support a diagnosis of autoimmune thyroid failure.36

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Sphenoid Sinus Carcinoma presenting as Bilateral 6th Nerve Palsy

Mugundhan Krishnan¹, Ani Thampi², Jamkho Pum Baite², P Arul³

75-year-old female, known diabetic for 10 years on regular treatment, presented with history of double vision for 6 months. On examination, she was conscious, oriented, the vitals were normal. Pupil 3mm equally reacting to light on both sides. Bilateral lateral rectus palsy was present. Fundus was normal. Other cranial nerves were normal. There was no motor weakness noted. All the deep tendon jerks were normal. Plantars were flexor. Sensory, cerebellar systems were normal. Blood investigations including blood biochemistry were normal. HbA1c was 5.6%. Magnetic resonance imaging (MRI) T1, T2 and contrast T1 axial – isointense enhancing sphenoid sinus mass lesion causing erosion of walls of sphenoid, clivus with infiltration of cavernous sinus and encasement of internal carotid arteries (Figures 1, 2 and 3). Diagnosis of sphenoid sinus carcinoma presenting as bilateral 6th nerve palsy was made. She was treated for the same and improving.

Bilateral isolated sixth-nerve palsy is a much less common clinical entity. Anatomically, the abducens nerve is located much closer to the internal carotid artery in the cavernous sinus compared to the oculomotor, ophthalmic, and trochlear nerves which are located at the lateral wall of the sinus. The anatomical proximity between abducens nerve and the internal carotid artery might be a factor for the isolated sixth-nerve involvement.

The most common causes of neurologically isolated CN 6th Palsies are not as grave. Eighty three percent of nontraumatic, neurologically isolated palsies are associated with either undetermined etiology (34%), hypertension (28%), coexisting hypertension and diabetes (17%), diabetes alone (4%). 8% are associated with multiple sclerosis and only 2% are associated with neoplasm.¹

An MRI is recommended for older adults if the 6th CN palsy does not resolve within 3 to 6 months, the esotropia is progressing after 2 weeks from its onset, other neurologic signs or symptoms are present, or if the patient has a previous history of malignancy.² A bilateral 6th CN palsy should never be considered vascular in origin.³ MRI is required to find out the cause for these patients.

Sphenoid carcinoma constitutes only 0.3 per cent of sinus cancer.⁴ Its symptoms and signs are nonspecific until the sinus wall is penetrated. Once it is involved, specific neuro-ophthalmological symptoms and signs develop, resulting from involvement of anatomically contiguous structures. These are characterized most commonly by the sphenocavernous syndrome and less frequently by isolated sixth nerve palsies. Treatment, principally with radiotherapy supplemented by chemotherapy, has been disappointing with most patients dead by three years.

This case highlights the rarity and importance of bilateral isolated 6th nerve palsy in diagnosing neuro-ophthalmological syndromes.

References


Pictorial cme
Megalencephalic Leucoencephalopathy [Van Der Knaap Disease] in a Non Agarwal Family

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A 13 year old girl born of non consanguineous marriage, full term normal delivery in a Hindu family from Tamilnadu. Her parents noticed progressive increasing of head size. She attained social smile by 6 months and head control by 7 months of age. She was not able to walk herself. Her younger brother who is 11 years old has similar complaints in the form of progressive increasing in head size with delayed mile stones.

On examination, there was macrocephaly with head circumference of 57 cms. Spastic weakness of both lower limbs and upper limbs was present. All DTRS were brisk with extensor plantars. Sensory and cerebellar systems were normal. Abdominal and eye examinations were unremarkable. MRI BRAIN showed bilateral symmetrical white matter hypointensity on T1W sequence (Figure 1A) and hyperintensity on T2 W sequence (Figure 1B) suggestive of demyelination. MRI BRAIN also showed well defined symmetrical subcortical cysts in the anterior temporal lobe which are hyperintense on T2W (Figure 2A) and suppressed in T2 Flair (Figure 2B) sequence consistent with a diagnosis of megalencephalic leucoencephalopathy. They were treated symptomatically along with physiotherapy.

Megalencephalic Leucoencephalopathy [Van der Knaap Disease] is a autosomal recessive disorder described by Van der Knaap in 1995. The new entity neurodegenerative disorder is characterised by infantile onset macrocephaly, cerebral leucoencephalopathy, mild neurological symptoms [pyramidal, extrapyramidal], slow course of functional deterioration, mental decline and seizures. MRI BRAIN shows diffuse symmetrical white matter demyelination with sparing of corpus callosum, internal capsule and brainstem with symmetrical subcortical cysts in the anterior temporal lobe¹. In India, majority of the patients belong to Agarwal community.² Our patient did not belong to this community. Indian patients with megalencephaly and MRI showing extensive demyelination with temporal cysts should raise the suspicion for MLC. This disease is linked to the gene, MLC1 and is localised on chromosome 22qtel.

This case highlights the new entity neurodegenerative disorder with a typical MRI finding in a non-Agarwal community.

References


Fig. 1a and 1b: MRI BRAIN shows bilateral symmetrical white matter hypointensity on T1W sequence (Fig. 1a) and hyperintensity on T2 W sequence (Fig. 1b) suggestive of demyelination

Fig. 2a and 2b: MRI BRAIN shows well defined symmetrical subcortical cysts were noted in anterior temporal lobe which are hyperintense on T2W (Fig. 2a) and suppressed in T2 Flair (Fig. 2b) sequence
Multiple Heritable and Acquired Risk Factors in a Case of Recurrent Retinal Vein Occlusion

Aniket Prabhudesai¹, Shrimati Shetty¹, Kanjaksha Ghosh², Bipin Kulkarni¹

Abstract
A 40 year old female presented with branch retinal vein occlusion in the right eye followed by a second episode, a year later, of central retinal vein occlusion in the left eye. The patient was found to be heterozygous for factor V Leiden and factor V HR2 haplotype G5380A. She had a history of use of oral contraceptives, had reduced levels of tissue plasminogen activator, positive for lupus anticoagulant and diagnosed with hypertension post second episode of RVO. Presence of both heritable and acquired thrombophilia along with hypofibrinolysis induced by reduced levels of tissue plasminogen activator might have led to the recurrence of retinal vein occlusion in this patient. This case illustrates the contribution of multiple hereditary and acquired risk factors in the clinical manifestation of recurrent retinal vein occlusion thereby warranting the application of a more thorough work-up in such cases. The case also briefly touches on the fact that treatment for every RVO cannot be the same and should be decided by taking into consideration the associated risk factors.

Introduction
Retinal vein occlusion (RVO) is a common ocular disease leading to acute visual loss with a prevalence of 8 per 1000 individuals reported in rural central India.¹ The pathogenesis is poorly understood. Being multifactorial, treatment is always a challenge and individualized or causal treatment for RVO is to be decided by clinician. Based on the site of vascular occlusion, RVO is divided into two types: (a) Central vein retinal occlusion (CRVO) and (b) Branch retinal vein occlusion (BRVO). BRVO is approximately seven times more common than CRVO [1]. Hypertension, diabetes mellitus, arteriosclerosis and hyperlipidemia, glaucoma, advancing age are established risk factors for RVO however; the role of thrombophilia in RVO is still controversial.² Recurrent RVO is not frequently encountered in young adults. In RVO cases, extensive laboratory testing including thrombophilia is not indicated.³ We report a case of recurrent RVO in a young female due to presence of multiple risk factors stressing on the warrant of a more thorough work-up in RVO cases with clinical features such as young age, recurrent presentations, or bilateral involvement.

Case Report
A 40 year old woman presented with a 11-day history of decreased vision in her right eye. Ophthalmoscopic examination showed retinal haemorrhages along with multiple cotton wool spots. A diagnosis of infero-temporal branch retinal vein occlusion (BRVO) with macular oedema was confirmed by fluorescein angiogram. Assessment of risk factors revealed her to be using oral contraceptives for the management of adenomyosis for the management of adenomyosis since two years. She received an intravitreal Avastin (Bevacizumab) injection for the right eye and her vision subsequently improved with conservative management. The use of oral contraceptives was discontinued. However, a year later she experienced blurring vision in her left eye. Ocular examination revealed non-ischemic central retinal vein occlusion (CRVO) with optic disc and macular oedema in the left eye. She received an intravitreal combination of Triamcinolone acetonide and Bevacizumab. Due to recurrence of RVO, warfarin therapy was initiated and continued for three months.

An extensive laboratory workup was done to find the cause of the occlusion (Table 1). Full blood count, blood glucose, erythrocyte sedimentation rate, lipid profile, bleeding and clotting time, prothrombin time, HLA B27 and serum homocysteine were all normal with slightly prolonged activated partial thromboplastin time (APTT). Clotting factors VIII, IX and XI were all normal. Inherited thrombophilia markers Protein C and S levels, antithrombin III levels were also normal. Moreover, genomic DNA was isolated from peripheral blood lymphocytes and genotyped for Factor V Leiden[R506Q] and other common polymorphisms implicated in thrombosis (Table 1). She was heterozygous for factor V Leiden and factor V HR2 haplotype G5380A. She was also heterozygous for methylene tetrahydrofolate reductase (MTHFR) C677T mutation. Acquired thrombophilia markers i.e. anticardiolipin antibodies, β2-glycoprotein 1 antibodies were absent however she was strongly positive for lupus anticoagulants (LA) (Siemens Healthcare Diagnostics, Marburg, Germany) which could have prolonged the APTT in the patient. All the fibrinolytic parameters including plasminogen, plasminogen activator inhibitor-1, thrombin activatable fibrinolysis inhibitor and alpha-2-antiplasmin were normal except for tissue plasminogen activator (tPA) levels which were reduced (Assay Pro, MO, USA).

Patient was diagnosed with

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A combination of inherited and acquired thrombophilia and presence of vascular risk factors could have led to the recurrent RVO in this patient. She was heterozygous for both Factor V Leiden mutation and for Factor V HR2 haplotype G5380A. This co-existence imparts increased risk of venous thromboembolism by contributing to the activated Protein C resistance.4 Though pathogenesis and risk factors of RVO are different from those of deep vein thrombosis and other systemic diseases,5 Factor V Leiden has been implicated in increasing the risk of RVO including recurrence.6–10 Patient also carried MTHFR C677T mutation with normal homocysteine levels.

The patient tested positive for LA. LA are immunoglobulins, which bind to complexes of various proteins with phospholipids, associated with the cell membrane. It is a well established acquired risk factor for venous as well as arterial thrombosis. Though not commonly found, LA may constitute a contributory factor in RVO.11

Patient has a history of adenomyosis which is a heterogenous gynaecological condition and women with adenomyosis may experience heavy menstrual bleeding, dysmenorrhoea, and longer menstrual cycles than normal or may even remain asymptomatic.12 She was on oral contraceptive pills for the management of adenomyosis for two years before the first episode of RVO. Oral contraceptive is known to be a strong risk factor for development of RVO.13 She was also diagnosed with hypertension after second RVO. It is also plausible that hypertension may have been a side effect of the use of oral contraceptives as a result of alteration of the renin angiotensin system.14 Hypertension, an established strong risk factor for RVO,15 was either overlooked or delayed and could have resulted or increased recurrence risk.

Fibrinolytic parameters are rarely studied in RVO. Abnormal fibrinolysis due to deficiency of tPA has been associated with retinal vein occlusion.16 The patient was found to have reduced tPA level. However, we could not detect any sequence variations in tPA gene associated with decreased tPA levels. LA has already been associated with increased plasminogen activator inhibitor levels (PAI) in stroke patients.17 A follow up sample still tested positive for LA with reduced tPA levels. Whether intravitreal tPA administration could have normalized patient’s hypofibrinolytic state and prevented the recurrence is not clear.16 A follow up sample still tested positive for LA with reduced tPA levels.

**Conclusion**

This case illustrates the contribution of multiple thrombophilic and vascular risk factors in clinical manifestation of recurrent retinal vein occlusion suggesting that RVO development is more likely multigenic and heterogeneous than being caused by a single risk factor. This case also stresses on the warrant of a more thorough work-up in RVO cases with clinical features such as young age, recurrent presentations, or bilateral involvement. This case also raises a question as to whether causal or individualized treatment should be taken up by the clinicians for better outcome in such cases. Effective prophylaxis can be achieved by identifying the risk factors in RVO cases and help decreasing its incidence.

**References**

Massive Hematuria Due to Congenital Renal Arteriovenous Malformation Successfully Treated by Renal Artery Embolization

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Abstract
Congenital renal arteriovenous malformations (AVMs) are rare benign vascular lesions and a rare cause of massive hematuria in females predominantly involving right kidney. Clinical presentation in a male with involvement of the left kidney is very rare. Only a few case series describing the outcome of congenital renal AVMs have been reported in the literature. We report a challenging case of a male patient with life threatening massive hematuria with congenital renal AVMs in left kidney. Successful embolization was performed using coils and gel foam.

Introduction
Renal arteriovenous malformations (AVMs) are rare benign vascular lesions which may be acquired or congenital. Congenital renal AVMs are usually small and asymptomatic and close spontaneously.1 Congenital renal AVMs are more common in females in the third or fourth decade of life and involve the right kidney.2 Acquired renal AVMs also known as arteriovenous fistulae, account for about 70% to 80% of all AVMs and may occur as a result of renal biopsy, blunt or penetrating trauma, inflammation, malignancy, or renal surgery.3 Hematuria is the most common symptom. Other clinical manifestations include hypertension, left ventricular hypertrophy, high output cardiac failure and abdominal pain.4 The usual treatment of AVMs is nephrectomy but transcatheter arterial embolization (TAE) can be considered as an alternative. We present a rare case of massive life threatening hematuria in an adult male with congenital AVMs involving left kidney which was successfully treated using TAE.

Case Report
A 46 year old male patient presented to the urology outpatient department of our hospital with repeated episodes of massive hematuria and urinary retention for the last 2 months. Patient had no significant past medical history involving renal injury, renal biopsy or known nephrolithiasis. He denied history of bleeding disorder or any medications. His physical examination revealed blood pressure of 100/70 mm Hg, heart rate was 96 beats/minute, body temperature was 37.4 °C and pallor and no continuous bruist could be appreciated over flanks. Biochemical, hematological and coagulation parameters revealed creatinine of 1.1 mg/dl, blood urea of 29 mg/dl and eGFR of 105.36 ml/minute, hemoglobin of 7.8 g/dl, platelet count of 178 x 10³/mm³, aPTT of 31.7 sec and PT of 13.6 sec. For severe anemia patient required multiple packed red blood cell transfusions. Urine analysis showed erythrocytes but malignant cytology was negative. Ultrasonography of abdomen revealed no bladder or kidney stones. CECT and MRI abdomen revealed thickened wall of left pelvis and upper ureter and since these findings may represent urothelial malignancy, cystoscopy and retrograde studies were conducted but were negative. Retrograde study of the left pelvicaliceal system revealed active bleeding. Based on these findings renal arteriography was planned.

Renal arteriography was performed using a right transfemoral approach and a 6- French sheath and initially an aortogram was taken to delineate the renal arteries using the 6-French pigtail catheter. Left renal artery was then cannulated with 6-French juddkins right catheter and selective left renal angiogram revealed AV malformation involving the posterior segmental branch of the left renal artery. It was also selectively cannulated with

5-French Judkins right catheter with Terumo wire support and selective angiogram revealed AV malformation arising from the posterior segmental branch of the left renal artery (Figure 1). Digital subtraction arteriography (DSA) demonstrated the feeding artery to the AVMs. The lesion was selectively catheterized with 5-French left coronary bypass catheter with Terumo wire support. After confirming the feeding vessel of AV malformation and positioning the catheter into its origin, coil embolization of feeding vessel was done using three MREye embolization coils (Cook Medical Inc. Bloomington, IN, USA) – two 5mm and one 4mm coils. At the end of the procedure complete occlusion of the AVM was confirmed using DSA with no procedural complications (Figure 2).

On 7th postembolization day, massive hematuria recurred with hypotension requiring inotropes and hence patient was again taken up for an emergency selective renal arteriography and embolization. Left renal artery was selectively cannulated using 6-French Judkins right catheter and left renal angiogram revealed multiple feeding vessels from anterior segmental artery as well as vessels arising directly from the left renal artery which were not present in previous angiogram (Figure 3). Initially selective embolization of the anterior segmental artery feeders was attempted with coils but despite occlusion of these feeding vessels left renal AVM was seen filling through the feeders from the left main renal artery. Hence, coil embolization followed by gel foam embolization was done to left main renal artery. Repeat contrast injection revealed no refilling of left renal AVM (Figure 4). Blood supply of the left kidney had to be compromised to save the life of the patient from the catastrophic bleeding. TAE avoided an inevitable emergency laparotomy and nephrectomy. Patient was observed for recurrence of hematuria, hypertension and postembolization syndrome. No recurrence of hematuria was observed but patient developed postembolization syndrome (PES) with flank pain, fever, nausea and vomiting and was managed conservatively with parenteral opioid analgesics (morphine and fentanyl), antiemetics (ondansetron), antipyretics and intravenous fluids. PES resolved over the next 3-4 days. Subsequent hospital course was uneventful with no worsening of renal function with creatinine of 1.1mg/dl and eGFR of 105.56 ml/minute on discharge.

Discussion

AVMs, first described by Varela in 1928 are rare vascular lesions. Congenital renal AVMs are considered to represent focal spontaneous failures of vascular development occurring between the 4th and 10th week of life. However they usually remain asymptomatic until the 3rd or 4th decade of life.

On angiographic examination depiction of renal veins in the early stages of the arterial phase confirms the diagnosis of renal AVMs. Congenital AVMs may be classified as cirsoid and aneurysmal. Cirsoid type AVMs consists of multiple small and dilated varix like arteriovenous communications with multiple feeding arteries and draining veins and they represent a truly congenital form of arteriovenous malformation. Cirsoid type AVMs develops from a nidus in the submucosa of renal pelvis. Aneurysmal type consists of a single feeding artery and a single draining vein. Acquired AVMs etiology may be idiopathic or secondary. Idiopathic renal AVMs present later in life and develop when pre-existing renal aneurysms form shunts with adjacent renal segmental vein. Secondary renal AVMs are caused by iatrogenic injuries, penetrating renal trauma or blunt renal injury. Renal biopsy is the most common cause of secondary AVMs. Renal malignant tumors may cause shunts between pseudoaneurysms and renal segmental veins resulting in AVMs. Life threatening hematuria is more characteristic of the congenital AVMs and is present as the primary symptom in 3 out of 4 patients. Aneurysmal type of congenital AVMs is generally asymptomatic and is often incidentally detected on CT abdomen or ultrasonography.
AVMs are complex lesions and are almost never entirely cured and may recur. The goal of treatment should be to control the symptoms and perform repeated embolizations if needed. Patients should be counseled that treatment may be life-long and that currently there is no cure. Indications for treating AVMs are increase in the size of the fistula, recurrent or persistent hematuria, hemodynamic effects such as hypertension and high output cardiac failure. TAE has become the treatment option of choice for the management of severe hematuria caused by renal AVMs, even in case of AVMs complicating pregnancies.7 Embolic materials used for TAE include gelatin sponge, metallic coil, absolute alcohol, lipiodol, and n-butyl 2-cyanocrylate. In our case platinum coils and gel foam was used for successful treatment of AVMs. TAE is a safe procedure with a relatively low rate of complications. The most common complication is PES affecting 90% of patients.8 PES usually present with flank pain, fever, nausea, vomiting, paralytic ileus, and/or leukocytosis for 1 to 3 days after renal artery embolization (RAE).9 Treatment is supportive, consisting of analgesics, antipyretics, and antiemetics as needed, until symptoms resolve. For this reason, it is recommended that patients be observed in a hospital after RAE for monitoring and control of symptoms. Coil migration is an unusual, but serious complication, occurring in less than 2% of cases.7 It is commonly detected at the end of the procedure and can be rectified using endovascular grasping device (snare). Non-target embolization can result in spine, lower extremity, and bowel infarction.10-12 Reflux of embolization material can result in loss of renal function and subsequent hypertension. Other complications include access site hematoma, infection and contrast induced nephrotoxicity.

Conclusions

A middle aged male with life threatening hematuria after ruling out common causes of hematuria underwent renal angiogram to reveal features of congenital renal AVM in the left kidney and subsequently an emergency embolization was successfully performed using coils and gelfoam. Clinical presentation of congenital renal AVM’s in a male with involvement of the left kidney is very rare. Our case also highlights the fact that symptoms, history and imaging may be misleading in renal AVM’s. In cases of suspected renal AVMs, selective renal arteriography and DSA can be both diagnostic and therapeutic modality. The patient is in our follow up with no recurrence of hematuria or worsening azotemia.

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A Rare Etiology of Severe Thrombocytopenia in Patient with Chronic Liver Disease

Mohammad Zeya Ansari, R Tolstoy, G Jagadeeswaran

Abstract
Thrombocytopenia is a common complication in patients with chronic liver disease and is multi-factorial. It complicates the management and worsens the prognosis. Treatment options are costly and include platelet transfusion, splenectomy, splenic artery embolization, TIPPS and thrombopoietin (TPO) agonists.

Here we are presenting a patient with decompensated liver disease with known chronic alcoholism and profound thrombocytopenia despite multiple platelet transfusions. On further work up we found a coexistent autoimmune etiology. Thrombocytopenia promptly responded to steroids, a cost effective option.

Introduction
Thrombocytopenia, a common complication in patients with chronic liver disease, is seen in nearly 75% of cirrhotic patients. The pathogenesis of thrombocytopenia in chronic liver disease is multifactorial. Initially it was thought that thrombocytopenia in CLD is only due to portal hypertension where there will be an enlargement of spleen which causes destruction of platelets. So initially treatment for thrombocytopenia was aimed at reversing portal hypertension. But persistently decreased platelets were noted even in patients without splenomegaly. So other factors like intrasplenic production of autoantibodies and plasma expansion resulting in hemodilution also contribute to thrombocytopenia. Suppression of platelet production in bone marrow is also another factor which is seen in HCV infection and alcohol related chronic liver disease. Antiviral therapy like interferon alfa also induces thrombocytopenia. In some patients of CLD there is an evidence based autoantibodies related destruction of platelets and it is mostly observed in HCV related cases. Here autoantibodies are directed against platelet surface antigens and enhance the removal of platelets by splenic and hepatic reticuloendothelial systems where by triggering rapid destruction as seen in chronic ITP. TPO is a potent cytokine produced by liver, bone marrow and kidney which regulates megakaryocytes and platelet production. In cirrhotic patients with thrombocytopenia, low circulating levels of TPO is seen compared to cirrhotic patient with normal platelet count. The treatment options available for severe thrombocytopenia are platelet transfusion, splenic artery embolization, splenectomy and TIPS. Platelet transfusion is indicated in patients with less than 10,000-20,000/µl platelets in uncomplicated patients and less than 50,000/µl in patients undergoing procedures. Newly derived options include recombinant interleukin-11, eltrombopag and recombinant TPO.

Case Summary
A 50 year old male patient with ethanol related chronic liver disease and no other comorbidities, came to EMD with the complaints of melaena, gum bleed and haematuria for 10 days, fever with chills, abdominal pain and distention for 3 days.

On examination, patient was pale and febrile with stable vital parameters. He had minimal ascites and epigastric tenderness.

Serial CBC, LFT and RFT are summarized in Table 1. Upper GI endoscopy showed esophageal varices and portal gastropathy and EVL done immediately. Ultrasound abdomen showed features of CLD and portal hypertension with medical renal disease. Ascitic fluid analysis had no evidence of peritonitis. Urine culture showed significant bacteria (E.coli) and managed accordingly. He had severe thrombocytopenia which was managed with platelet transfusions. Bone marrow aspiration and biopsy showed dimorphic anemia with thrombocytopenia, megaloblastic erythroid hyperplasia and mild megakaryocytic hyperplasia. His serum B12 and folate level were within normal range. Hepatitis B, C, HIV, Dengue virus, Helicobacter pylori, scrub typhus, leptospirosis infection and Coomb’s test were negative. Renal failure was stabilized with hemodialysis.

As his thrombocytopenia persisted despite multiple platelet transfusions (total 19 units) and other common causes of thrombocytopenia being ruled out, we suspected of some uncommon etiology including an autoimmune condition. ANA tested was positive with fine granular++, cytoplasmic+ pattern. He was positive for smooth muscle antibody and negative for anti-ds DNA Ab and hence he was diagnosed to have autoimmune hepatitis type-1 with associated ITP. We started steroids (Inj. methylprednisolone 125 mg IV OD for 3 days followed by oral prednisolone 60mg OD). His platelet count started improving from 2nd day of IV steroid.

On follow-up visits, his platelet count was in safe range (> 1 lakh / cu.mm) with low dose oral steroid and is currently being managed as ITP.

Discussion
The causes of thrombocytopenia in chronic liver disease may be due to sequestrating function of spleen, presence of antplatelet antibodies and impaired thrombopoietin production in cirrhotic patients. It is very important to differentiate ITP from common cause of thrombocytopenia in CLD as the management differs. Hypersplenism in liver disease due to portal hypertension...
causes increased sequestration of platelets within spleen leaving less in circulation. However it is also to be clear that thrombocytopenia can occur in liver cirrhosis without splenomegaly.2 Thrombopoietin is a cytokine produced by the liver which plays a key role in platelet production and subsequent function may be low in cirrhosis. Thrombocytopenia in liver disease without evidence of cirrhosis, splenomegaly and interferon is recognized especially in patients with hepatitis C and autoimmune hepatitis.

Based on persistent thrombocytopenia, ANA and anti SMA positivity we diagnosed him as AIH type-1 and associated ITP. The International Autoimmune Hepatitis Group proposed a scoring system to standardize the diagnosis, useful for clinical trials, but that may be inaccurate in individual cases.8 Liver biopsy was not done for two reasons—like rheumatoid arthritis, Sjogren’s syndrome and autoimmune thyroiditis but association with idiopathic (immune) thrombocytopenic purpura has been rarely reported.9-13

ITP is an autoimmune disease characterized by a low platelet count, mucocutaneous bleeding, normal bone marrow findings and the absence of other causes of thrombocytopenia in which anti-platelet autoantibodies such as PAIgG induces platelet destruction.14 There is a case series of 5 patients with AIH type-2 where patients had at least one associated autoimmune disorder including IgE-induced IgA deficiency, ITP, and arthritis.13 In an Indian case series of 10 patients with AIH, three had underlying rheumatic disease (SLE, Sjogren’s and Rheumatoid arthritis each one), while others had primary AIH. In the same report, 2 patients were found to have autoimmune thrombocytopenia and were managed by immunosuppressant.16 Indeed prednisolone administration is a treatment option for AIH and is also effective for ITP. Therefore ITP should be considered when liver dysfunction is accompanied by severe thrombocytopenia particularly in the autoimmune types of liver disease.

Though in our patient there was normal bilirubin, SGOT and SGPT (which is usually elevated in hepatitis) but persistent thrombocytopenia and positive ANA with SMA made us to consider it AIH type-1.

### Table 1: Blood investigation (CBC, LFT, RFT) reports

<table>
<thead>
<tr>
<th></th>
<th>Normal</th>
<th>Day1</th>
<th>Day3</th>
<th>Day5</th>
<th>Day7</th>
<th>Day10</th>
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<td>Hb (g/dl)</td>
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<td>6.4</td>
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<td>PCV (%)</td>
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<td>WBC count/µl</td>
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<td>5.4X10⁶</td>
<td>5.0X10⁶</td>
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<td>76X10⁶</td>
<td></td>
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<tr>
<td>MCV (fl)</td>
<td>80-100</td>
<td></td>
<td></td>
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<tr>
<td>Neutrophils (%)</td>
<td>40-80</td>
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<td>Lymphocytes (%)</td>
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<tr>
<td>Monocytes (%)</td>
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<td>Eosinophils (%)</td>
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<td>Platelet count/µl</td>
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<td>6X10⁶</td>
<td>3X10⁶</td>
<td>4X10⁶</td>
<td>36X10⁶</td>
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<td>Serum Protein (g/dl)</td>
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<td>Serum Albumin (g/dl)</td>
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<td>2.3</td>
<td>2.6</td>
<td>2.9</td>
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<td>Serum globulin (g/dl)</td>
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<td>Total bilirubin (mg/dl)</td>
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<td></td>
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<td>Serum creatinine (mg/dl)</td>
<td>0.8-1.25</td>
<td>2.3</td>
<td>4.43</td>
<td>3.95</td>
<td>3.4</td>
<td>3.2</td>
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<td>Direct/indirect</td>
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<td></td>
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<td>5-38</td>
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<td>15</td>
<td></td>
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<td>205</td>
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<td>GGT (u/l)</td>
<td>10-66</td>
<td>409</td>
<td></td>
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<tr>
<td>Serum albumin (g/dl)</td>
<td>3.4-4.8</td>
<td>7.95</td>
<td>3.95</td>
<td>3.4</td>
<td>3.2</td>
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### Conclusion

It is worthy to evaluate for an alternative autoimmune etiology for CLD if thrombocytopenia is severe or persisting as there are better and cost effective treatment options i.e. steroids.

### Learning points

1. All CLD with history of alcohol ingestion is not purely alcohol related.
2. Thrombocytopenia in CLD should be evaluated for causes other than alcohol and hypersplenism.
3. All autoimmune hepatitis may not have gross LFT derangement.

### References

Myopericytoma-An Alternate Cause of Persistent Knee Pain in Rheumatoid Arthritis

Lahunlang Sohliya1, John Mathew1, G Ishitha2, Jyoti Panwar3, Korula Mani Jacob4

Abstract
Rheumatoid Arthritis can present with consistent pain over peripheral joints. The manner of presentation of a subcutaneous tumour such as Myopericytoma may be very similar to that of an inflamed joint leading to the high frequency of it being overlooked and inadequately treated. Knowing the radiological and pathological differences will direct us in the right road to timely and adequate treatment.

Introduction
Myopericytoma (MPC), originally described as Hemangiopericytoma (HPC) in 1942,1 was a term used to describe a subcutaneous tumour mainly seen in distal extremities. Previous reports have talked about the misdiagnosis of these tumours frequently as Sarcomas. In our particular field of interest, their manner of presentation which can closely resemble an inflamed joint, may be overlooked, hence leading to inadequate treatment of the tumour.

We present the case of a lady known to have Rheumatoid Arthritis with persistent pain at the knee joint. The differential diagnosis of Myopericytoma particularly in patient’s with Inflammatory Arthritis will be described in this report.

Case
A 55 year old lady diagnosed with Rheumatoid Arthritis on treatment with Disease Modifying Antirheumatic Drugs (DMARDs) presented with consistent pain over the right knee for 2 years and swelling for 1 year. All the other joints were not swollen or tender. Local inspection of the right knee revealed a 1.5 cm diffuse swelling on the medial aspect of the knee joint with tenderness on palpation. An X-ray of the knee joint (Figure 1 A, B) revealed a hypoechoic lesion with prominent vascularity in the deep soft tissue. MRI (Figure 3 A-C) showed a 10x7 mm ovoid lesion with internal vascularity adjacent to the medial margin of the patella.

With a clinical and radiological suspicion of a Glomus tumour, local excision and histopathology was done. This showed monomorphic oval to spindle shaped cells with scant cytoplasm. There were inconspicuous nucleoli, fine chromatin and multilayered concentric growth around blood vessels (Figure 4 A, B). There were also many thin walled vascular channels with hemangiopericytoma like pattern at the periphery.

Immunohistochemistry showed perivascular myoepithelial cells positive for smooth muscle actin (SMA) (Figure 5). A few cells were positive for S100. Blood vessels were positive for CD31 and CD34.
Histopathological features and immunophenotype are mentioned in Table 1.

It is treated by a simple surgical excision and has a low recurrence rate. Recurrence may occur due to poor circumscription of the lesion. Malignancies are rarely seen. It is therefore important to be aware of the manner of presentation of such tumors in order to manage them adequately. This joint symptom can otherwise be managed as active joint inflammation, with unnecessary hike in immunosuppression and anti-inflammatory medications.
Conclusion

Diffuse swelling of a joint can be due to various causes one of which is a tumour such as Myopericytoma. Awareness of this entity is important as it can change a patients’ plan of management.

References


HLH - Unusual Trigger and Positive Outcome

Aravind Duruvasal1, Lakshmi2, Srinivasan3, Sowmya4, Preetam Arthur5

Abstract

Hemophagocytic Lymphohistiocytosis (HLH), is an uncommon, aggressive and life threatening syndrome of excessive immune activation. We report an unusual case of HLH, in a 34 year old male, who was admitted with Subarachnoid hemorrhage and cerebellar contusion in a Neurosurgical Intensive care unit, whose trigger is not clear.

Case Report

3 4 year old gentleman was admitted in Neurosurgical ICU of tertiary care centre at Chennai in April 2016 with subarachnoid hemorrhage (SAH) and left cerebellar contusion following an assault. Patient was treated conservatively with antiedema (Injection mannitol) and antiepileptic (Injection phenytoin) drugs. Since seizures were not controlled with single antiepileptic agent, leviteracetam and clobazam were added. On day 6 of admission, patient developed high grade fever. Repeat CT Brain done showed complete resolution of cisternal bleed. Patient was transferred under general medicine due to persistent fever which was high grade associated with chills and rigors, continuous in nature; dysuria was present. There was no associated complaints of cough, expectoration, abdominal pain, loose stools, skin rash, nausea or any bleeding manifestations.

On examination, patient was febrile with temperature of 102°F. General and systemic examination revealed no abnormality. Clinically urinary tract infection was suspected and he was started on Inj. cefaperazone with sulbactum. Patient continued to have persistent fever spikes and hence a possibility of CNS infection was also suspected and lumbar puncture was done. CSF Sugar and Protein were abnormal (Sugar – 106 mg/dl; Protein – 61 mg/dl ) CSF WBC were 35 /Cumm and RBC were 2150 /Cumm, suggesting a diagnosis of SAH / ? Partially treated bacterial meningitis and antibiotics were changed to vancomycin and ceftriaxone. Urine culture report showed Enterococcus faecalis which was covered with above treatment.

Patient continued to have persistent fever spikes and total WBC counts were on decreasing trend (18400 -14100 - 8300 - 6300 - 2000) associated with anaemia (bicytopenia). Possibility of hemophagocytosis was considered. Ferritin 8291 ng/dl (Normal-28-397) and Triglycerides 411 mgs/dl were elevated. USG Abdomen done revealed splenomegaly. Liver enzymes were elevated (SGOT -234 IU /SGPT- 168 IU); On day 19 patient started developing rashes all over the body (Figures 1 and 2). Bone marrow aspiration was done and revealed marked hypocellular marrow with suppressed erythropoiesis. Only early erythroblasts were seen. Some erythroblasts showed large basophilic intranuclear inclusions and cytoplasmic budding, suggestive of Parvo virus infection. Macrophages – Present, some show Hemophagocytosis, suggestive of Pure Red Cell Aplasia (PRCA) with hemophagocytosis (Figures 3 and 4).

Patient was treated as per HLH 2004 protocol with Inj. Dexamethasone 8 mg twice a day, Inj. Etoposide 250 mg once a day and T. Cyclosporin 175 mg twice a day. Rashes worsened over next 3 days and were maculopapular with ulceration of mucus membranes suggesting Steven Johnson’s Syndrome probably secondary to phenytoin. Dermatologist opinion was obtained. Skin rashes improved after phenytoin...
was stopped. Parvo Virus IgM was done and found to be negative. Patient condition improved over the next few days.

**Our Patient had the following**

- Fever
- Splenomegaly
- Decrease in two cell lines
  - Hemoglobin – 9.1 gms %
  - WBC – 1600 / cu mm
- Hypertriglyceridemia
- Increased ferritin levels
- Bone marrow aspirate showing hemophagocytosis

**2009 HLH diagnostic criteria**

Identification of a HLH-associated gene mutation: (PRF1, UNC13D, STX11, STXBPI, Rab2A, SH2D1A, or BIRC4)

Or

Three of the following four clinical criteria: a) Fever >38.5°C (b) Splenomegaly (c) Peripheral blood cytopenia : at least two cell lines (d) Hepatitis

and

One of the following four laboratory criteria:

a. Hemophagocytosis in bone marrow, spleen, lymphnode or Liver

b. Ferritin >500 ng/mL

c. Elevated soluble CD25
d. Low or absent NK cell activity

**Supportive criteria :**

1. Hypertriglyceridemia
2. Hypofibrinogenemia
3. Hyponatremia

**Discussion**

Hemophagocytosis, an aggressive and life threatening syndrome of excessive immune activation. It is the engulfment of hematopoietic cells by activated macrophages acting outside of usual immune system regulations. It can occur as a familial or sporadic disorder. Though infection is a common trigger both in those with primary and secondary HLH, there can be other causes like malignancy, connective tissue disorder. The excessive inflammation is thought to be caused by a lack of normal downregulation of activated macrophages and lymphocytes. The most common viral trigger is Epstein-Barr virus and it is very rarely associated with Parvo virus infection. In our case bone marrow showed erythroblasts with intranuclear eosinophilic inclusions and pure red cell aplasia is suggestive of Parvovirus B19 infection. Drugs like amoxicillin induced hypersensitivity reaction causing hemophagocytosis has been published in literature before. So the possibility of phenytoin being the trigger cannot be ruled out. Our patient was treated as per HLH 2004 protocol (Table 1). Clinically our patient had shown improvement. Cell counts normalized. Patient is on follow up and there is no recurrence as of now.

**Conclusion**

Early diagnosis and aggressive adequate treatment is the key in management of HLH. HLH should be suspected when there is cytopenia, high grade persistent fever and organomegaly. In conclusion a diagnosis of HLH was made in a patient who was admitted for subarachnoid hemorrhage and the probable trigger could be parvo virus or phenytoin or both.

**References**

Hepatitis E Virus-Associated Acute Encephalitic Parkinsonism

Shaik Afsar Pasha¹, Shaik Arif Pasha², T Suhasini², D Ankamma Rao³

Abstract
Hepatitis E virus (HEV) is a common infection worldwide and is an emerging infectious disease in the developed countries. The unique characteristics of HEV is that it displays different epidemiological and clinical characteristics between developing and developed countries. Neurological disorders are emerging extra hepatic manifestations of both acute and chronic Hepatitis E virus infection. We report a 17 year old sportsman presenting with acute encephalitic Parkinsonism concurrent with acute hepatitis. Serology was positive for Hepatitis E virus (HEV) and HEV RNA was confirmed. Patient improved completely with symptomatic treatment. We suggest offering diagnostic testing for Hepatitis E virus in patients of neurological disorders with concurrent liver impairment.

Introduction
Neurological manifestations of Hepatitis E virus (HEV) infection are rare and underrecognized. Usually HEV infection manifests as a self-limiting acute hepatitis. A literature review found 25 reports of neurological manifestations in both acute and chronic infections of HEV.¹,² Most common are Guillain Barre syndrome,¹ brachial neuritis,¹ seizures, Bell’s palsy, cranial nerve palsies, meningitis, encephalitis,² transverse myelitis,³ pseudotumour cerebri, ataxia,¹ proximal myopathy and painful sensory peripheral neuropathy.² We report an unusual presentation of acute encephalitic Parkinsonism associated with Hepatitis E virus infection.

Case Report
A 17 year old boy, with a history of recent travel, came with complaints of high grade fever, diffuse dull aching headache and flu like symptoms for 10 days. He had dysphagia and drooling of saliva on third day followed by jaundice. On Day 6 patient developed severe tightness of the limbs, paucity of limb movements with reduced blink rate and facial expression. No history of psychosis, seizures, or use of psychotropic drugs or alcohol abuse. On examination he was mentally slow at obeying commands and had icteric eyes with severe asymmetrical akinetic rigid parkinsonism characterized by axial neck dystonia, aminea, anarthria, limb rigidity more on the left side, with generalised hyporeflexia and striatal toes. He did not have any tremor. Clinical differential diagnoses of meningo-encephalitis of viral and malarial etiology were considered.

Laboratory evaluation (at the time of admission) was suggestive of acute viral hepatitis with significant transaminitis, >25 times the normal level ie; AST - 933 IU/L (N=15-37 IU/L) and ALT - 1951 IU/L (N=30-65 IU/L), bilirubin of 3.2 mg (N=0-0.3 mg/dl), and Alkaline phosphatase- 250 U/L (N=50-136 U/L), and plasma ammonia 78 (N= 20-70 micrograms/dl). Serology was positive for anti-HEV immunoglobulin IgM (Index 5.59 against a threshold value of 1- ELISA test) in serum which was confirmed with detection of HEV RNA in Serum. Other Hepatitis viruses like A, B, C and Delta and HIV were negative. Peripheral smear for Malaria parasite was negative.

MRI Brain (Figure 1a - 1d) revealed T2 and FLAIR hyper intensities noted in bilateral basal ganglia (right more than left), temporal and fronto-parietal region with thickened gyri, and

Fig. 1: (a) T2 Axial MRI Brain showing hyperintensities in bilateral basal ganglia, thalamus, insular, frontal, temporal and parietal regions (Arrow) (b-c) DWI MRI brain (b) showing the hyperintensities of bilateral frontotemporal regions with hypointensity on ADC MRI Brain (c) (Arrow) (d) T1 coronal Post contrast MRI showing enhancement of the leptomeninges

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medication and low dose steroids. was treated with anti parkinsonian reversible parkinsonism. Patient scale4 (MDS- Movement Disorder was found to be negative. slit lamp bio microscopy) was done and 24 Hr urinary copper, and KF ring by (serum copper, Serum ceruloplasmin, disease was considered. Work up including cortical regions of frontal, in the form of diffuse encephalitis. 5

Viral Parkinsonism usually has two types of clinical course like 'acute transient reversible' and 'chronic persistent permanent Parkinsonism'. Prototype of acute Parkinsonian syndrome was von Economo disease (ED) which has distinct criteria different from PEP (Post Encephalitic Parkinsonism). Our case had acute viral hepatitis E with cerebral involvement in the form of diffuse encephalitis involving cortical regions of frontal, temporal as well as sub-cortical basal ganglia manifesting as acute Parkinsonism. Similarities in this case and ED are the evidence of encephalitis and Parkinsonism while contrasting features are no evidence of hyper somnolence and Obsessive compulsive behavior, gaze palsy, oculogyric crises, and pyramidal signs.

Although phenomenology of viral Parkinsonism and idiopathic Parkinson disease are similar, it is unlikely that the pathophysiology is due to abnormal Lewy body and neurofibrillary tangle deposition in the brain tissue. The pathophysiological mechanisms of how HEV gains access to CNS is uncertain; however neurotropic quasi-species may be directly neuropathogenic.

Literature review on neuroimaging of HEV encephalitis had shown only few single case reports where in the imaging findings ranged from normal7 to diffuse white matter signal changes in both supratentorial and infratentorial brain parenchyma, bilateral symmetrical basal ganglionic and substantia nigral hyperintensities8-10 and hippocampal signal changes.11

Conclusion
The diagnosis of hepatitis E virus infection should be considered in any patient with transaminitis, concomitant with neurological symptoms and signs, regardless of age or travel history. The diagnosis may be suggested by HEV serology, however confirmation should be done by molecular documentation of HEV RNA in the serum, or CSF, or both.

References

Table 1: Association of virus and parkinsonism

<table>
<thead>
<tr>
<th>Viral genome</th>
<th>Virus family</th>
<th>Virus</th>
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<tbody>
<tr>
<td>DNA</td>
<td>Herpes viridae</td>
<td>Herpes simplex virus (HSV)</td>
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<td></td>
<td></td>
<td>Varicella zoster virus (VZV)</td>
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<td></td>
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<td>Epstein barr virus (EBV)</td>
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<td></td>
<td></td>
<td>Cytomegalovirus (CMV)</td>
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<tr>
<td>RNA</td>
<td>Orthomyxoviridae</td>
<td>Influenza type A</td>
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<td></td>
<td>Paramyxoviridae</td>
<td>Measles</td>
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<td></td>
<td>Picornaviridae</td>
<td>Coxsackie</td>
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<td></td>
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<td>Echo</td>
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<td></td>
<td></td>
<td>Polio</td>
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<tr>
<td>Retroviridae</td>
<td>Human immunodeficiency virus (HIV)</td>
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</tr>
<tr>
<td>Flaviviridae</td>
<td>West Nile virus</td>
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<tr>
<td></td>
<td>Japanese B encephalitis</td>
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</table>
Efforts to develop and refine percutaneous catheter-based procedures for cardiac valve repair and replacement have advanced over the past several years. Such clinical strategies were initiated as early as in the 1950s with the introduction of simple catheter devices for treating pulmonary stenosis. Treatment of stenotic lesions matured in the early 1980s with the advent of balloon valvuloplasty, which became the predominant therapy for pulmonary, mitral and aortic stenotic lesions. However, percutaneous balloon valvuloplasties yielded largely unfavorable results and are now seldom performed because of their short-lived benefits. But these techniques also showed that it is possible to reach the heart valves from both the antegrade and retrograde direction, and that one can use different balloon systems mounted on one or two guide-wires, double balloons, or special types of balloon.

Catheter valve procedure for aortic stenosis was developed in France, initially performed in 2002 on April 16 by Prof. Alain Cribier in Hospital Charles Nicolle, at the University of Rouen. It is now approved in more than 50 countries and is effective in improving functioning in the patients with severe aortic stenosis. Percutaneous valve implantation is mainly a development of a foldable heart valve that can be mounted on an expandable stent, delivered percutaneously through standard catheter-based techniques and implanted within a diseased valve annulus (see Israel stamp). In cases with severe aortic stenosis the diseased valve has to be pre-dilated. It is imperative that an implant has a fixed and stable intraluminary position, that provides adequate hemodynamics, and in the case of an aortic valve, that it does not compromise coronary arteries.

Percutaneous valve replacement and repair in valvular heart disease is now one of the fastest developing areas of cardiology. Transcatheter aortic and pulmonary valve replacement and a variety of mitral valve therapy approaches have been successfully performed in hundreds of patients. A number of problems encountered with the technique or with specific devices are being solved. So far these procedures have been shown to be safe; the risk of embolization is low, and complications arising from catheter use (dissection, perforation, tears, dislocation and bleeding) are uncommon.

A catheter-based valve implant as an alternative to surgery could significantly reduce morbidity and mortality. Recent reports indicate that endovascular procedures may provide an alternative to open heart operations. In addition, a less invasive therapy might permit treatment of valvular heart disease at an earlier stage and thereby prevent early onset of ventricular dysfunction. Patients also show a strong preference for minimally invasive therapies in general. Hence successful use of percutaneous approaches to valve replacement and repair could have a substantial positive economic impact, by virtue of the associated reductions in ICU and hospital stays. Potential benefits of these innovations may result in a paradigm shift, challenging surgical treatment for valvular heart diseases. However, valve durability remains unknown and long term follow-up to show the safety and effectiveness of this new treatment modality is absolutely necessary.
1st time in India

VoliboM
(Voglibose 0.2/0.3 mg + Metformin 500 mg)

Boost
PPHG Control

Preserve
β-cell function

Control
65% β-cell

T2DM
48% β-cell
Simplified Protocol to be Followed in Dental Management of Pregnant Women: Indian Perspective

Thorakkal Shamim
Dental Assistant Surgeon, Government Taluk Head Quarters Hospital, Malappuram, Kerala

Sirs,

Oral health counseling and dental examinations should be made mandatory for pregnant women. Second trimester is considered as the safest phase to do emergency and elective dental treatment procedures such as dental extractions, periodontal surgeries and root canal treatment. Left lateral supine position is the ideal position for treating pregnant women in dental set up. Dental amalgam is the most common restorative material used in dentistry and it was recommended that pregnant women should postpone having dental amalgam filling placed or removed during pregnancy to avoid its harmful effect on the foetus. The pregnant women can either go for aesthetic restorations such as glass ionomer and composite.

Clinically, the pregnant woman with dental erosion caused by prolonged pregnancy-induced vomiting will present with hypersensitivity of palatal surfaces of teeth. The dental erosion will be managed initially with monovalent and polyvalent fluorides as toothpastes, solutions, rinses, varnishes and gels and finally with adhesive techniques.

Dental radiographs can be taken during all the trimesters of pregnancy if standard radiation hygiene protocols are followed. In dental infections, paracetamol is the preferred analgesic of choice and amoxicillin, cephalosporin and clindamycin are the antibiotics of choice for pregnant women. The local anaesthesia of choice for dental procedures for pregnant women is lignocaine with adrenaline.

Good plaque control measures (regular tooth brushing, flossing the interdental areas, supragingival scaling (removing dental plaque and calculus by dental professional)) should be instituted to minimize gingivitis in pregnant women. It is important that all pregnant women with periodontitis have to initiate periodontal treatment (scaling and root planning procedures).

Oral pregnancy tumor seen in 2nd and 3rd trimester of pregnancy has to be surgically excised if it interferes with mastication. Proper oral hygiene, removal of dental plaque and use of soft toothbrushes are very important to avoid occurrence of a pregnancy tumor. This is the simple protocol to be followed in dental management of pregnant women.

Conflict of Interest

No potential conflict of interest relevant to this article was reported.

References


A Patient of Chronic Hepatitis C Complicated by Thalassemia Major and Chronic Osteomyelitis: A Therapeutic Challenge for a Clinician

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Sirs,

We had a 14 year old female patient who presented to us with acute onset pain of the right leg. She was a known case of thalassemia major, on monthly blood transfusion. Recently, she had also been diagnosed with chronic hepatitis C infection. The exact duration of this infection was not known. At presentation, the patient was severely emaciated with a body weight of 23 kg. She had severe pallor, moderate hepatosplenomegaly and a discharging sinus below the right tibial tuberosity.

Initial tests revealed hemoglobin of 3 g/dl, a total leukocyte count of 18000/μL, bilirubin of 3.6 mg/dl and SGOT/SGPT of 120/76 IU/L respectively. Her prothrombin time was normal and ultrasonography of liver did not show any fibrosis. Imaging of the right tibia showed diffuse inflammation of the entire bone. HCV viral genotype was 3 and the initial HCV viral load (by Taq-Man) was 1.02 million IU/ml. Serum ferritin was 1220 ng/ml.

The patient was given blood transfusion to raise the hemoglobin to 9 g/dl. After consultation with the orthopaedics department, treatment for the osteomyelitis was started with iv cefuroxime 750 mg thrice daily and vancomycin 15 mg/kg twice daily. However, the contentious issue was treatment of the hepatitis C infection. In the multidisciplinary meeting, one group was in favour of deferring this treatment till the osteomyelitis was resolved. But the orthopaedics colleagues were unsure of the duration of therapy needed for the osteomyelitis. It could take years and also need repeated surgeries. Hence, a decision was reached to treat the hepatitis C infection. She was started on oral sofosbuvir 400 mg and daclatasvir 60 mg once daily. After 4 weeks, her viral count became undetectable and after 12 weeks of this therapy, the viral count remained undetectable at 12, 24 and 48 weeks. She needed regular blood transfusion to maintain hemoglobin above 8 gm/dl and the discharging sinus remained at 6 months. She was drug regimens promoted by different guidelines. But sometimes a clinician may face certain other comorbidities with hepatitis C where the treatment regimen needs to be balanced according to various considerations.


A Patient of Chronic Hepatitis C Complicated by Thalassemia Major and Chronic Osteomyelitis: A Therapeutic Challenge for a Clinician

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Sirs,

The treatment of hepatitis C infection has evolved rapidly in the recent past and has opened up a lot of new options for clinicians. There are various
unable to walk on the right leg till then. For HCV genotype 3, treatment options now include sofosbuvir combined variably with daclatasvir, velpatasvir, ribavirin or interferon-alpha. 3 However, associated comorbidities will often decide the actual drug combination.

Interferon is generally avoided in patients with bacterial infection. 2 Interferon therapy is known to predispose to various bacterial infections. Although there is no specific data on the effect on interferon alpha on osteomyelitis, it was generally agreed upon by experts in our hospital to avoid it in a patient with chronic severe skeletal infection. Velpatasvir is still not available in Eastern India. Ribavirin could not be used as it is directly contraindicated in congenital haemolytic anemias like thalassemia. 3 Although sometimes ribavirin has been used in thalassemia patients, it leads to an increase in transfusion induced hepatitis C. 4 5 Hence, associated transfusion transmitted infections like osteomyelitis. 6 Many professional associations at the global as well as national level have published their own algorithms on initiation, titration and intensification of insulin regimens. In these algorithms, the regimen options vary, glycemic targets also vary but the aim is to guide the treating physicians at large. So, these algorithms are very relevant in the present era of evidence based medicine.

However I have the following areas of concern

1. The titration algorithms: Having different titration schedules for different blood glucose levels in ambulatory setting defeats the purpose of these guidelines in Indian population. The simplest titration schedules widely advocated are 2 units every 3rd day and is based on clinical trials. 7

2. Titration of twice daily premix insulin/co-formulation regimens:

As per these guidelines the titrated dose adjustments have to be made either at pre-breakfast or pre-dinner dose. But here the regimen is twice daily premix insulin/co-formulation regimens. Most of the guidelines split the calculated titrated insulin dose between the pre-breakfast and pre-dinner doses.

3. The guidelines are silent on the concept of “overbasalization”. What should be the limit of basal insulin dose after titrations? At what dose of basal insulin should intensification be considered?

References

3. RIDDICK Clinical Practice Recommendations for Management of Type 2 diabetes Mellitus - 2015 [Last accessed on 2017 Mar 5].
Olmesar
Omlarsartan Medoxomil 10 / 20 / 40 mg Tablets
BP control...every hour, 24 hours

ROSUMAC GOLD
Rosuvastatin 10 / 20 mg + Aspirin 75 mg + Clopidogrel 75 mg
3D MAGIC

Nexvas
Candesartan 5/10/20 mg Tablets
The Nex...for Cardio Renal Protection

Etizola
Etizolam 0.25 / 0.5 / 1.0 mg
Shorter action... Lesser side effects
Z Protection at 50% reduced price

Start EARLY in Hypertension

ZILARTA 80, ZILARTA 80
Effective Blood Pressure Tablets

24-hour POTENT & PRUDENT BP CONTROL