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Bedside Ultrasound: Ideal Diagnostic Approach for Patients with Undifferentiated Shock?

Trupti H Trivedi

Shock is defined as a state of acute circulatory failure leading to decreased organ perfusion, with tissue hypoxia due to reduced oxygen delivery, increased oxygen consumption or inadequate oxygen utilization. The effects of shock on end-organs are reversible if appropriate therapy can be administered early before multi-organ failure (MOF) sets in. Shock is classified as hypovolemic—due to fluid loss and hemorrhage, distributive—as in septic, anaphylactic, toxic, neurogenic or endocrine causes, cardiogenic due to myocardial failure, arrhythmias, valvular disease, and obstructive as in-pulmonary embolism, cardiac tamponade and pneumothorax. At times patient can have more than one reason for shock. While there are adequate studies on specific types of shocks individually, there is limited data on epidemiology of different types of shock in adult patients presenting in emergency department. Available information from pediatric data suggests that septic shock and hypovolemic shock are commonest followed by cardiogenic, obstructive and anaphylactic. Patients with no clear cut history of pre-existing illness or precipitating event and obvious clinical findings of cause are considered as having undifferentiated shock.

Goal in management is to recognize shock and quickly identify and treat the cause and stabilize patient. Shock index (SI) of >0.5-0.8, calculated as heart rate divided by systolic blood pressure, is more accurate predictor of shock than hypotension and tachycardia alone. Classically cool extremities, low BP, raised jugular venous pressure (JVP) and lung crepitations are characteristics of cardiogenic shock. Obstructive shock has clear chest and may have signs of cardiac tamponade. Hypovolemic shock is characterized by tachycardia, low JVP and signs of dehydration. Septic shock has initial warm shock due to hyperdynamic circulation, followed by cold sock. But, clinical assessment alone is not always sufficient to classify shock. A study that compared JVP measured by cardiologists to right atrial pressures measured by a pulmonary arterial catheter in 96 patients found an elevation over the clavicle to be only 65% sensitive and 85% specific. A number of laboratory tests are typically performed after initial stabilization with fluids, oxygenation and vasopressor administration but there is no test that is confirmatory of diagnosis. Elevated lactate levels and metabolic acidosis are seen in all patients with significant shock. Leukocytosis, elevated CRP are common findings in septic shock but not specific. Chest X ray and ECG are done in most patients, but are confirmatory of etiology in limited number of patients. Some of the specific investigations like angiography, 2D echo with color Doppler, for cardiogenic shock and CT pulmonary angiography for pulmonary thrombo-embolism (PTE) are either time consuming, invasive and may involve shifting critically ill patient elsewhere and do not serve the purpose in setting of shock. Radiological tests using contrast are harmful in patients with renal failure. Laboratory tests for markers of heart failure and sepsis like N-terminal pro b-type Natriuretic Peptide (NT-BNP), procalcitonin (PCT) are frequently used but have limited therapeutic application and are more useful for prognosis rather than diagnosis. Hence, evaluation by bedside investigation which is not time consuming or invasive is ideal.

Point of care (POC) ultrasound with RUSH (Rapid Ultrasound in Shock) protocol involves a 3-part bedside physiologic assessment of heart first, followed by ultrasound of the chest and abdomen and major blood vessels simply defined as “the pump,” “the tank,” and “the pipes”. When performed by trained personnel this serves as a quick diagnostic tool in critically ill patients with undifferentiated shock to classify them in broad categories and guide fluid therapy, vasopressor administration and even for therapeutic procedures like pericardiocentesis in cardiac tamponade. In this issue of journal, Tanvi Vaidya, et al have evaluated ultrasound as a tool to classify shock based on findings of cardiac, lung and abdominal parameters, performed within 1 hour of admission to ICU. They have selected patients with clinically undifferentiated shock and compared ultrasound based diagnosis with subsequent diagnosis based on clinical, biochemical parameters and other specific tests. Individual ultrasound parameters that predicted type of shock are also evaluated. In this study ultrasound showed maximum sensitivity, specificity, negative and positive predictive values in the setting of obstructive shock and least in distributive shock. However, clinical and biochemical parameters, used as “gold standard” cannot always accurately differentiate between types of shock and at times there can be overlap as in hypovolemic and distributive shock, which formed majority of shock patients in this study. Also, evaluation should begin earlier in emergency department (ED) as sometimes there is considerable time lapse before patient is shifted to ICU. Overall ultrasound helped in early classification of type of shock and forming management strategies and authors have rightly recommended use of ultrasound as modality of first choice for assessment of patients with undifferentiated shock. Its utility on patient’s outcome should be assessed in future studies.

In summary, POC ultrasonography is portable, inexpensive, rapid and
safe modality of diagnosis that does not expose the patient to ionizing radiation. It helps to narrow the differential diagnosis and identify a potentially treatable etiology for patients with clinically undifferentiated shock. In a prospective observational study of 110 critically ill patients with undifferentiated shock, the use of ultrasound was associated with reduced infusion of intravenous fluids, increased administration of vasopressors, and improved 28-day survival. Major disadvantage of POC ultrasonography is its limited sensitivity for many of the etiologies associated with shock like pulmonary embolism that necessitates other definitive investigations to rule out PTE in critically patients. Due to bed-side definitive investigations to rule out PTE embolism that necessitates other sensitivity for many of the etiologies POC ultrasonography is its limited availability, speed, noninvasive nature and its ability to provide repeated assessment of physiology during resuscitation, this modality has now found a place into resuscitation protocol in emergency department to augment clinical evaluation and guide resuscitation of shock patients. In India, efforts are going on towards training doctors working in emergency department for performing emergency ultrasound with a short 4 days workshop so that the knowledge can be applied to managing critically ill shock patients in both trauma and non-trauma setting. But clinicians must realize that many forms of shock may coexist in a given patient. For example, hypovolemia may be present along with cardiogenic shock and may result in discordant hemodynamic features. In such cases, therapeutic response to empiric therapies (fluid challenge) may allow the clinician to determine which form of shock is predominant. While septic shock is the most common cause of distributive shock, other causes requiring totally different therapy like anaphylaxis, neurogenic shock, liver failure and adrenal insufficiency can present with similar physiological derangements and this needs to be determined clinically. Also, sepsis can present with characteristics of distributive, hypovolemic, and even cardiogenic shock. Clinicians have to consider broad differential diagnosis while evaluating patients with distributive pathophysiology to avoid missing treatable options. Bed side ultrasonography should be used as complimentary to clinical evaluation, keeping in mind its limitations in evaluating undifferentiated shock patients presenting in ED.

References


Role of Ultrasound in Evaluation of Undifferentiated Shock in ICU Settings

Tanvi Vaidya¹, Pradeep D’costa², Satish Pande³

Abstract
Objective: To classify shock, using ultrasonography as the modality of choice for imaging and to assess the diagnostic accuracy of ultrasound as a tool to classify shock.
Design: Prospective study
Setting: KEM Hospital, Pune in the ICU (Intensive care unit)
Study Population: 100 patients admitted to the ICU with undifferentiated shock.
Methods: Bedside ultrasound examination was performed within 1 hour of admission to the ICU. These patients were also evaluated clinically and biochemically to confirm the type of shock. All patients immediately received standard diagnostic emergent interventions including physical examination, intravenous access for whole blood assays, arterial gas analysis, electrocardiography, continuous cardiac monitoring, supplemental oxygen and chest radiograph. Clinical parameters, urine output, ECG and biochemical tests were performed within 12 hours of USG. Additional investigations were performed wherever required. The ultrasonographic diagnoses were compared with the respective final clinical diagnoses by employing the Cohen kappa inter-rater coefficient of agreement. In addition, various ultrasound parameters were also analyzed to assess the best predictors for each type of shock.
Results: The ultrasound diagnosis showed an overall good agreement (Cohen’s kappa coefficient > or = 0.6) with the final clinical diagnosis, in identifying the type of shock, in the emergency setting, when ultrasound was done within 1 hour after admission to the ICU. In our study, ultrasound showed maximum sensitivity, specificity, negative and positive predictive values in the setting of obstructive shock. In addition, perfect agreement was seen between the ultrasound and clinical diagnosis, with a Cohen kappa coefficient of 1 in obstructive shock. The least sensitivity, specificity, negative and positive predictive values of ultrasound were seen in the setting of distributive shock. Least agreement between the ultrasound and clinical diagnosis was also seen in distributive shock, as most ultrasound findings were found to overlap with those in the other types of shock. (Cohen kappa coefficient of 0.6).
Conclusions: Ultrasonography carried out within 1 hour of admission to the ICU plays a major role in correct diagnosis of the type of shock and subsequent patient management. The best ultrasonographic predictors for diagnosis of each type of shock, can help the clinician to start timely specific interventions in critical care settings for each type of shock.

Introduction
Shock is one of the leading causes of death worldwide. The fundamental approach to management, therefore, is to recognize overt and impending shock in a timely fashion and to intervene urgently to restore perfusion.

Evaluation of a patient in shock can be challenging owing to its complex pathophysiology and the spectrum of overlapping clinical findings. It is essential for the intensivist to identify the type and etiology of shock so as to formulate an emergency plan of management to prevent disastrous outcomes. The aim of our study was to outline the role of emergency bedside ultrasound in the evaluation of the patient in shock. We, performed a prospective study in the ICU, using bedside ultrasound to evaluate patients admitted with undifferentiated shock so as to classify shock into 4 categories, ie. hypovolemic, distributive, cardiogenic and obstructive or any combination of the above; and to assess the diagnostic accuracy of ultrasound as a tool to classify shock, by comparing the diagnosis on ultrasound with the final diagnosis, based on clinical and biochemical evaluation.

Methods

Patient Selection

The prospective study was carried out at KEM Hospital, Pune in the ICU (Intensive care unit). A total of 100 patients of undifferentiated shock were included in the study. The duration of the study was 385 days ranging from 5th January 2014 to 25th January 2015.

Patients included in the study, had age >18 years, systolic blood pressure < 90 mmHg at presentation, and presence of at least one of the following signs or symptoms of hypoperfusion: unresponsiveness, altered mental status (including unexplained severe anxiety), syncope, respiratory distress, profound asthenia with fatigue and malaise, and severe chest or abdominal pain. Patients were excluded from the study if they had a clear cause of shock diagnosed before the ultrasonographic evaluation mandating prompt life-
saving treatment, such as external bleeding, trauma, and pregnancy related complications.

Equipment Used

Machines used for the study were Sonosite M-Turbo and Voluson ultrasound machines. The straight linear array probe- 5 – 12 MHz, Curvilinear probe- 2-5 MHz and Sector array ultrasound probe 1-5 MHz were used for the study. The R Statistical software was used for data analysis.

Ultrasonographic Technique

A comprehensive ultrasonography exam was carried out with the following parameters being studied. It was based on the RUSH protocol.1

Cardiac Parameters

The parasternal long axis(PLAX) and the apical four-chamber (A4C) views were used to evaluate :
1. Left ventricular ejection fraction (EF) using Teicholz formula.3 EF < 50% was considered as hypodynamic (Figure 1) while EF> 75% was considered as hyperdynamic.
2. Cardiac tamponade characterized by massive pericardial effusion with diastolic right atrial and ventricular collapse.1
3. Right heart strain1 indicated by dilatation of the right atrium and ventricle.

Lung Parameters

A curvilinear probe (2 to 5 MHz) was used to visualize the lungs. A straight linear array probe 5 – 12 MHz frequency, was used for the assessment of pneumothorax. Lungs were assessed for the presence of ‘A’ lines, ‘B’ lines, and presence of consolidation. The ultrasonography profiles which were commonly seen were 3,4 ‘A’ profile - A lines with sliding movements suggestive of normal lung, ‘B’ profile with multiple B lines suggestive of pulmonary edema and ‘C’ profile suggestive of consolidation (Figure 2). ‘A’ profile with absence of lung sliding and identification of lung point were considered diagnostic of pneumothorax. Pleural effusion was looked for in the dependent lung areas delineated by the chest wall and the diaphragm.

Abdominal Parameters

Fast Examination15

The standard curvilinear ultrasound probe was used. Specific areas to assess include the space between the liver and kidney (Morison pouch), perisplenic space, and the area around and behind the bladder (pouch of Douglas). A dark or anechoic area in any of these 3 potential spaces represents free intraperitoneal fluid.1

IVC Evaluation

An estimate of the intravascular volume can be determined noninvasively by looking initially at the IVC.6 Measurement of the IVC size and collapsibility was performed at the point just inferior to the confluence with the hepatic veins, at a point approximately 2 cm from the junction of right atrium and IVC.1 The maximum and minimum diameters of the IVC tracing were measured to determine IVC collapsibility.6 The IVC collapsibility is given by the formula: 6 (Maximum expiratory diameter – Minimum inspiratory diameter)/Maximum expiratory diameter.

Table 1 shows the relationship between IVC size and collapsibility7 and outlines the parameters for IVC measurement. A normal IVC measures between 1.5 to 2.5 cm in diameter and shows >50% collapsibility with inspiration.

A smaller caliber IVC with an inspiratory collapse greater than 50% roughly correlates to a CVP of less than 10 cm of water. This phenomenon is observed in hypovolemic and distributive shock states. A larger sized IVC that collapses less than 50% with inspiration correlates to a CVP of more than 10 cm of water.1 This may be seen with cardiogenic and obstructive shock (Figure 3).

Evaluation of the Vasculature

Aortic Aneurysm and Dissection

Using a curvilinear probe, the abdominal aorta was evaluated from epigastrium to iliac bifurcation. The diameter of the abdominal aorta was measured in short axis view, a measurement >30 mm was considered a sign of dilatation.1 The presence of aortic dissection was evaluated by colour flow imaging which delineated 2 lumens (Figure 4).

Deep Vein Thrombosis

The deep veins of the leg were examined for collapsibility in the short axis using a linear 5—12-MHz probe. Absence of collapsibility, presence of an echogenic thrombus within the lumen, and absent or decreased flow on colour doppler imaging were considered diagnostic for intra luminal thrombosis.1

Table 1: IVC size and collapsibility7

<table>
<thead>
<tr>
<th>IVC size</th>
<th>IVC collapse with inspiration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Small &lt; 1.5 cm</td>
<td>Normal&gt;50%</td>
</tr>
<tr>
<td>Normal 1.5 to 2.5 cm</td>
<td>Abnormal &lt; 50%</td>
</tr>
<tr>
<td>Dilated &gt;2.5 cm</td>
<td>Dilated IVC: No change</td>
</tr>
</tbody>
</table>

* - necessarily present.

Based on our ultrasonography findings, we classified shock into 5 types as follows:

1. Hypovolemic:
   - Heart: Hyperkinetic left ventricle *
   - Inferior vena cava: Collapsed IVC or IVC diameter <1.5 cm with >50% collapse *
   - Lungs: ‘A’ profile
   - Abdomen: Aortic aneurysm/Aortic dissection

2. Distributive:
   - Heart: Raised/decreased/normal EF.
   - Inferior vena cava: Diameter < 2.5 cm. with >50% collapse.
   - Lungs: ‘A’ profile or ‘C’ profile.
   - At least 2 of these signs must be present.

3. Cardiogenic:
   - Heart: Hypokinetie left ventricle
   - Inferior vena cava: 1.5-2.5 cm. or > 2.5 cm. with <50% collapse
   - Lungs: ‘B’ profile*
   - Peripheral veins: normal.
   - *- necessarily present.

4. Hypovolemic / Distributive shock:
   - Features of distributive shock
   - Presence of free fluid*
   - *- necessarily present.

5. Obstructive shock:
   - Heart: Cardiac tamponade / Right heart strain’
   - IVC: <50% respiratory collapse and IVC diameter >2.5 cms.*
   - Lungs: ‘A’ Profile / Pneumothorax’.
   - Peripheral veins: Deep vein
software and Microsoft Excel were used for each type of shock.

Parameters to assess the best predictors of shock were calculated. In addition, we used ultrasound to diagnose each type of shock and obstructive shock in our study were: free fluid seen in 100% cases (n=5 out of 5), right heart strain in 40% cases (n= 2 out of 5 cases), right heart strain in 50% cases (n=3 out of 5), ‘A’ profile on lung ultrasound in 100% cases (n=5 out of 5), distended IVC with <50% collapsibility in 100% patients (n= 5 of 5).

The sensitivity, specificity and positive predictive value of ultrasound in diagnosing different types of shock were also statistically evaluated and is depicted in table 2. Table 3 depicts Correlation between Clinical Diagnosis and Ultrasound Diagnosis for Shock and the Cohen kappa Inter-Rater Coefficient of Agreement between them.

Table 2 depicts that ultrasound showed the highest Sensitivity, Specificity and Positive predictive value in diagnosing obstructive shock. The lowest specificity and Positive predictive value was seen in diagnosing distributive shock, and the lowest sensitivity was seen in diagnosing hypovolemic shock.

Table 3 shows that ultrasound showed an overall good correlation with the final diagnosis in the evaluation of shock. The highest degree of agreement was seen in obstructive shock and the least was seen in distributive shock.

In addition, we statistically evaluated each ultrasound parameter to ascertain the best predictors of each type of shock, shown in Table 4. This evaluation was not performed by other investigators in the setting of shock. Hence our study differed from other similar studies.

Table 4 outlines the collective parameters which predict the diagnosis of each type of shock on ultrasound evaluation.

Discussion

Bedside ultrasonography is an excellent diagnostic methodology to evaluate the etiology of undifferentiated hypotension at bedside. A rapid, yet comprehensive multi-organ protocol improves the diagnostic accuracy in cases of challenging clinical situations in the intensive care unit. The ultrasound diagnosis showed an overall good agreement (Cohen’s kappa coefficient > 0.6) with the final clinical diagnosis, in identifying the type of shock, in the emergency setting, when ultrasound was done within 1 hour after admission to the ICU with >50% collapsibility in 83.3% cases (n=11 of 13), normal caliber IVC with >50% collapsibility in 100% (n=10 of 10) patients.

The sensitivity, specificity and positive predictive value of ultrasound in diagnosing different types of shock

Table 3: Correlation between final diagnosis and ultrasound diagnosis for shock and the Cohen’s kappa inter-rater coefficient of agreement between them

<table>
<thead>
<tr>
<th>Types of shock</th>
<th>Final diagnosis</th>
<th>Ultrasound diagnosis</th>
<th>Cohen’s kappa coefficient</th>
<th>Strength of agreement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypovolemic</td>
<td>10</td>
<td>6</td>
<td>0.73</td>
<td>Good</td>
</tr>
<tr>
<td>Distributive</td>
<td>39</td>
<td>28</td>
<td>0.6</td>
<td>Good</td>
</tr>
<tr>
<td>Cardiogenic</td>
<td>22</td>
<td>18</td>
<td>0.79</td>
<td>Good</td>
</tr>
<tr>
<td>Hypovolemic/Distributive</td>
<td>24</td>
<td>32</td>
<td>0.8</td>
<td>Good</td>
</tr>
<tr>
<td>Obstructive</td>
<td>5</td>
<td>5</td>
<td>1.0</td>
<td>Very good</td>
</tr>
</tbody>
</table>

The ultrasonographic findings in hypovolemic shock in our study were: increased ejection fraction of >70% in 60% cases (n= 6 of 10), ‘A’ profile in 90% patients (n=9 of10), IVC diameter <1.5 cm. in 80% patients (n=8 of 10), IVC collapsibility >50%, in 100% (n=10 of 10) patients.

The ultrasonographic findings in distributive shock in were: Normal ejection fraction in 71.8% (n= 28 of 39), ‘A’ profile in 79.5% cases (n=31 of 39), normal caliber IVC with >50% collapsibility in 79.5% cases (n=31 of 39).

The ultrasonographic findings in cardiogenic shock in our study were: reduced ejection fraction of <55% in 100% cases (n=22 out of 22), ‘B’ profile on lung ultrasound in 81.8% cases (18 of 22), IVC collapsibility <50% in 66.67% patients (n= 14 of 22 cases).

The ultrasonographic findings in hypovolemic/distributive shock in our study were: free fluid seen in 100% cases, (n=24 of 24), normal ejection fraction in 75% patients (n=18 of 24); ’A’ profile on lung ultrasound in 95.8% patients (n=23 of 24), pleural effusion in 46% cases (n=11 of 24), normal caliber IVC with >50% collapsibility in 83.3% patients (n=20 of 24).

The ultrasonographic findings in obstructive shock in our study were reduced ejection fraction of <55% in 100% cases (n=5 out of 5), cardiac tamponade in 40% cases (n= 2 out of 5 cases), right heart strain in 60% cases (n=3 out of 5), ‘A’ profile on lung ultrasound in 100% cases (n=5 out of 5), distended IVC with <50% collapsibility in 100% patients (n= 5 of 5).

The total number of patients in our study was 100. The average age of patients was 51.5 years (range=30-80 years). The predominant type of shock in our study was distributive shock (39 %), followed by hypovolemic/ distributive type, (24 %), cardiogenic shock (22%), hypovolemic shock (10%). The least common type of shock was obstructive shock (5%) cases.

Accordingly, the type of shock was classified into 5 categories namely: hypovolemic, distributive, cardiogenic, hypovolemic/distributive and obstructive types. These patients were also evaluated clinically and biochemically to confirm the type of shock. Additional investigations were performed wherever required. The biochemical and clinical parameters were evaluated by the intensive care physician and the final diagnosis was established based on these and also depending on the response to treatment. The diagnostic accuracy of ultrasound to classify shock was then assessed by statistical analysis.

Statistical Evaluation

The ultrasonographic diagnoses were compared with the respective final clinical diagnoses by employing the Cohen kappa inter-rater coefficient of agreement. Values assumed by the coefficient in the analysis performed, were reported with the 95 % confidence intervals. For our statistical hypothesis test, p < /=0.05 was considered significant. The sensitivity, specificity, positive and negative predictive values of ultrasound to diagnose each type of shock were calculated. In addition, we also analyzed the various ultrasound parameters to assess the best predictors for each type of shock. The R Statistical software and Microsoft Excel were used for statistical calculation.

Results

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Table 4: Collective parameters which predict the diagnosis of each type of shock

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Hypovolemic (n=10)</th>
<th>Distributive (n=39)</th>
<th>Cardiogenic (n=22)</th>
<th>Hypovolemic/Distributive (n=24)</th>
<th>Obstructive (n=5)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ejection fraction</td>
<td>&gt;70% (n=6)</td>
<td>55-70% (n=28)</td>
<td>&lt;55% (n=22)</td>
<td>55-70% (n=16)</td>
<td>&lt;55% (n=5)</td>
</tr>
<tr>
<td>Right heart strain</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>Present (n=3)</td>
</tr>
<tr>
<td>Cardiac tamponade</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>Present (n=2)</td>
</tr>
<tr>
<td>Lung profile</td>
<td>-</td>
<td>‘C’ profile (n=8)</td>
<td>‘B’ profile (n=18)</td>
<td>‘A’ profile (n=23)</td>
<td>-</td>
</tr>
<tr>
<td>Pleural effusion</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>IVC size</td>
<td>1.5 cm (n=10)</td>
<td>1.5 to 2.5 cm. (n=31)</td>
<td>1.5 to 2.5 cm. (n=17)</td>
<td>1.5 to 2.5 cm. (n=20)</td>
<td>&gt;2.5 cm. (n=5)</td>
</tr>
<tr>
<td>IVC collapsibility</td>
<td>&gt;50% (n=10)</td>
<td>&gt;50% (n=31)</td>
<td>&gt;50% (n=14)</td>
<td>&gt;50% (n=24)</td>
<td>&gt;50% (n=5)</td>
</tr>
<tr>
<td>Free fluid</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Aortic aneurysm</td>
<td>Present (n=2)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Aortic Dissection</td>
<td>Present (n=1)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Deep vein thrombosis</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>Present (n=3)</td>
</tr>
</tbody>
</table>

Fig. 1: Evaluation of ejection fraction using M mode echocardiography. Distance A represents the end systolic diameter and distance B represents the end diastolic diameter. Ejection fraction by Teicholz method was 39.1% in this case (hypodynamic), seen in a case of cardiogenic shock in our study.

Fig. 2: 'C' profile in a case of distributive shock in our study.

Fig. 3: Absent collapsibility of the IVC on M Mode in a case of obstructive shock in our study.

ICU. Thus, our protocol was effective in providing an initial diagnosis in cases of undifferentiated hypotension in the emergency department.

In our study, ultrasound showed maximum sensitivity, specificity, NPV (negative predictive value) and PPV (positive predictive value) in obstructive shock. In addition, perfect agreement was seen between the ultrasound and clinical diagnosis, with a Cohen kappa coefficient of 1 in obstructive shock. The least sensitivity, specificity, NPV and PPV of ultrasound was seen in distributive shock. Least agreement between the ultrasound and clinical diagnosis was also seen in distributive shock. Least agreement between the ultrasound and clinical diagnosis was also seen in distributive shock, as most ultrasound findings were found to overlap with those in the other types of shock. (Cohen kappa coefficient of 0.6).

Our study also revealed how a combination of ultrasonographic findings can reliably predict the diagnosis of each type of shock in the emergency setting. Identification of the best predictors of each type of shock, can help the radiologist and the intensivist to predict the type of shock and plan emergent interventions accordingly. This would significantly influence clinical decision making and have an invaluable role in the management of critically ill patients.

Our study had a few limitations. One of these is that the differentiation of hypovolemic from distributive shock is often difficult, as the ultrasonographic findings may overlap in many cases. However clinical differentiation is also not always possible. This limitation was also encountered in the study by Volpicelli et al. In the study by Postma, Wood D.R., Wallis L.A, there was no “gold standard” investigation to compare the ultrasound findings with, hence they were not able to objectively assess the diagnostic accuracy of ultrasound. This limitation was not encountered in our study and the studies by Volpicelli et al and Ghane et al, as the gold standard was a diagnosis based on a combination of clinical and biochemical investigations.

Conclusion

Bedside ultrasonography in patients with undifferentiated shock is useful for rapid evaluation of various causes of shock and offers accurate diagnosis for subsequent treatment. Bedside ultrasonography, within 1 hour of admission is an excellent diagnostic
Glycemic Status at the Time of Presentation in Acute Organophosphorous Poisoning and its Correlation with Severity and Clinical Outcome

R Raghapriya¹, Rupal V Dosi²*, Aeshal Parmar³

Abstract

Background: Organophosphorus insecticides (OPI) are one of the most extensively used classes of insecticides. Huge scientific body of evidence suggests that OPI exposure is a major toxicological threat that may affect human and animal health because of their various toxicities such as neurotoxicity, endocrine toxicity, immunotoxicity, reproductive toxicity, genotoxicity and ability to induce organ damage, alterations in cellular oxidative balance and disrupt glucose homeostasis. Mortality among organophosphorous (OP) poisoning patients despite advancements in its management is of concern. Of the various contributing factors, extremes and fluctuation in the glycemic status is a well-documented parameter affecting the outcomes in critical illness although studies with respect to OP poisoning are deficient. All varieties of glycemic changes from hypoglycemia to hyperglycemia and ketoacidosis in OP poisoning along with other toxicological effects are reported, studies corroborating these findings are only few. The present endeavor was undertaken to study various glycemic changes in acute OP poisoning and its bearing on clinical severity and clinical outcome.

Aims and Objectives

1. To assess the glycemic status by estimating random blood glucose level at the time of admission in cases of acute organophosphorous poisoning (the fluid administration limited by lung sonography protocol). J Crit Care 2012; 27:533.

References


Introduction

Organophosphorus (OP) poisoning is a major health problem all over the world, particularly in a predominantly agrarian country like India. National crime bureau of India shows suicide by consumption of pesticides account for cases of suicidal poisoning per year. OPI exposure is a toxicological threat that may affect human and animal health because of their various toxicities such as neurotoxicity, endocrine toxicity, immunotoxicity, reproductive toxicity, genotoxicity and ability to induce organ damage, alterations in cellular oxidative balance and disrupt glucose homeostasis.
2. To assess severity of the poisoning with various poisoning scales (PSS and POP) and level of serum pseudocholinesterase.

3. To correlate the documented blood glucose level with the severity and clinical outcome.

Method: A prospective analytical study of 100 patients with diagnosed acute poisoning, above the age of 18 years, non diabetic, with no history of mixed poisoning or condition affecting blood glucose levels and fulfilling the inclusion and exclusion criterias was done over a period of one year. The glycemic status at the time of presentation was documented and the patients were grouped into hypoglycemics, euglycemics and hyperglycemics and the same was correlated with the severity and clinical outcome using descriptive statistics, association and test of significance using MedCalc.

Results: A prospective analytical study of 100 patients of acute organophosphate poisoning was done and on the basis of blood glucose levels at the time of presentation were further categorised into hypoglycemics (37%), euglycemics (52%) hyperglycaemic (11%). The outcome in terms of mortality was 59.45%, 9.6% and 63.63% in the respective groups. The ventilator requirements among the three groups were 94.59%, 53.84% and 100% respectively.

Chisquare test to study the association between the presentation Random Blood Glucose (RBG) and the established Peradeniya Organophosphorous Poisoning Scale (POP) (Table 1) and Poisoning Severity Scale (PSS) (Table 2) revealed the study to be statistically significant (p value= 0.001)indicating both the extremes of glycemic status are associated with higher clinical severity and poorer outcomes.

Conclusion: We conclude that the glycemic status at the time of presentation in acute organophosphate poisoning patients is a simple, cheap, reliable marker in guiding the clinical severity and outcome when considered with clinical severity scores and S.ChE in a resource limited country like India.

Thus, this study was done to assess the Glycemic status at the time of presentation in acute organophosphorous poisoning and its correlation with clinical severity and outcome.

Material and Methods

Material
Source of data

Data was collected from patients fulfilling the inclusion and exclusion criteria Admitted to the S.S.G. Hospital, Vadodara. Informed written consent was obtained from patient or a responsible attendant before including the patient in the study. In addition to Baroda city, a large cross section of population comes to SSGH from Central and North Gujarat as well as from the states of Rajasthan, Madhya Pradesh and Maharashtra.

Study design: Prospective Analytical study

Sample size: According to data obtained from previous studies and considering the local current rates of admission with organophosphorous poisoning in our hospital the sample size of 96 patients rounded off to 100 has been considered.(Ref. Medcalc software)

Data collection: 1 year period-Nov 2016 to Nov 2017

Patients fulfilling following inclusion and exclusion criteria were enrolled for the study.

Inclusion criteria
1. Patients or the relatives who have given informed written consent.
2. Patients who are above 18 years of age.
3. Patient with alleged history of organophosphorous poisoning (ingestion / inhalational / contact) and diagnosed to have organophosphorous poisoning.

Exclusion Criteria
1. Patients with age less than 18 years.

Table 1: Peradeniya organophosphorus poisoning scale (POP scale)

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Criteria</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pupil size</td>
<td>≥2 mm</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>&lt;2 mm</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Pinpoint</td>
<td>2</td>
</tr>
<tr>
<td>Respiratory rate</td>
<td>&lt;20/min</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>≥20/min</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>≥20/min with central cyanosis</td>
<td>2</td>
</tr>
<tr>
<td>Heart rate</td>
<td>&gt;60/min</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>41-60/min</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>&lt;40/min</td>
<td>2</td>
</tr>
<tr>
<td>Fasciculation</td>
<td>None</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Present, generalized/ continuous</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Both generalized and continuous</td>
<td>2</td>
</tr>
<tr>
<td>Level of consciousness</td>
<td>Conscious and rationale</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Impaired response to verbal commands</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>No response to verbal commands</td>
<td>2</td>
</tr>
<tr>
<td>Seizures</td>
<td>Absent</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Present</td>
<td>1</td>
</tr>
</tbody>
</table>

Note: 0-3, mild poisoning; 4-7, moderate poisoning; 8-11, severe poisoning

Table 2: Poisoning severity scale

<table>
<thead>
<tr>
<th>System</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastrointestinal system</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Respiratory system</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nervous system</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CVS</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Metabolic derrangement</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Liver</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kidney</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blood</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Muscular system</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Skin / Local</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Eye</td>
<td></td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

The results of various studies in critically ill patients have shown that stress-induced hyperglycaemia as well as hypoglycemia are strong predictors of increased mortality and adverse clinical outcome.1-3

Extremes in glycemic status is found to be associated with increased risk of infectious complications and septic shock, reduced immune response, dehydration and electrolyte imbalances and lethal multiple organ failure in traumatic and acute ischaemic events.4-5

Although poisoning is one of the important causes of significant morbidity and mortality, and appropriate management is very important in critically ill poison patients, acute poisoning induced hyperglycaemia and hypoglycemia has not been previously studied in these patients.

The rising mortality despite adequate poisoning management forces us to investigate for other possible contributory factors. The glycemic status is one such variable that affects the outcome in critical illness.

Thus, this study was done to assess the Glycemic status at the time of presentation in acute organophosphorous poisoning and its correlation with clinical severity and outcome.
2. Patients with history Diabetes Mellitus.
3. Patients already treated at other centres and referred to our centre for further management with no details available at the time of first presentation.
4. Patients who had consumed alcohol, drugs, mixed poisoning that could affect the glycemic status of the patients.

**Methods**

**Patients**

The prospective analytical study was done in SSG Hospital, Vadodara. Patients aged over 18 years with a diagnosis of acute organophosphorous poisoning were included in the study. The diagnosis was based on history of short term exposure or contact, characteristic clinical signs and symptoms, decrease in serum cholinesterase activity. Subjects wherein the exact nature of the poisoning could not be established and known diabetics were excluded from the study.

A detailed history including particulars regarding age sex, type of compound consumed, time-lag between consumption and initiation of treatment was taken followed by a thorough clinical examination. The severity of the poisoning was graded by POP scaling and PSS.

Severity of Poisoning: Mild (score 0-3), Moderate (score 4-7), Severe (score 8-11)

Hyperglycemia and hypoglycemia were defined as random blood glucose of more than 200 mg/dL and hypoglycemia as less than 80 mg/dL. Glycosuria was detected using ketodiastix strips.

The presence of hyperglycemia or glycosuria or hypoglycemia or ketosis was correlated with the severity of the poisoning with respect to the nature of the compound consumed, the time lag between consumption and initial treatment, the clinical grade of poisoning, the serum pseudocholinesterase level and the requirement of assisted ventilation and outcome.

Following investigations were carried out in each patient.

**Investigations**

1. Random blood glucose level at the time of admission.
2. Pseudocholinesterase levels at the time of admission.
3. Complete blood count.
4. Liver function tests.
5. Serum creatinine and blood urea.
6. Urine analysis.
7. HbA1C. (if hyperglycemia documented)
8. ECG.

Other relevant investigations if required.
Table 6: Association of glycemic status (RBG) of patients with different grades of POP score

<table>
<thead>
<tr>
<th>POP</th>
<th>&lt;55-80 mg/dL</th>
<th>101 to 200 mg/dL</th>
<th>&gt;200 mg/dL</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 to 3 (Mild)</td>
<td>53</td>
<td>17</td>
<td>36</td>
</tr>
<tr>
<td>4 to 7 (Moderate)</td>
<td>47</td>
<td>20</td>
<td>16</td>
</tr>
<tr>
<td>8 to 11 (Severe)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td>100</td>
<td>37</td>
<td>52</td>
</tr>
</tbody>
</table>

Fig. 4: Association of glycemic status of patients with different grades of POP score

Table 7: Association of glycemic status (RBG) of patients with different grades of PSS

<table>
<thead>
<tr>
<th>PSS</th>
<th>&lt;55-80mg/dL</th>
<th>101 to 200 mg/dL</th>
<th>&gt;200 mg/dL</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 to 3 (Mild)</td>
<td>25</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>4 to 7 (Moderate)</td>
<td>57</td>
<td>23</td>
<td>7</td>
</tr>
<tr>
<td>8 to 11 (Severe)</td>
<td>18</td>
<td>12</td>
<td>4</td>
</tr>
<tr>
<td>Total</td>
<td>100</td>
<td>37</td>
<td>52</td>
</tr>
</tbody>
</table>

Fig. 5: Association of glycemic status of patients with different grades of PSS

Results

The demographic and clinical characteristics of 100 patients revealed a male preponderance (63%) and females (37%). The mean age of the study population was 25.5±8 (range 18-65 yrs). The overall incidence was higher in married group and the most common cause of poisoning was suicidal (83%) followed by accidental (16%) and unknown (1%). Ingestion (88%) was the most common mode of poisoning followed by inhalational (12%).

The population in grade 1 and grade 2 POP scores were 53% and 47% respectively. The percentage of population in grade 1,2,3 of PSS were 25%, 57% and 18% respectively.

Out of 100, 74% patients developed respiratory failure necessitating ventilator requirement. The overall mortality was 34% and 66% patients were discharged.

The ventilator requirement and mortality was higher with higher grades of and POP (Table 3 and Figure 1) and PSS (Table 4 and Figure 2)

As per on presentation RBG,37% had hypoglycemia,52% were euglycemic and 11% were hyperglycemics. The ventilator requirement in the three groups were 94.59%, 53.84% and 100% respectively and the mortality was 59.45%, 9.6% and 63.63% respectively (Table 5 and Figure 3). Hence a very strong correlation between the glycemic status, ventilator requirements and mortality was established.

Further, the RBG was compared with POP and PSS to look for statistically significant association between the extremes of glycemic status and higher grades of these clinical severity scores using Chi-square test in MedCalC. The results were statistically significant (p=0.0001, Chisquare=18.643, DF=2 for POP and p=0.0001, Chisquare=28.748, DF=4 for PSS) (Tables 6, 7 and Figures 4, 5).

The association between extremes of glycemic status and the grades of POP is statistically significant (P<0.0001, Chi Square 18.643, DF = 2).

The association between extremes of glycemic status and the grades of PSS is statistically significant (P<0.0001, Chi Square 28.748, DF = 4)

Discussion

Among 100 patients studied, the poisoning was more common among males, age group of 18-40 years and married cohort. The most common cause was suicidal and the most common mode was ingestion. The mean time lag between the consumption and medical attention seeking was 5±2.6 hrs.

Vomiting, abdominal pain, altered sensorium and breathlessness were the most common symptoms. In emergency department, most patients had POP grade 1 and on further follow up in critical care unit, the majority developed grade 2 and 3 PSS. Respiratory failure necessitating the need for ventilator was the most lethal and most common complication.

Of the study group, the glycemic status on presentation was in the following order of decreasing frequency-euglycemia (52%) followed by hypoglycaemia (37%) and hyperglycemia (11%) whereas the study by Ali Mohammad Sabzghabee et al. showed 62%, 14% and 23% respectively (hyperglycemics more than hypoglycemics).

Our study showed that the severity of poisoning was of grade 2 or more in both the extremes of glycemic status (100% in hyperglycemia and 90% in hypoglycaemia) and majority of the euglycemics had grade 1 poisoning which is in correlation with study by Ali Mohammad Sabzghabee et al.

The ventilator requirements and complications were 94.59%, 53.84% and 100% among hypoglycemics, euglycemics and hyperglycemics respectively. The study by Preeti G Pendkar et al. showed the incidence of complications to be 73% in hyperglycemics, 27% in normoglycemics and hypoglycemics were not included in the study.

The mortality in Ali Mohammad Sabzghabee et al. was 10.4%, 3.71% and 15% in hypoglycemics, euglycemics and hyperglycemics whereas the overall mortality was higher in our study but keeping in trend with the previous study in the order of decreasing frequency-hyperglycemia (63.63%), hypoglycaemia (59.45%) and normoglycaemia (9.6%).

Understanding the mechanism of glycemic variability in OP poisoning and its burden on the clinical outcomes are of importance as our study shows a significant association between the extremes of the glycemic status and complications and outcome.

Although the studies enlightening the mechanisms of glycemic variability in acute OP poisoning are few, the following plausible reasons could be attributed:3–12

1. The effect of stress hormones,
2. Overproduction of
proinflammatory cytokines,
3. Pancreatic insufficiency,
4. Altered hepatic metabolism due to depletion of enzymes by the toxin that play major role in glucose metabolism and
5. The prior nutritional status of the patient.

Hyperglycemia and fluctuation in the glycemic status are known to be deleterious in critical illness as they increase the overall complications, morbidity, hospital stay and mortality.

A strong association with hyperglycemia and critical illness neuropathy is documented that contributes to increased need and duration of mechanical ventilator support and other complications and mortality.

Likewise, hypoglycemia is an independent marker of severity and mortality in critical illnesses. The five cause death categories in patients with critical illness and hypoglycemia are\textsuperscript{16}
1. Neurologic
2. Cardiovascular
3. Hypoxic respiratory failure
4. Liver related and
5. Others.

Individual hypoglycemic episodes are associated with biologic toxicity by increasing the systemic inflammatory response, inducing neuroglycopenia, inhibition of corticosteroid stress response and cerebral vasodilation.

Hence we urge that the management of both the extremes of glycemic status and the fluctuation is of prime importance in acute OP poisoning like any other critical illness for better outcomes.

The management protocol for stress hyperglycemia\textsuperscript{14} as per ADA 2012 is by targeting a goal of 130-180 mg/dL. The dose of the intravenous insulin administration as per the RBG is as follows:

- \(140-179\text{mg/dL} \) - Start I.V infusion at 1IU/hr
- \(180-199\text{mg/dL} \) - Start I.V infusion at 2IU/hr
- \(200-249\text{mg/dL} \) - Bolus 2IU iv insulin followed by infusion at 2IU/hr
- \(250-299\text{mg/dL} \) - Bolus 4IU iv insulin followed by infusion at 2IU/hr
- \(>300\text{mg/dL} \) - Bolus 4IU iv insulin followed by infusion at 4IU/hr.

Management of hypoglycemia requires continuous glucose monitoring, identification of symptoms, treating the precipitants and prompt administration of intravenous dextrose.

Conclusion

We conclude that the extremes of glycemic status at presentation in acute Organophosphate poisoning is strongly associated with the severity, complications and the mortality hence can be used as a cheap, simple, reliable marker of prognosis along with the s. chE, and other clinical scores like POP and PSS in a resource limited country like India.

However the studies to understand the Organophosphate induced glycemic variability and it’s bearing on the severity and outcomes are very few. Prospective studies regarding the same in a large cohort are desirable with focus on mechanistic association between the glycemic status and outcomes. Also the importance of continous glucose monitoring and the management of the fluctuations in critical care settings needs to be investigated and emphasised.

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13. Godinjak A, Iglica A, Jusufovic A, Tancica I, Kukuljac A. Medical Intensive Care Unit, Clinical Center University of Sarajevo, Sarajevo, Bosnia and Herzegovina Clinic for Endocrinology, Diabetes and Metabolic Disorders, Clinical Center University of Sarajevo, Sarajevo, Bosnia and Herzegovina
Association of Non-HDL Cholesterol, Homocysteine and Vitamin D in Acute Coronary Syndrome

Arun Bahulikar¹, Vidya Tickoo², Deepak Phalgune³*

Abstract

Background: The role of Low Density Lipoprotein Cholesterol (LDL–C) in the pathogenesis of Coronary Heart Disease (CHD) has been well established. In many studies it was found that Non-HDL cholesterol (total cholesterol minus High Density Lipoprotein Cholesterol [HDL–C]) is a better predictor of CHD risk than LDL–C alone. High homocysteine levels are associated with increased risk of cardiovascular and cerebrovascular disease. An inverse relation has been seen between vitamin D serum level and coronary artery calcification. Studies are inadequate among Indians to establish the role of these non-conventional risk factors in acute coronary syndrome.

Objectives: To correlate the values of non-HDL cholesterol, vitamin D and homocysteine in patients with acute coronary syndrome (ACS) with controls

Methods: For this retrospective study cases were the patients admitted in Poona Hospital and Research Centre between November 2013 and November 2015 with acute coronary syndrome whereas controls were patients admitted in Poona Hospital and Research Centre during the same period with diagnosis other than Acute coronary syndrome. Each patient was subjected to detailed clinical history, clinical examination and investigations such as lipid profile, serum homocysteine, and Vitamin D3. Unpaired t-test was used to compare the quantitative data whereas Chi-square test or Fisher’s exact test was used for qualitative data.

Results: ACS group had significantly higher mean total serum cholesterol, mean LDL cholesterol, mean non-HDL cholesterol, and mean plasma homocysteine as compared to control group. However, there was no statistically significant difference between the two groups in Vit D levels. Odds ratio was maximum for Non HDL cholesterol, followed by LDL cholesterol, HDL cholesterol, Serum Homocysteine, and Total cholesterol

Conclusions: Non-HDL cholesterol was a better predictor of cardiovascular diseases than LDL–C, HDL–C or total cholesterol.

Introduction

Atherosclerotic vascular disease, which encompasses coronary heart disease (CHD), cerebrovascular disease, and peripheral arterial disease, is responsible for the majority of cases of cardiovascular disease (CVD) in both developing and developed countries. The Framingham Heart Study and many other large prospective cohort studies¹ have demonstrated the importance of major CVD risk factors in the appearance of vascular events. It is apparent, however, that a substantial proportion of cardiovascular events occur in individuals who exhibit none of these classic risk factors. This has led to an increasing interest in identifying novel biomarkers that might improve the global risk prediction of CVD. In recent years, a number of emerging markers have been proposed as significant predictors of atherosclerosis and its thrombotic complications.

The role of Low Density Lipoprotein Cholesterol (LDL–C) in the pathogenesis of CHD has been well established. This is the most well studied coronary risk factor.² In many studies it was found that Non-HDL cholesterol (total cholesterol minus High Density Lipoprotein Cholesterol [HDL–C]) is a better predictor of CHD risk than LDL–C alone.³ Vitamin D deficiency is prevalent in most parts of the world. 25-hydroxyvitamin D is a marker of vitamin D status in the human body. Some population based studies have shown that 60%-65% of Indians have 25-hydroxyvitamin D deficiency.⁴ Most body cells, including cardiomyocytes, vascular smooth muscles and the endothelium of the vessels have vitamin D receptors. Recent studies are indicative of a relation between vitamin D deficiency and cardiovascular disease, increased blood pressure, increased insulin resistance, heart failure and fatal strokes.⁵

High homocysteine levels are associated with increased risk of cardiovascular and cerebrovascular disease although there are studies that show no increase in risk and there is still debate as to the strength and validity of the association.

Studies are inadequate among Indians to establish the role of these non-conventional risk factors in acute coronary syndrome. Hence, an attempt is made in the present study to correlate the values of non-HDL cholesterol, vitamin D and homocysteine in patients with acute coronary syndrome with controls

Material and Methods

Cases were the patients admitted in Poona Hospital and Research Centre between November 2013 and November 2015 with acute coronary syndrome whereas controls were patients admitted
Table 1: Characteristics of cases and controls

<table>
<thead>
<tr>
<th>Laboratory investigations</th>
<th>ACS (N= 145)</th>
<th>Control (N = 145)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age (SD)</td>
<td>58.25 (± 12.28)</td>
<td>57.27 (± 11.42)</td>
<td>0.77</td>
</tr>
<tr>
<td>Gender (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Males</td>
<td>85 (58.62)</td>
<td>88 (60.69)</td>
<td>0.811</td>
</tr>
<tr>
<td>Females</td>
<td>60 (41.38)</td>
<td>57 (39.31)</td>
<td></td>
</tr>
<tr>
<td>BMI (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 23</td>
<td>44 (30.34)</td>
<td>65 (44.83)</td>
<td>0.015</td>
</tr>
<tr>
<td>≥ 23</td>
<td>101 (69.66)</td>
<td>80 (55.17)</td>
<td></td>
</tr>
<tr>
<td>Sedentary lifestyle (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>114 (78.62)</td>
<td>103 (71.03)</td>
<td>0.176</td>
</tr>
<tr>
<td>No</td>
<td>31 (21.38)</td>
<td>42 (28.97)</td>
<td></td>
</tr>
<tr>
<td>Diabetes mellitus (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>52 (35.86)</td>
<td>51 (35.17)</td>
<td>0.999</td>
</tr>
<tr>
<td>No</td>
<td>93 (64.14)</td>
<td>94 (64.83)</td>
<td></td>
</tr>
<tr>
<td>Hypertension (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>67 (46.21)</td>
<td>57 (48.28)</td>
<td>0.814</td>
</tr>
<tr>
<td>No</td>
<td>78 (53.79)</td>
<td>75 (51.72)</td>
<td></td>
</tr>
<tr>
<td>Smoking (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>23 (15.86)</td>
<td>10 (6.9)</td>
<td>0.025</td>
</tr>
<tr>
<td>No</td>
<td>122 (84.14)</td>
<td>135 (93.1)</td>
<td></td>
</tr>
</tbody>
</table>

Table 2: Laboratory investigations in cases and controls

<table>
<thead>
<tr>
<th>Laboratory investigations</th>
<th>ACS (N= 145)</th>
<th>Control (N = 145)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean total serum cholesterol (SD)</td>
<td>193.90 (±23.98)</td>
<td>155.86 (±14.90)</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Mean LDL cholesterol (SD)</td>
<td>120.41 (±16.72)</td>
<td>89.83 (±12.23)</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Mean non-HDL cholesterol (SD)</td>
<td>159.02 (±24.20)</td>
<td>114.74 (±13.57)</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>VIT D level (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 30 ng/ml</td>
<td>119 (82.07)</td>
<td>116 (80.0)</td>
<td>0.14</td>
</tr>
<tr>
<td>≥30 ng/ml</td>
<td>26 (17.93)</td>
<td>29 (20.0)</td>
<td></td>
</tr>
<tr>
<td>Plasma Homocysteine (µmol/L)</td>
<td>14.69 (±6.68)</td>
<td>12.00 (±3.63)</td>
<td>&lt; 0.01</td>
</tr>
</tbody>
</table>

Non-ST elevation MI: A patient with unstable angina with evidence of myocardial necrosis, as reflected in abnormally elevated levels of biomarkers of cardiac necrosis.

ST elevation MI: Angina with objective ECG evidence of ST elevations of at least 1 mm in limb leads and 2 mm in precordial leads with raised cardiac enzymes.

Exclusion Criteria

Valvular heart disease, peripartum cases, patients on lipid lowering drugs and patients with previous history of coronary heart disease.

Selection of Controls

A control group comprising of individuals visiting Blood Bank for blood donation, patients visiting OPD or patients admitted in Poona Hospital and Research Centre with diagnosis other than acute coronary syndrome. The controls were matched with cases for age, gender and co morbid conditions such as Diabetes mellitus, Hypertension

Data Collection

Each patient was subjected to detailed clinical history, clinical examination and Investigations as per the study proforma. Blood for serum homocysteine and lipid profile was taken in fasting state. Blood for Vitamin D3 was taken irrespective of the time of the meal. The samples were collected within 24 hours of onset of ACS.

Patients with BMI ≥23 kg/m² were considered overweight / obese.\(^6\)

Definition for hypertension by JNC VII (Joint National Committee) - defined as a systolic blood pressure >140 mmHg and/or a diastolic blood pressure >90 mmHg based on the average of 2 blood pressure measurements at the time of admission\(^8\), or a patient’s self-reported history of hypertension or antihypertensive drug use, supported by documents. Although definition of hypertension was not specifically addressed in JNC VIII guidelines, thresholds were adopted for the treatment of blood pressure that are generally consistent with the definitions provided by JNC VII.\(^9\)

Diabetes was diagnosed if fasting plasma glucose was >126 mg/dL or 2 hours post prandial > 200 or HbA1c>6.5 or patient was on anti-diabetic medications. (According to ADA guidelines)\(^11\)

Smokers were defined as those smoked daily. Ex-smokers and occasional smokers were classified as nonsmokers.

Expected values of total cholesterol (NCEP ATP III)

Desirable: <200mg/dl
Borderline high: 200 – 239 mg/dl
High: ≥ 240 mg/dl
Cardiovascular diseases are one of the major causes of morbidity and mortality in the contemporary society. Advances in our understanding of the ways in which the traditional cardiovascular risk factors interact to initiate atherosclerosis and promote the development of cardiovascular disease have enhanced our ability to assess risk in the individual patient. In addition, there is substantial interest in identifying new risk factors for cardiovascular disease, to improve our understanding of disease biology and to account for the cases of cardiovascular disease that cannot be explained by known risk factors. In recent years, debate has arisen regarding the validity and usefulness of these new measures.

In the present research, 145 patients of ACS admitted in the study period with mean age of 58.25 ± 12.28 years and 145 matched controls having mean age of 57.27 ± 11.42 years were included. The ACS group had 58.62% male and 41.38% female patients whereas the control group had 60.69% males and 39.31% females. 78.62% of ACS patients, and 71.03% of controls had sedentary lifestyle. Diabetes mellitus was present in 35.86% of patients with ACS and in 35.17% of controls. 46.21% of ACS patients and 48.28% of controls had hypertension. In all above variables, P value was more than 0.05, hence both the groups were matched in respect of age, gender, sedentary lifestyle, presence of diabetes mellitus and hypertension.

In our study, 69.66% patients with ACS had BMI ≥ 23 kg/m² whereas 55.17% of controls had BMI ≥ 23 kg/m². According to Kasama K et al., Asians with BMI ≥ 23 kg/m² are considered to be at high risk. 4.15.86% of ACS patients were smokers whereas 6.9% of controls were smokers. In these variables, P value was less than 0.05, hence the two groups were not matched by BMI and smoking habit. These two variables were confounding variables in the present research.

It can be seen from Table 3 that odds ratio was maximum (18.8) for Non HDL cholesterol, followed by LDL cholesterol (13.38), HDL cholesterol (7.04), Serum Homocysteine (6.67), and Total cholesterol (4.00).

**Total cholesterol**

Mean total serum cholesterol for ACS patients was 193.90 ± 23.98 whereas for controls it was 155.86 ± 14.90. Mean serum cholesterol was significantly elevated in patients of ACS as compared to controls. This is consistent with the study conducted by Nobilli et al. 4 where they found that total cholesterol was independently associated with risk of myocardial infarction. Odds ratio with Total cholesterol > 200 mg/dl as exposure was 4.00 (95% CI, 2.03 – 7.86) for ACS patients.

**Low Density Lipoprotein Cholesterol**

Mean serum LDL C for patients of ACS was 120.41 ± 16.72 mg/dl. It was significantly more as compared to LDL C of controls (89.83 ± 12.23 mg/dl). Similar results were reported by K Maruyama et al. in patients of ACS where mean serum LDL C levels were raised in patients of ACS as compared to controls. Odds ratio with exposure as LDL cholesterol ≥ 100 mg/dl was 13.38 (95% CI, 7.13 – 25.12) in ACS patients.

**Non-HDL Cholesterol**

Mean Non-HDL Cholesterol was significantly higher in patients of ACS (159.02 ± 24.20 mg/dl) as compared to controls (114.74 ± 13.57 mg/dl). A meta analysis from 68 studies 6 reported that non-HDL-C was the best predictor among all cholesterol measures, for Coronary artery disease events. Significantly raised non-HDL cholesterol in patients presenting with ACS was reported in many other studies as well. 6,7,17 Odds ratio for non-HDL cholesterol ≥ 130 mg/dl as exposure was 18.80 (95% CI, 9.34 – 37.84) in ACS patients.

**Vitamin D**

In the present study, it was found that insufficient vitamin D (< 30 ng/ml) was not an individual risk factor for acute coronary syndrome. 82.07% of individuals in the ACS group had vitamin D < 30 ng/ml whereas 80% of individuals in control group had vitamin D < 30 ng/ml. Although Vitamin D was deficient in > 80% of population, there was no statistically significant difference between the two groups.

Thomas J. Wang et al. 19 studied 1739 Framingham Offspring Study participants (mean age 59 years; 55% women) without prior cardiovascular disease. They concluded that vitamin
D deficiency was associated with incidence of cardiovascular disease. There is clear evidence that patients with cardiovascular disease have lower levels of 25(OH)D, but a similar association exists for a large number of other medical conditions like DM, hypertension, obesity etc., suggesting that this association may be confounded by reduced levels of physical activity and time spent outdoors in those with cardiovascular and other diseases. Odds ratio with Serum 25 (OH) D < 30ng/ml as exposure was 1.74 (95 % CI, 0.64 – 2.06) in ACS patients.

At present, there is insufficient evidence to support vitamin D supplementation as a way of improving cardiovascular outcomes. However, many cardiovascular patients are frail and immobile and are at risk of markedly reduced vitamin D levels and osteoporosis. Supplementation of such patients is justified to prevent very low levels of 25(OH)D, with their squeal of musculoskeletal pain, myopathy and accelerated bone loss.

Homocysteine

In the present study we found that mean homocysteine was significantly higher in patients with ACS (14.69 ±6.68μmol/L) as compared to controls. (12.0 ±3.63μmol/L). Many studies have established a correlation between hyperhomocysteinemia and elevated risk for cardiovascular events, but the precise role of plasma homocysteine in cardiovascular disease is unclear. Plasma homocysteine increases with aging and is associated with smoking and diet patterns. Most of the studies conducted on effect of homocysteine on cardiovascular diseases reported an association of plasma homocysteine with the risk for cardiovascular events. Other studies reported that the effect disappears following adjustment for other risk factors, because homocysteine co segregates with other risk factors. It has been difficult to identify an independent effect of homocysteine on cardiovascular disease. Homocysteine can be modified to some extent by vitamin supplementation. Homocysteine reduction may have benefit in reducing cardiovascular risk particularly in the elderly. E Arnesen et al. concluded in their study that raised homocysteine was associated with myocardial infarction. (mean homocysteine of 12.7 μmol/L in cases vs 11.6 μmol/L in controls).20 Odds ratio with serum homocysteine ≥ 15 μmol/L as exposure was 6.67 (95 % CI,3.99 – 11.16) in ACS patients.

In the present study, Non HDL cholesterol was a better predictor of ACS than others. Odds ratio in ACS patients was Non HDL- C (18.80), LDL-C (13.38), HDL-C (7.04), Homocysteine (6.67) and Total cholesterol (4.0). Odds ratio was maximum for non HDL cholesterol followed by LDL C and total cholesterol. Hence, non HDL-C predicts cardiovascular risk better than LDL-C and total cholesterol in our study population. In our study non HDL C was the best predictor of cardiovascular risk. Non HDL C was followed by LDL C, low HDL C, homocysteine, and total cholesterol.

Limitations

Although we attempted to choose a control group that was matched with the cases with respect to most of the conventional cardiovascular risk factors, but smoking, and BMI could not be matched. Hence, they may act as confounding factors.

This study was conducted in a single tertiary care hospital and represents only a small population mostly urban.

Patients may have other cardiovascular risk factors like chronic inflammatory diseases, raised high sensitivity C- reactive protein, raised fibrinogen etc. which were not studied or ruled out.

Conclusions

Significant association was found between non-HDL – C, LDL cholesterol, Total cholesterol, and homocysteine with acute coronary syndrome.

Non-HDL cholesterol was a better predictor of cardiovascular diseases than LDL-C, HDL-C or total cholesterol.

References

Frequency of Macrovascular Complications in Patients of Newly Diagnosed Type 2 Diabetes Mellitus and its correlation with Major Cardiovascular Risk Factors; A Hospital Based Study

Gaganpreet Singh Taneja¹, Rajesh Kumar²*, Rajiv Merwah³, Surinder Thakur⁴

Abstract

Objective: Frequency of macrovascular complications in newly diagnosed patients of type 2 diabetes mellitus and its correlation with major cardiovascular risk factors; A Hospital Based Study.

Methods: All consecutive newly diagnosed type 2 diabetics were enrolled and evaluated for the presence of cardiovascular risk factors and macro vascular complications i.e. Coronary Artery disease (CAD), Cerebrovascular Disease (CVD) and peripheral vascular disease (PVD).

Results: 105 newly diagnosed subjects with diabetes with a mean age of 56.55±7.43 years were enrolled in the study amongst them 53 were male and 52 were females. The mean plasma glucose of these patients was 178.40±52.05 mg%, out of 105 patients enrolled in the study 20 (19.05%) of the patients had macro vascular complications at the time of diagnosis of type 2 diabetes.

Conclusion: Type 2 diabetes mellitus can present with or without symptoms and with chronic vascular complications at the time of diagnosis, opportunistic screening for diabetes should be done in high risk patients along with screening for the vascular complications.

Material and Methods

The study was carried out in all consecutive newly diagnosed diabetic patients admitted in the department of Medicine and patients attending diabetic clinic of Indira Gandhi medical college Shimla H.P. over a period of one year. A total of 105 newly diagnosed drug naïve patients were included in the study after obtaining informed consent.

Diabetes was diagnosed as per ADA 2013 guidelines. The risk factor like hypertension defined as per JNC VIII, dyslipidemia as per NCEP-ATPIII guidelines. Smokers were defined according to US Center for Disease control and prevention definitions. Patients were labeled as obese if they fulfilled Indian consensus Guidelines for Obesity. The vascular complications...
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Table 1: Frequency distribution of presenting symptoms in newly diagnosed type 2 diabetes (n=105)

<table>
<thead>
<tr>
<th>Type of presentations</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asymptomatic –routine check-up</td>
<td>24 (24.76%)</td>
</tr>
<tr>
<td>Asymptomatic-pre-op check-up</td>
<td>15 (14.26%)</td>
</tr>
<tr>
<td>ACS/MI</td>
<td>10 (9.52%)</td>
</tr>
<tr>
<td>Stroke/TIA</td>
<td>5 (4.76%)</td>
</tr>
<tr>
<td>Vascular claudication</td>
<td>3 (2.86%)</td>
</tr>
<tr>
<td>Paresthesia’s</td>
<td>8 (7.62%)</td>
</tr>
<tr>
<td>Visual Disturbances</td>
<td>4 (3.81%)</td>
</tr>
<tr>
<td>Swelling Feet</td>
<td>1 (0.95%)</td>
</tr>
<tr>
<td>Polyuria / polydipsia / polyphagia / weight loss</td>
<td>19 (18.09%)</td>
</tr>
<tr>
<td>Infections</td>
<td>14 (13.33%)</td>
</tr>
</tbody>
</table>

CAD was defined by the presence of any of the following:

Documented Acute myocardial Infarction (AMI) based on history of chest pain, EKG changes and elevated levels of markers of myocardial necrosis.

History of CABG / PTCA.

History of chest pain with inducible ischemia on stress.

ECG evidence of silent myocardial infarction identified by Minnesota code 1:1, 1:2.

ECG evidence of LBBB with RWMA on Echocardiography.

Cerebrovascular disease (CVD) was defined as history of Transient Ischemic Attack (TIA) or Focal deficit or evidence of Stroke on Computerized tomography C.T. scan. Peripheral vascular disease (PVD) was defined as history of intermittent claudication or rest pain associated with any, absent or feeble peripheral pulse or Ankle brachial index (ABI) <0.9. Carotid intima media thickness (CIMT) was measured by B mode scanning of both carotid arteries in each patient by USG 7.5 MHZ linear probe of i-33 Phillips Echo machine. The intimal plus medial thickness was measured as the distance from the leading edge of first echogenic line to the second echogenic line. CIMT of both right and left side was measured and average CIMT was calculated. IMT of > 0.9 was taken as increased intima media thickness (IMT).

Statistical analysis

Data was recorded on a Microsoft excel spreadsheet, statistical analysis was performed using Epi Info 2000 (center for diseases control and prevention, Atlanta, GA, USA) and SPSS student version16.0 (SPSS Inc., Chicago, USA). All discrete variables were expressed as percentages. The differences in distribution of discrete variables were analyzed using chi-square test. Significance of differences in continuous variables were analyzed by students t test and p value of <0.05 was considered as statistically significant.

Results

This was a prospective observational cross-sectional study conducted in department of Medicine, Indira Gandhi Medical College Shimla Himachal Pradesh from June 2013 to May 2014. 105 consecutive newly diagnosed patients of type 2 diabetes were included in the study.

Baseline characteristics of the study group

Age and Sex distribution

Mean age of patients in the study was 56.55±7.3 years (males 54.71±8.32; females 53.86±10.13) with a range of 39-77 years. Out of these 105 patients 53 (50.48%) were females and 52 (49.52%) were males. 46 (43.81%) of patients were from rural background in the study.

Presenting symptoms

64 (61.95%) of patients out of 105 were symptomatic in the study. Out of these 64 symptomatic patients, 19 (18.09%) patients presented with classical symptoms of polyuria, polydipsia and weight loss and 14 (13.33%) had some infection at the time of diagnosis. 10 (9.52%) patients presented as acute coronary syndrome. 5 (4.76%) patients presented with stroke/TIA and 3 (2.86%) patients had lower limb vascular ischemia. Of the 41 (39.05%) asymptomatic patients, 26 (24.76%) were diagnosed on routine check-up while 15 (14.29%) were detected to have diabetes during pre-operative check-up for fitness for surgery.

Mean fasting plasma glucose in this study was 178.40±52.05mg % (180.92±52.00 mg % in males and 175.92±52.47 mg % in females). Mean post prandial plasma glucose was 262.54±55.11 mg % (264.40±52.41mg% in males and 260.70±58.07 mg % in females). The mean HbA1c level were 8.12±1.24 % (8.22±1.17% in males and 8.01±1.30% in females). Majority (81%) of the patients in this study had HbA1c in the range of 6.5 to 9.0% while 19% of the patients had HbA1c more than 9.0% (Table 2). Mean total cholesterol in this study was 188.79±42.74mg% (190.62±49.14 mg % in males and 187.00±37.72 mg% in females), mean Triglycerides 157.25±60.19mg% (males 160.02±38.20 mg%,females173.83±72.12 mg%), mean HDL cholesterol 47.18±7.13 mg% (46.80±7.55 mg% in males and 47.54±6.74 mg % in females, mean LDL cholesterol was 96.09±32.27 mg% (96.19±39.47 mg% in males and 96.00±23.3mg% in females). Mean weight was 79.60±15.80 mg% (77.59±17.99 mg% in males and 81.91±13.77 mg % in females). Mean height was 160.62±7.14 cm (160.89±7.11 cm in males and 159.86±7.15 cm in females).

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Risk factors

In this study 35 (33.33%), males 13 (12.38%) and females 22 (20.95%) patients had family history of diabetes, 39 (37.14%) males 33 (31.43%) and females 6 (5.71%) were smokers (p <0.001), 16 (15.24%) male and 12 (11.43%) females were obese, 27 (25.71%) male and 23 (21.90%) females were hypertensive, 25 (23.81%) females and 16 (15.24%) males had dyslipidemia.

In the study 34 (32.88%) patients had one risk factor, 30 (28.57%) patients had two, 21 (20%) had three and 6 (5.71%) had four and only two patients had all five risk factors i.e. family history of Diabetes, smoking, obesity, hypertension and dyslipidemia. The 20 (19.05%) patients out of 105 patients included in the study had only macro vascular complications while 4 (3.81%) had both micro vascular and macro vascular complications whereas 25 (23.80%) had only micro vascular complications. Amongst macro vascular complication the prevalence of CAD, CVD and PVD was 11.4%, 6.7%, 4.8 % respectively. 37 (35%) of the patients presented as acute myocardial infarction (AMI) based on history of chest pain, EKG changes and elevated levels of markers of myocardial necrosis.
enrolled had increased CIMT ≥.90 mm. Amongst the total number of patients with increased CIMT (n=57), 6 (16.22%) had CAD where as 6 (8.82%) of patients with normal CIMT (n=68) had CAD and this correlation was not statistically significant. 7 (18.92%) of the patients in this study with CAD had increased CIMT whereas none of the patients with normal CIMT had CIMT in the study (p< .0001). 4 (10.81%) patients with PVD had increased CIMT while one patient with normal CIMT had PVD and was statistically significant (p=0.032).

Discussion

The Asian Indian phenotype refers to certain unique clinical and biochemical abnormalities like increased insulin resistance, higher waist circumference despite lower BMI, lower adiponectin and high level of hs CRP making Asians more prone to diabetes and premature coronary artery disease (CAD). Although the classical symptoms of diabetes are present less often in newly diagnosed diabetics and approximately 40% of them may be asymptomatic, one third newly diagnosed patients also have associated vascular (Macro-Micro) complications of diabetes at the time of diagnosis highlighting importance of opportunistic screening of high risk individuals. Patient of the sub continent develop diabetes a decade earlier as compared to their western counter part as the mean age of patients in this study was 56.55±7.3 years with a range of 39-77 years majority (73.38%) being between 40-60 years. The incidence was similar to other studies like CINDI and study in Nagpur by Saoji showing that majority of patients with type 2 diabetes are in the range of 45-64 years which is in contrast to developed countries in which age at diagnosis of type 2 diabetes is >65 years in majority of patients.7

There is clustering of risk factors in subjects diabetes as compared to normal subjects. In this study of newly diagnosed diabetics, 14 (13.44%) patients had no risk factor, 34 (32.38%) patients had at least one risk factor and 57 (54.31%) of patients had 2 or more risk factors. The common risk factors in this study was hypertension (47.61%), followed by dyslipidemia (39.04%) smoking (37.14%), positive family history (33.33%) and obesity in (26.66%) of patients. 49 (46.66%) patients have vascular complications, of these 20 (19.05%) of patients had macro vascular complications and was similar to the observations made in the landmark UKPDS-6 study in which half of the newly diagnosed type 2 diabetics had one or more vascular complication at diagnosis. In a study conducted at Poland, at the time of diagnosis macro vascular complications were present in 12% of patients. Gupta A et al8 and a study from Nagpur by Saoji6 has also reported vascular complications in their newly diagnosed type 2 diabetics as 38.57% and 53.03% respectively, which is similar to present study. The increased prevalence of vascular complications (micro and macro vascular) in almost 50% of patients at the time of diagnosis emphasizes the need for screening of chronic complications at the time of diagnosis and aggressive treatment for glycaemia and cardiovascular risk factors.

Excess mortality in type 2 diabetes is caused by large vessel disease, particularly myocardial infraction and stroke. The pathological changes of atherosclerosis in diabetics are similar to non-diabetic patients, but they occur early in life and are more extensive and severe. The prevalence of coronary artery disease (CAD) in this study was 11.40%. Various studies have shown prevalence of CAD from 4.8-40%. Ruigomez and Rodriguez30 in UK have reported prevalence of CAD in newly diagnosed type 2 diabetes as 17%. In UKPDS-6 study of 2337 newly diagnosed patients, 18 % of the patients had abnormal ECG and 1% had MI. In African continent, the prevalence of CAD in newly diagnosed type 2 diabetes was 4.8% in a study by Namubya et al,31 and it was 21% in a study from Sri Lanka by Weerasuriya et al.32 In multicentric CNDI study 6% of newly diagnosed patients had CAD. The prevalence of CAD was 7.61% in newly diagnosed type 2 diabetics in a study by Gupta et al,10% of patients had CAD in a study by Shukla et al,33 the variable prevalence of CAD in newly diagnosed type 2 diabetics in different studies is due to non-uniform criteria used in the diagnosis of CAD.

6.7% of the patients enrolled in this study had cerebrovascular diseases (CVD). The prevalence of CVD reported in the studies conducted outside India is between 1-5.6%. A low (1%) prevalence of CVD was seen in UKPDS4 study of newly diagnosed diabetics. Prevalence of CVD was 3.22% in a study by Gupta et al3 from Agra India. Higher prevalence of CVD in this study could be because it being hospital based cross sectional study conducted in tertiary care referral hospital with CT scan facility catering large area of south and central Himachal.

The prevalence of PVD in Hoorn Screening study14 was 10% and 12% in a study by Ruigomez and Rodriguez. In UKPDS-6 study the prevalence of PVD in newly diagnosed patients with type 2 diabetes was 13%. In India the prevalence of 1-3.5% of PVD has been reported in various studies. The prevalence of 1% was reported by Gupta et al and Shukla et al. respectively. Mohan V et al34 have reported prevalence of PVD in newly diagnosed patients 3.5%. The prevalence rate of PVD are higher in western countries as compared to Asia and India and the result of this study i.e. prevalence of 4.80% was comparable to other studies conducted in India.

Conclusion

Type 2 diabetes mellitus can present with or without symptoms and with chronic vascular complications at the time of diagnosis, opportunistic screening for diabetes should be done in high risk patients along with screening for the vascular complications. Once diagnosed type 2 diabetes should be aggressively treated and all cardiovascular risk factors should be treated to target with periodic monitoring so as to reduce chronic vascular complications. Education of high risk population regarding diabetes related complications must be started to encourage earlier medical consultation.

References

Comparison of Safety and Efficacy of Glimepiride-Metformin and Vildagliptin- Metformin Treatment in Newly Diagnosed Type 2 Diabetic Patients

Jatinder Kumar Mokta¹, Ramesh²*, Ashok Kumar Sahai³, Purshottam Kumar Kaundal³, Kiran Mokta⁴

Abstract

Objectives: To compare the safety and efficacy of combination of Glimepiride – Metformin with Vildagliptin – Metformin in type 2 diabetic patients with HbA1c between 7.5to10.

Methods: A randomized, prospective, comparative and interventional study was conducted at Indira Gandhi Medical College, Shimla. The level of hemoglobin A1c (HbA1c), fasting blood sugar (FBS) and postprandial blood sugar (PP) were the primary outcomes, whereas, the evidence of hypoglycemia, quality of life and weight gain were recorded as secondary outcomes. 215 patients newly diagnosed with type 2 diabetes mellitus were randomized into Glimepiride-Metformin group (Group1) having 111 patients and Vildagliptin-Metformin group (Group 2) having 106 patients. Patients were followed up at 3 month, 12 month, 24 month and then after completion of 30 month of treatment.

Results: A comparable FPG, PPPG and HbA1c were observed from baseline at the end of 12 weeks in both groups. However, at the 130-week endpoint a significantly more pronounced reduction in HbA1c was observed in vildagliptin group compared to Glimepiride-metformin (1.96%) arm. A similar significant more pronounced reduction was demonstrated in both FPG (48.25% vs. 41.70%) and PPPG (49.40% vs. 42.95%) in vildagliptin-metformin group compared to Glimepiride-metformin group. The proportion of patients who achieved an A1C <7% at 130-weeks was 49% in the vildagliptin group and 41% in the Glimepiride group. Statistically significant more weight gain was observed in Glimepiride arm compared to vildagliptin arm (2.09 kg vs. 0.69 kg) and 8-fold lower incidence was observed in vildagliptin group.

Conclusion: Vildagliptin –metformin represent a more effective combination in terms of number of patients achieving guidelines recommended A1C target of less than 7% at the end of 30 months, less weight gain, and a lower risk of hypoglycemia in newly diagnosed type 2 diabetic patients with moderate glycemia.

Introduction

Diabetes mellitus (DM) is one of the most common chronic disorders attaining epidemic proportion, worldwide. As per International Diabetes Federation (IDF) there were 366 million people with diabetes in 2011; by 2030 the number will rise to 552 million all over the world.¹ India is one of the epicenters of the global diabetes epidemic and has the second highest number of people with the disease in the world with 69.2 million individuals as of 2015 and this number is set to increase to 109.5 million by 2030.² The primary objective of treatment of type 2 diabetes (T2DM) is to achieve and maintain good glycemic control to minimize the long-term micro- and macrovascular complications.³ Though, to accomplish this objective, requires attention too many factors beyond glycemic control, however,

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Accepted: 18.04.2018
glucose control appears to be the most effective in preventing and progression of diabetes related complications. Recently, several clinical studies have demonstrated that tight glycemic control reduces the disability and premature death from diabetes related chronic complications in type 2 as well as type 1 diabetic patient. In the traditional guidelines recommended step-up approach, a patient passes through non-pharmacological to monotherapy to combination therapy; the glycemic control remains sub-optimal and exposed the patient to glycemic burden for years and leaves him or her at increased risk of complications. Type 2 diabetes results from complex pathophysiological defects including insulin resistance, impaired insulin secretion and impairment in incretin system. Combination therapy using agents with complimentary mechanism of action to correct multiple pathophysiological defects; early in the natural course of T2DM offers optimal glycemic control and is cost effective and safe approach to manage T2DM.

Treating type 2 diabetes early is especially important because early and aggressive blood glucose reduces the diabetes related morbidity and mortality. Up to 50-80% of β-cell function has already been lost and nearly 32.55% of patients already have some sort of complications at diagnosis of T 2 diabetes; so early diabetes as currently defined is already a late stage in the natural course of Type 2 diabetes. A proactive approach, adding a second agent to treat diabetes aggressively from the time of diagnosis is critically important.

Vildagliptin is new classes of oral hypoglycemic agents. It is highly selective dipeptidyl peptidase-4 (DPP-4) inhibitors and increases the levels of glucagon like peptide-1(GLP-1) by preventing the degradation of endogenous glucagon-like peptide-1 and glucose-dependent insuliniotropic peptide (GIP). Vildagliptin lowers blood glucose by increasing insulin secretion and decreasing glucagon secretion and is effective either as monotherapy or combination with other oral agents. Vildagliptin displays good adverse effect profiles and does not cause weight gain and severe hypoglycemia.

Glimepiride; a second generation sulfonylurea is a potent oral hypoglycemic agent. It is commonly prescribed as a monotherapy or in combination therapy with other oral agents. Glimepiride though effective in lowering glucose, is associated with weight gain and severe hypoglycemia.

In present study we compared the combination of Glimepiride-metformin treatment to vildagliptin-metformin treatment in newly diagnosed treatment naïve type 2 diabetic patients with moderate hyperglycemia and evaluated over 130 weeks.

**Material and Methods**

**Patient population**

Consecutive patients of T2DM attending Medicine OPD at IGMC, Shimla, were screened for possible enrolment in the study. All patients who fulfilled the inclusion criteria (age ≥18 years, newly diagnosed type 2 diabetic patients with HbA1c between 7.5 to 10 and newly diagnosed type 2 diabetic patients with HbA1c >10% not willing to insulin therapy) were included. This study complies with WHO diagnostic criteria for diabetes mellitus, i.e., a random or casual plasma glucose concentration ≥200mg/dl or fasting plasma glucose ≥126 mg/dl or 2-hour plasma glucose ≥200 mg/dl during standard 75 g oral glucose tolerance test. Patients were excluded if they had Type 1 diabetes mellitus, acute complication of diabetes like hyperglycemia hyperosmolar state/diabetic ketoacidosis, significant renal or liver disease, congestive heart failure, acute coronary syndrome, age <18 years and >80 years and pregnancy. Due informed consent was taken from each participant and ethical clearance from the institution’s ethical committee was obtained.

**Study design**

The study was a randomized, prospective, comparative and interventional study.

**Study duration**

Study was started in February 2013 with follow up done till July 2015.

**Randomization procedure**

After base line clinical and lab investigations patients were randomized to assign group 1 or group 2 treatment through Block Randomization Technique. Allocation sequence was generated by the person not involved in the study. Randomization for Group 1 and Group 2 were concealed using Sequentially Numbered Opaque Sealed Envelope (SNOSE) technique.

**Intervention**

Patients randomized to group 1 were treated with Glimepiride 2 mg OD and Metformin 1 gm BD and group 2 with Vildagliptin 50 mg BD and Metformin 1 gm BD. Due to difficult geographical terrain, patients were advised to come for follow up between 3 to 6 month at their convenience and study participants were followed up at 3, 12, 24 and 30 months. Patients who failed to respond with study drugs were switched over to insulin therapy. The doses of drugs were adjusted during follow up depending upon patient’s A1C levels and the drugs and their dosages were recorded in both the study groups. On completion of 30 months of intervention, the specified outcome parameters were reassessed.

**Data collection**

Name, age, sex, contact number, educational status and occupation of the patients were noted. Family history of diabetes if any was also noted. Dietary history and history of smoking and alcohol were recorded. At baseline, the patient’s history was recorded and a thorough physical examination conducted. Anthropometric measurements: weight, height, waist (at the level of anterior superior iliac spine in standing position) and body mass index (weight in kilogram divided by height in meter square) were recorded. Fasting plasma glucose, post prandial plasma glucose, A1C and blood pressure were recorded. Plasma glucose levels were measured by using glucose oxidase and A1C was measured by radioimmunoassay. All patients underwent routine blood tests i.e. complete hemogram, liver and kidney functions and lipid profile at base line. X-ray chest and thyroid function test were done where clinically indicated. Patient’s telephone number and address were recorded and they were advised to follow at 3-6 month intervals. At base line, patients were educated regarding the symptoms of hypoglycemia and about the corrective measure if hypoglycemia occurs.

**Follow up**

FPG, PPG and HbA1c were recorded during each follow up period...
and patients were enquired about anorexia, nausea, gastrointestinal intolerance and any other symptoms experienced after starting the study drug. Symptoms of minor as well as major hypoglycemia were noted. Subjective feeling of wellbeing i.e. quality of life was enquired.

Hypoglycemia:15 “Any abnormally low plasma glucose concentration that exposes the subject to potential harm” and defined as:

Biochemically: Based on documented blood glucose levels < 70 mg/dl.

Overall hypoglycemia: any event classified by study investigators as such (from history: patient had one or other symptom of hypoglycemia and symptom resolved on taking sugar without knowing the blood glucose level).

Statistical analysis

Data was analyzed using Epi Info version3.4.3. Discrete values were expressed as percentage and continuous variables as mean ± SD. Student t test was applied to assess the significance of difference in mean values and chi-square test was for evaluation of frequencies of variable. ‘p’ value <0.05 was considered significant.

Results

A total of 217 patients were enrolled for the study, out of which 111 were enrolled in the Group 1 (Glimepiride-Metformin) and 106 patients were enrolled in group 2 (Vildagliptin-Metformin). However, in group 1, 8 patients were lost during follow up at 3 months and 3 patients had to be shifted to insulin because of the unsatisfactory treatment response. Finally, 100 patients completed the entire study period in this group.

Similarly in group 2, 4 patients were lost to follow up at 3 months whereas, 2 patient required insulin, thus a total of 100 patients completed study period in this group.

The demographic and risk factor profile of the patient population among the Group 1 and Group 2 were similar and shown in Table 1.

Efficacy of glucose control

In group 1, there was a significant (p<0.01) decline of 51.63% in the level of mean FBG from 187.85 (±34.81) mg/dl at baseline to 90.86 (±18.95) mg/dl at 3 months. At 30 months, mean FBG was 109.50 (±18.28) mg/dl, which showed a significant (p<0.01) reduction (41.70%) from baseline. The mean change in PPPG level from baseline of 295.90 (±55.89) mg/dl was 139.32 (±11.78) mg/dl at the end of 3 month. This exhibited a percentage decline of 52.81%, which was highly significant statistically (p<0.01). Similarly, a significant (p<0.01) decline (42.95%) in PPPG level was observed at the end of 30 month from baseline of 295.90 (±55.89) mg/dl to 168.80 (±29.60) mg/dl (Figures 1 and 2). The mean HbA1c level exhibited a 3.10% decline from baseline of 9.03% to 5.93% at 3 months which was

Table 1: Demographic and risk factor profile at baseline

<table>
<thead>
<tr>
<th>Variable</th>
<th>Group 1 (100) (Glimepiride-Metformin)</th>
<th>Group 2 (100) (Vildagliptin-Metformin)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>49.41 (±8.87)</td>
<td>50.88 (±9.30)</td>
</tr>
<tr>
<td>Sex (M)</td>
<td>59 (59 %)</td>
<td>60 (60%)</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>160.4 (±8.90)</td>
<td>160.86 (±8.02)</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>67.97 (±8.48)</td>
<td>69.48 (±10.27)</td>
</tr>
<tr>
<td>Waist (cm)</td>
<td>92.27 (±8.08)</td>
<td>93.50 (±7.74)</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>26.44 (±2.74)</td>
<td>26.81 (±3.15)</td>
</tr>
<tr>
<td>FPG mg/dl</td>
<td>187.85 (±34.81)</td>
<td>202.60 (±67.70)</td>
</tr>
<tr>
<td>PPPG mg/dl</td>
<td>295.90 (±55.89)</td>
<td>307.10 (±70.96)</td>
</tr>
<tr>
<td>A1C</td>
<td>9.03%</td>
<td>9.07</td>
</tr>
<tr>
<td>Family H/O HTN</td>
<td>5 (5%)</td>
<td>10 (10%)</td>
</tr>
<tr>
<td>Family H/O DM</td>
<td>30 (30%)</td>
<td>23 (23%)</td>
</tr>
</tbody>
</table>

Key: BMI – Body mass index; HTN – Hypertension; DM- Diabetes Mellitus; FPG- Fasting Plasma Glucose; PPPG- Post-Prandial Plasma Glucose; A1C- Glycated hemoglobin

Fig. 1: Comparison of reduction in fasting blood sugar at 3 and 30 months between glimepiride and vildagliptin

Fig. 2: Comparison of reduction in post prandial blood sugar at 3 and 30 months between glimepiride and vildagliptin

Fig. 3: Comparison of HbA1c over 30 months between two groups
A significant (p<0.01) reduction of 1.67% was observed at the end of study (from 9.03% to 7.36%) (Figures 3 and 4). The proportion of patients who achieved HbA1c<7 were 83% on completion of 3 months of treatment and 31% at the end of study.

In group 2, a significant (p<0.01) decline of 57.44% in mean FBG from a baseline of 202.60 (±67.70) mg/dl to 86.22 (±8.66) mg/dl at the end of 3 months was observed. The fasting plasma glucose remained significantly decreased by 48.25% from a baseline of 202.60 (±67.70) to 104.84 (±7.72) at the end of 30 month. The PPPG decreased significantly (55.34%) from a mean of 307.1 (±70.96) mg/dl to 137.15 (±13.73) mg/dl at 3 months (p<0.01). At 30 months, the mean value of PPPG was 155.39 (±33.34) mg/dl, thus reduction observed from baseline to end of treatment was 49.40%, a highly significant difference (p<0.01) (Figures 1 and 2). The mean HbA1c was decreased significantly from 9.07 to 5.84% (↓ by 3.23%) at 3 month and from 9.07% to 7.11% (↓ by 1.96%) at the end of 30 months (Figures 3 and 4). The proportion of patients who achieved HbA1c<7 were 94 % on completion of 3 months of treatment and 39% at the end of study.

The comparison of the levels of FBS, PPPG and HbA1c of two groups revealed that there was no significant difference at baseline (p>0.05). At 3 months, the levels of FBS and HbA1c exhibited significant difference among two groups (significantly lower in vildagliptin compared to Glimepiride) having p values of 0.05 and 0.03, respectively, however a non-significant difference (p value=0.93) in the level of PPPG. At 30 months all these variables (FPG, PPPG 7 HbA1c) showed significant difference (p<0.01) among the two groups (significantly lower in vildagliptin compared to Glimepiride).

**Incidence of hypoglycemia**

The overall incidence of hypoglycemia (minor) was higher in patients treated with Glimepiride-metformin combination as compared to the patients treated with Vildagliptin-Metformin combination. A total of 66 patients experienced at least 1 episode of hypoglycemia in group 1 as compared to 8 patients in group 2 (p<0.01) (Figure 5). All episodes were minor except for 9 episodes in Glimepiride which were recorded to be of moderate in intensity.

**Changes in body weight**

In present study, a variation in body weight had been observed among the two treatment groups. A significant weight gain was observed in group 1 (2.07 kg) as compared to (.69 kg) in group 2 (p<0.01) at the end of study (Figure 6).

**Treatment outcome**

On completion of 3 months of treatment, of 100 patients in group 1, 60% of patients were switched on to metformin and pioglitazone combination, while 40% needed the initial combination of Glimepiride and metformin. All patients were followed up till 30 months and it was observed that there was gradual increase in the HbA1c levels from 18 months onwards to the end of study and escalation of therapy was needed. Consequently, at 30 months, 72% patients needed three medicines (Glimepiride + metformin and Pioglitazone), 4% patients required the addition of fourth drug (DPP-4 inhibitor or acarbose inhibitor), 2% patients were shifted to pre-mix insulin and 22% patients required metformin and Pioglitazone to achieve glycemic control (A1C <7%).

In group 2, on completion of 3 months of treatment, of 100 patients, 80% were switched on to combination of metformin and Pioglitazone (vildagliptin discontinued) and only 20% of patients required the combination of vildagliptin and metformin. Though, there was also gradual increase in the A1C levels from 18 month onwards, however it was quite small. Consequently, at the end of 30 month, 65 % of patients needed escalation of therapy from two drugs to three drugs (vildagliptin + metformin+ Pioglitazone), 4% patients required the addition of fourth drug (Sulphonylurea or acarbose inhibitor) and 1% were shifted to pre-mix insulin and remaining 30% were able to maintain their glycemic control with two drugs (metformin+ pioglitazone).

**Cost-effectiveness**

The two groups differ in their cost effect, as treatment with vildagliptin
group was 4.3 fold costlier than with sulfonylurea till 3 months of treatment. However, this difference lessens to 2.0 fold and 2.50 fold in 24 months and 30 months respectively, as more number of patients were able to maintain on metformin and pioglitazone in group 2 compared to group 1 with the progress of treatment duration. The difference in the cost between vildagliptin and Glimepiride decreases at the end of the study because more number of patients in Glimepiride group needed escalation of therapy compared to vildagliptin group.

Discussion

The primary results of our study showed that the initial combination therapy at the time of diagnosis provided significant and durable glycemic control up to 130 weeks period; second that the combination of vildagliptin - metformin improved the durability of glycemic control better than Glimepiride- metformin combination at 30 month (A1c 7.11 vs. 7.31 p=<0.001) and displays a favorable adverse effect profile with no weight gain and less episodes of hypoglycemia. The better glycemic control in the later part of study period in vildagliptin-metformin group could not be explained by difference in baseline characteristics and difference in drug adherence and body composition.

In our study A1C decreased significantly at the end of 3 months in both groups (from 9.03% to 5.93% decreased by 3.10%) in group1 and (from 9.07% to 5.84% decreased by 3.23%) in group 2 (Figure 3) and 84% and 85% of the patients achieved the target of A1C <7%. Similar reductions were observed in FPG and PPPG levels at the end of 3 months. Similar reduction in glycemic parameters were observed in various previous studies and support the results of our study.16,17

At the end of study period (120 weeks), all three parameters (FPG, PPPG and A1C) remained significantly lowered compared to baseline values in both groups. Consistent with the results of our study, the durability in glycemic control with initial combination therapy was also observed in other previous studies and supports the results of our study.16,17. The reduction in glycemic levels in Glimepiride- metformin was associated with significantly higher incidence of hypoglycemia (66% vs. 8%) and weight gain (2.07 kg vs. 0.69 kg) (Figures 5 and 6) and consistent with the results reported in various previous studies.16,17,19

At the end of study period, 39% of participants in vildagliptin-metformin group and 31% in Glimepiride-metformin group achieved the target of A1C <7% and comparable with other studies.20,21 The A1C levels were comparable in both groups up to 18 month of treatment,16,21 when A1C start rising in both group, albeit, more pronounced rise in A1C was observed in Glimepiride-metformin group compared to vildagliptin-metformin group that reached at a significant levels at 24 and 30 month (at 24 month A1C 6.79 vs. 6.61 p<0.001 and at 30 month A1C 7.36 vs. 7.11 p<0.001 ( Figure 3). At the end of 30 month, A1C decreased by 1.96% from base line (from 9.07% to 7.11%) in vildagliptin group compared to 1.67% reduction in Glimepiride group (from 9.03% to 7.36%) (Figure 4), despite more patients in latter required the addition of another oral agent to maintain the A1C <7%. The statistically significant increase in A1C levels in Glimepiride compared to vildagliptin group at 24 and 30 month in this study showed that the combination of vildagliptin and metformin reduced the rate of treatment failure compared with combination of Glimepiride and metformin and is in lieu with previous studies.22,23 The significant rise in A1C after 24 month of treatment in drug naïve patients in Glimepiride group is attributed to more pronounce β-cell failure seen with sulphonylurea treatment.24,25 Similar to our study, better response among Asian diabetic patients to DPP-4 inhibitors has been shown in other studies, resulting into durable glycemic control.24,25 Consistent with this; more study participants in Glimepiride group required more escalation of drug therapy compared to vildagliptin group (80% vs. 70% at 30 month).

This study like various previous studies showed that vildagliptin-metformin treatment displays better side effect profiles compared to Glimepiride – metformin treatment with less weight gain and lower incidence of hypoglycemia.11,12,16,17 Recently several clinical trials have shown strong association between adverse clinical outcome and hypoglycemia.24 The occurrence of any severe hypoglycemia constitutes a marker of vulnerability to a primary cardiovascular events or death. Cardiovascular events are the major cause of mortality in type 2 diabetic patients, considering the potential C-V risk associated with severe hypoglycemia,29 the use of medications associated with lower risk of hypoglycemia for the management of blood glucose in type 2 diabetic patients would be prudent.

Cost is a limiting factor for DPP-4 inhibitors use. In this study, the initial 4-fold higher cost in vildagliptin group decreased to 2.75 fold at the end of 30 month. However, the lower cost in Glimepiride was associated with increased pill burden, increased incidence of hypoglycemia, increased weight gain and more number of patients with target A1C >7%.

In T2D, guidelines recommended glycemic targets significantly delayed the onset and progression of complications, however, the proportion of patients reaching these targets remains unacceptably low. In guidelines recommended step-up approach, a patient accumulate total glycemic burden of A1C >8% for 5 years and A1C >7 % for 10 years as patient passed through non-pharmacological to monotherapy to combination oral agents.30 A major, however, less recognized contribution of this glycemic burden is the response of clinicians to failing antihyperglycemic treatment as the A1C levels rise inexorably high above 9.0% before combination therapy is attempted by the clinicians.30 However, recent clinical trials indicate that earlier intervention and timely achievement of glycemic targets help in reducing the diabetes related chronic complications. Achieving the guidelines recommended glycemic targets very early (within 12 weeks) and maintaining these targets over prolonged period up to 120 weeks in this study with early use of combination therapy in drug naïve patient favours the early use of combination therapy in the treatment armamentarium of newly diagnosed type 2 diabetic patients with moderate hyperglycemia. Better glycemic sustainability and good AE profile was observed with vildagliptin therapy, albeit at a higher cost.
and many patients spend long time well outside the recommended glycemic range. New standard care of clinical practice guidelines entails initial combination therapy earlier in the treatment continuum than previous guidelines. However, resistance to initiate combination therapy at diagnosis, among physicians is widespread. As the principal responsibility for managing T2D continues to shift to primary care setting, PCPs must rise to the challenge of overcoming their own resistance.

Although the present study had limitation in terms of small number of patients, collectively the results indicate that the DPP-4 inhibitors –metformin represent a more effective combination in terms of number of patients achieving guidelines recommended A1C target of less than 7% at the end of 30 months, less weight gain, and a lower risk of hypoglycemia in newly diagnosed type 2 diabetic patients with moderate hypoglycemia.

References


Spectrum of Glomerular Diseases in Adults: A Study from North Eastern India

Md Jamil1*, PK Bhattacharya2, Vandana Raphael2, Yookarin Khonglah3, Monaliza Lyngdoh1, Akash Roy4

Abstract
Aims and Objectives: To study the clinical profile of patients with glomerular diseases and to study pattern of glomerular diseases in adults.

Methodology: A hospital based retrospective observational study from North Eastern India that includes biopsy proven glomerular disease (GD) in adults. Patients with inadequate biopsy sampling; incomplete medical data and biopsy of transplanted kidney were excluded.

Results and Observations: A total of 102 patients were included of which 25 (24.5%) were male and 77(75.5%) were female with M: F ratio of 0.32:1. The mean age of presentation was 30.6 years. Nephrotic syndrome (57.8%) was the commonest clinical diagnosis followed by acute nephritic syndrome (31.4%), unexplained AKI (5.9%), unexplained CKD with normal kidney size (2.9%) and asymptomatic urine abnormality (1.9%). On histo-pathological analysis primary GD and secondary GD was diagnosed in 46(45.1%) and 53(52.0%) respectively. Overall Lupus nephritis (LN) was found to be the commonest (41.2%) GD. Among the primary GD, MCD (11.8%) was the most frequent followed by MPGN (10.8%), Membranous Nephropathy, (5.8%), IgA nephropathy (5.8%) and Focal segmental glomerulosclerosis (5.8%). Three (2.9%) patients did not have any specific diagnosis and were labelled as chronic glomerulo-nephritis.

Conclusion: As the pattern of glomerular disease varies from one region to another, the pattern of glomerular disease in the north eastern India also varies from the other regions of India. Nephrotic syndrome remains the most common indication of renal biopsy in this region similar to the other parts of India. Unlike other studies from outside North Eastern India, this study show that females are more commonly involved with majority of them having secondary GD and this is due to LN which was diagnosed as the most common GD in the present study.

Background
Glomerular disease (GD) is one of the commonest forms of renal disease that may present clinically as varieties of syndrome but sometimes it may be diagnosed in patients who come for routine check-up and found to have asymptomatic urine abnormalities (AUA). Epidemiological study in relation to glomerular diseases (GD) requires good histopathological evidence along with clinical, biochemical and immunological correlation for proper diagnosis. It has been learned that pattern of GD varies from one country to another and also changes with time within the same country.1 In countries like India with a population of more than 1.2 billion, the pattern of GD even may vary from one region to another. Published reports show that membranous nephropathy (MN) is the commonest cause of GD in North India,2,3 report from South India shows minimal change disease(MCD) as more predominant,4,5 and in Western India among young adults, primary IgA nephropathy is more common.6 Published data also shows that pattern of GD varies among different ethnic groups of the world.7 As the population in north eastern India is different from the rest of the country genetically,8 with different socio cultural practice, we do expect that the pattern of the GD or any other disease will different from the pattern of diseases prevalent in other parts of India. As publish data is not available to the best of our knowledge, relating to the pattern of GD in adult population from north eastern India, we hereby present a study to find out the pattern of GD prevalent in North Eastern India among adult population.

Aims and objective of the present study are
a. To study the clinical profile of patients.
b. To study pattern of glomerular diseases.

Procedures
The present study is a hospital based retrospective study conducted in a tertiary care medical institute from North Eastern India. The study was approved by the Institute Ethical Committee. Data for the present study were collected from the patient’s medical record file and renal biopsy record from the histopathology section of department of Pathology. The study includes only adult patients (above 18 years of age) with biopsy proven GD, who attended the institute from January 2013 to September 2015. Patients with inadequate biopsy sampling, incomplete medical data and biopsy of transplanted kidney were excluded.

Renal biopsy in the institute is done under ultra-sonographic guidance with the help of disposable automatic biopsy gun by department of radio-intervention and biopsy samples

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were collected in normal saline and formalin bottles. Renal biopsy samples were subjected to light microscopy (Haematoxylin and Eosin, Periodic acid Schiff, Masson’s Trichrome and Periodic Methenamine Silver) and immunofluorescence study (Kappa light chain, Lambda light chain, IgG, IgA, IgM and C3). Electron microscopy could not be done due to non availability of the facility.

Patient related information collected in the present study were following: Central Registration no(CR no), In Patient no(IP no), name, age, sex, relevant medical history, indication for renal biopsy, histopathological diagnosis and laboratory reports that includes biochemical investigation reports (serum creatinine, blood urea, liver function test, lipid profile study, thyroid profile study, blood sugar), immunology and serology reports (anti nuclear antibody(ANA), anti dsDNA antibodies, C3, C4, pANCA, cANCA, anti GBM antibodies, RA factors, HBsAg, Anti HCV, HIV I&II), haematological reports, routine urine examination reports, 24 hours urinary protein estimation and other significant findings during data collection.

Indications for renal biopsy were categorized into following groups and standard definition for clinical syndrome was used: nephrotic syndrome, nephritic syndrome, acute kidney injury (AKI), chronic kidney diseases (CKD) and asymptomatic urinary abnormalities. In CKD, renal biopsy was performed if kidney size is within normal limit with intact corticomedullary differentiation for unexplained renal failure.

Data collected were entered in Microsoft Excel 2010 spread sheet for statistical analysis. Results are expressed as mean or medians standard deviation for continuous data and as percentage for categorical data.

### Results

A total 108 number of patients who had renal biopsy were analysed. Out of 108 patients, 6(six) were excluded from the study because of inadequate data available for these patients. Out of 102 patients who underwent renal biopsy four patients developed major complication, three of them required blood transfusion due to haemorrhage and one developed psoriasis abcess post biopsy. Out of 102 patients 25(24.5%) were male and 77(75.5%) were female, male to female ratio was 0.32:1. The mean age of presentation was 30.6 years (male- 33.3 and female- 29.7 years). Age and sex distribution in different types of GD are shown in Table 2.

### Discussion

The present study provide pattern of GD in adults (18 years or above) from North Eastern part of India. Population in this region differ from the rest of India. Genetically majority of the people in this region are more similar to east Asian population along with different cultural and food habit from the other parts of India. In present study, GD was found to be more common in female patients that is in contrast to other study reported from other part of India where it was reported to be more common in males but female predominance has been reported in studies from South Africa and Oman. In the present study commonest indication for the renal biopsy was nephrotic syndrome.
followed by nephritic syndrome, similar to the finding reported in the other studies from India and other SAARC countries. AUA as an indication for renal biopsy was found only in 1.9% of patients in our study but other studies shown AUA as an indication for renal biopsy in higher proportion of cases. In our study, primary glomerular disease constituted 48% and secondary GD 52.0% of the cases, this finding differs from the reports of other studies from other parts of India, where they reported primary GD as more common than secondary GD. The high proportion of GD and female predominance in the present study may be due to a very high prevalence of lupus nephritis in the region, as LN was found to be the commonest cause of GD in the present study which mostly affect the females. Similar finding of female predominance in association with high proportion of LN has been reported from Oman. Among the primary GD, minimal change disease diagnosed as most frequent with an overall percentage of 11.8% followed by MPGN (10.8%). MN, IgA nephropathy and FSGS rank third among the primary GD with 5.8% each. Comparison of the present study with some other studies from Indian and neighbouring Bangladesh has been shown in Table 3. Among the secondary causes of GD majority are due to LN that constitute almost 41.2% of the total GD. DN was diagnosed in three (2.9%) cases, all of them had microhematuria at presentation and two out of three had AKI. The present study shows a higher prevalence of DN compared to other studies. Secondary GD due to chronic infection was found in 2% of cases, all of them were due to chronic hepatitis C infection. One limitation of the present study was that none of the biopsy sample has been examined by electron microscope and this may be one of the reasons that disease like Alport’s syndrome, thin membrane diseases could have been missed.

Conclusion

As the pattern of glomerular disease varies from one region to another, the pattern of glomerular disease in the north eastern India also varies from the other regions of India. Nephrotic syndrome remains the most common indication of renal biopsy in this region similar to the other parts of India. Unlike other studies from outside North Eastern India, this study show that females are more commonly involved with majority of them having secondary GD and this is due to LN which was diagnosed as the most common GD in the present study.

References


Table 2: Different clinical manifestations at the time of presentation in different types of glomerular diseases

<table>
<thead>
<tr>
<th>Glomerular Disease</th>
<th>Number of Patients</th>
<th>Male/Female Ratio</th>
<th>Mean Age</th>
<th>Nephrotic Syndrome (n%)</th>
<th>Subnephrotic Proteinuria (n%)</th>
<th>HTN (n%)</th>
<th>Haematuria (n%)</th>
<th>Raised Serum Creatinine (n%)</th>
<th>Dyslipidaemia (n%)</th>
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<tr>
<td>MCD</td>
<td>12 (11.8)</td>
<td>0.3:1</td>
<td>32.1</td>
<td>12 (100)</td>
<td>0 (0)</td>
<td>6 (50)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>9 (75)</td>
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<tr>
<td>MN</td>
<td>6 (5.9)</td>
<td>2:1</td>
<td>33</td>
<td>5 (83.3)</td>
<td>1 (16.7)</td>
<td>4 (66.6)</td>
<td>1 (16.7)</td>
<td>0 (0)</td>
<td>6 (100)</td>
</tr>
<tr>
<td>FSGS</td>
<td>6 (5.8)</td>
<td>1:1</td>
<td>22.2</td>
<td>4 (66.6)</td>
<td>2 (33.3)</td>
<td>4 (66.6)</td>
<td>2 (33.3)</td>
<td>5 (83.3)</td>
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</tr>
<tr>
<td>MPTGN</td>
<td>11 (10.8)</td>
<td>1.7:1</td>
<td>37.1</td>
<td>10 (90.9)</td>
<td>1 (9.1)</td>
<td>8 (72.7)</td>
<td>8 (72.7)</td>
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<td>MesPGN</td>
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<td>DN</td>
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<td>1 (33.3)</td>
<td>2 (66.6)</td>
<td>3 (100)</td>
<td>3 (100)</td>
<td>1 (33.3)</td>
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<td>LN</td>
<td>42 (41.2)</td>
<td>0.02:1</td>
<td>26.3</td>
<td>14 (33.3)</td>
<td>28 (66.6)</td>
<td>21 (50)</td>
<td>20 (47.6)</td>
<td>10 (23)</td>
<td>9 (21.4)</td>
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<td>Anti GBM GN</td>
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<td>1 (50)</td>
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<td>Hep C GN</td>
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<td>Wegener GN</td>
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<td>3 (100)</td>
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<td>HTN Nep</td>
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<td>-</td>
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Diagnostic Accuracy of Stress Myocardial Perfusion Imaging in Diagnosing Stable Ischemic Heart Disease

G Varadaraj1*, GS Chowdhary2, R Ananthakrishnan3, MJ Jacob4, P Mukherjee5

Abstract

Objective: To determine the diagnostic accuracy of Stress Myocardial Perfusion Imaging (MPI) in diagnosing Stable Ischemic Heart Disease (SIHD).

Method: To analyze the sensitivity and specificity of Stress Myocardial Perfusion Imaging (MPI) in diagnosing Stable Ischemic Heart Disease (SIHD) by comparing with “gold standard” Coronary Angiogram.

Result: A total of 80 patients were studied (51 male, 29 female). 52 patients had significant stenosis in coronary angiography and 49 patients had reversible perfusion defect in myocardial perfusion imaging (MPI). MPI had a sensitivity of 88.46% and a specificity of 89.29% in diagnosing stable ischemic heart disease.

Conclusion: Coronary Angiography remains the near gold standard in diagnosing ischemic heart disease but is associated with serious complications like stroke, arrhythmias, acute renal failure, infection, etc. Though Myocardial perfusion imaging cannot replace coronary angiogram, it can be used as a reliable and sensitive non-invasive alternate investigation to diagnose stable ischemic heart disease in high risk individuals who are unwilling for angiogram.

Introduction

Coronary Artery disease (CAD) is the most prevalent form of cardiovascular disease (CVD) affecting millions of people all over the world. There has been an alarming increase over the past two decades in the prevalence of CAD and cardiovascular mortality in India and other south Asian countries.1 There has been a 4-fold rise of CHD prevalence in India during the past 40 years.2 Rapid urbanization and change in lifestyle that occurred during the past two decades have led to the growing burden of coronary risk factors in India.3

Hence, there is an urgent and pressing requirement for reliable and safe investigation procedure for early and effective diagnosis of CAD. Coronary Angiography (CAG) remains the procedure of choice to diagnose ischemic heart disease but carries significant risk of stroke, arrhythmias, acute renal failure, infection, etc. Non-invasive Myocardial perfusion imaging (MPI) by nuclear medicine techniques is now widely applied for the evaluation of ischemic heart disease. Radioisotopes are injected at rest and also during stress which produces images of regional myocardial uptake proportional to the blood flow. There occurs a five-fold increase in myocardial blood flow with maximal exercise, above the resting condition.4 Due to critical narrowing of the epicardial arteries (coronary stenosis), the perfusion to myocardium is impaired and it cannot be increased further. Due to the stenosis, there occurs a differential flow to the territory supplied by the stenosed...
vessel and uneven distribution of tracer isotopes.4

The results of myocardial perfusion imaging are compared to the results of invasive coronary angiography which is considered a ‘gold standard’. The diagnostic accuracy is finally determined by the comparison of results which is represented as ‘sensitivity’ and ‘specificity’ of MPI.

Several studies done across the globe to determine the diagnostic yield of MPI have yielded mixed results with majority of the studies showing a reasonable sensitivity and specificity. This study aims at establishing myocardial perfusion imaging as a reliable and accurate non-invasive investigation to diagnose stable ischemic heart disease (SIHD) in high risk individuals who are unwilling for coronary angiography apart from negating some of its serious complications.

Material and Methods

Place of study

The study was conducted in the Department of Cardiology in a tertiary care hospital setting.

Study design

A cross sectional study was undertaken.

Sample size

A total of 80 patients with stable ischemic heart disease were evaluated.

Selection of study population

The American College of Cardiology Foundation/American Heart Association (ACCF/AHA) has accepted the definition of Stable Ischemic Heart Disease (SIHD) to include Stable Angina or low risk unstable angina.5,6

Stable angina is chest pain or discomfort that most often occurs with activity or emotional stress (Table 1). Unstable Angina can be classified into Low risk, Intermediate risk and high risk unstable stable.

A total of 276 patients who visited the Cardiology OPD from Oct 2014 to Jul 2016 were identified to have stable ischemic heart disease. Of the 276 individuals who were selected for the study after analysing the inclusion and exclusion criteria mentioned below, 162 individuals were not willing to participate after explaining the course of the study in the language they understand.

The remaining 114 patients who consented to participate in the study after being explained, 34 patients withdrew their consent after undergoing myocardial perfusion imaging. Those who withdrew the consent were largely having a normal myocardial perfusion imaging.

Inclusion criteria

1. The study comprised of all consenting individuals having clinical signs of Stable ischemic heart disease
2. The probability of ischemic heart disease being > 5%.

Exclusion criteria

1. Patients who have undergone Cardiac intervention in the past.
2. Patients with known or freshly detected Cardiomyopathy.
3. Patients with Acute MI and intermediate or high risk Unstable Angina (UA) / NSTEMI.
4. Patients with known valvular heart disease.
5. Evidence of Right or Left Bundle branch blocks (RBBB/LBBB).
6. Patients who have undergone device implantation.
7. Patients with known or newly detected Cardiomyopathy.
8. All non-consenting individuals and individuals who withdrew consent during any part of the course of the study.

Patients with SIHD with pre-test probability more than 5% (combined Diamond/Forrester and Coronary Artery Surgery Study (CASS) data) are taken for Stress myocardial perfusion study with single day stress-rest protocol. Patient exercises on treadmill in Bruce or modified Bruce protocol till the endpoints are achieved. Images are analyzed and classified as normal, reversible perfusion defect (inducible ischemia) and fixed perfusion defect (infarct area).

The extent of disease by Coronary Angiogram is defined as 1-vessel (single vessel disease), 2-vessel (double vessel disease), 3-vessel (triple vessel disease), or left main disease, with a significant stenosis 70% diameter reduction; left main disease, however, has been defined as a stenosis 50%.7,8

Diagnostic accuracy of myocardial perfusion imaging is commonly represented by the terms sensitivity and specificity, which are calculated by comparing test results to the “gold standard” of the results of invasive coronary angiography.

### Table 1: Clinical classification of chest pain (Adapted from Braunwald et al5)

<table>
<thead>
<tr>
<th>Typical Angina (Definite)</th>
<th>Atypical Angina (Probable)</th>
<th>Non-cardiac chest pain</th>
</tr>
</thead>
<tbody>
<tr>
<td>(1) Sub-sternal chest discomfort with a characteristic quality and duration that is; (2) provoked by exertion or emotional stress and; (3) relieved by rest or nitroglycerin</td>
<td>Meets 2 of the above characteristics</td>
<td>Meets 1 or none of the typical anginal characteristics</td>
</tr>
</tbody>
</table>

Fig. 1: Distribution and comparison of age and vessels involved

Fig. 2: Diagram depicting distribution of vessel involvement
Table 2: Age distribution of male and female study participants

<table>
<thead>
<tr>
<th>Age</th>
<th>Single Vessel</th>
<th>Double Vessel</th>
<th>Triple Vessel</th>
<th>Normal</th>
<th>Chi square</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤60</td>
<td>20</td>
<td>5</td>
<td>2</td>
<td>20</td>
<td>15.00</td>
<td>0.002**</td>
</tr>
<tr>
<td>&gt;60</td>
<td>7</td>
<td>9</td>
<td>9</td>
<td>8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>27</td>
<td>14</td>
<td>11</td>
<td>28</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Result

A total of 80 patients were studied (51 male, 29 female). 52 patients had significant stenosis in coronary angiography and 49 patients had reversible perfusion defect in myocardial perfusion imaging (MPI). Our study carried a sensitivity of 88.5% and specificity of 89.3% for myocardial perfusion imaging in diagnosing stable ischemic heart disease. Further, the positive predictive value (PPV) was 93.9% and negative predictive value (NPV) was 80.7%.

The accuracy of myocardial perfusion imaging as demonstrated by various studies worldwide showed sensitivity ranging from 85% to 97.8% and specificity ranging from 66.7% to 91%.9-12

Discussion

Total of 80 patients were included in the study of which 51 were Male (63.8%) and 29 were Female (36.3%). Out of 80 patients included in the study, mean age of Male was 58.05±11.42 years and Female was 58.06±14.17 years. Further, the age group between 51-60 years was most commonly affected constituting 28.75% of the total study population. Angiographic evidence of double and triple vessel disease were most commonly found in elderly population (age more than 60 years) comprising 5 out of 9 patients for double vessel disease and 9 out of 11 patients for triple vessel disease. However, Angiographic evidence of single vessel disease involvement was most commonly found in patients less than 60 years of age (20 out of 27 patients) (Figure 1). The findings are similar to the results of the study conducted by Babu Ezhumalai et al.13

The INTERHEART case-control study done in 2006 identified eight common risk factors behind more than 90% of incident cases of Ischametic Heart Disease (IHD) in South Asian and Indian population.14 The risk factors include Dyslipidema, smoking or tobacco use, Hypertension, Diabetes, abdominal obesity, physical inactivity, low fruits and vegetable intake and psychosocial stress.14 In our study, all 80 patients had atleast one of the risk factors indicated by INTERHEART study.

Further, Hypertension was the commonest risk factor present in our study population, present in 60% of the individuals compared to 29% in the study conducted by Gupta R et al.15 The risk of cardiovascular events is from two to three times higher in people with Type 1 or Type 2 diabetes.1 Type 2 Diabetes was present in 44% of the individuals involved in the study. Other risk factors like Obesity, Dyslipidemia, smoking and family history of cardiovascular event were present in 55%, 50%, 43% and 26% respectively in the population under study. There was no significant difference in the prevalence of risk factors among Male and Female individuals except smoking. This may be due to the fact that smoking is relatively uncommon among female in Indian population.16 Also, many of the female patients hesitate to disclose smoking history as it carries significant social stigma.

Significant coronary vessel stenosis (suggested by CASS and modified by BARI study group) confirmed by coronary angiogram was present in 52 of the 80 patients studied (65.0%). Of the 52 patients, single vessel disease was the commonest type of vessel involved constituting 27 patients out of 52 (51.9%) followed by double and triple vessel disease constituting 14 out of 52 (26.9%) and 11 out of 52 (21.2%) respectively (Table 2).

When compared to age, vessel involvement showed a predominant single vessel disease among younger age group (age less than 60 years) with 20 out of 27 patients having single vessel disease are less than 60 years of age. Also, non-significant coronary stenosis (stenosis less than 70% diameter of LAD, RCA and LCx, less than 50% diameter of LMCA) or normal coronary vessels were also common among younger age group; 20 out of 28 patients having non-significant coronary vessel stenosis or normal angiogram were less than 60 years. In contrast, double vessel disease and triple vessel disease were more common in elderly group (age more than 60 years). 05 out of 09 patients (55.6%) having double vessel disease and 09 out of 11 patients (81.8%) having triple vessel disease were more than 60 years of age (Table 2).

A similar result was obtained by Babu Ezhumalai et al in which 64.7% of normal angiogram patients were less than 55 years of age.15 However, all types of vessel involvement namely single, double and triple vessel disease were more common in patients more than 55 years of age. In their study, 55.2% of single vessel disease, 60.0% of double vessel disease and 66.7% of triple vessel disease were seen in patients more than 55 years of age.13

In our study, among single vessel disease, LAD (Left Anterior Descending) is the most commonly involved coronary vessel involving 15 of the 27 patients (55.6%) having single vessel disease. The other commonly involved vessels in single vessel disease are RCA (Right Coronary Artery) constituting 25.9% and LCx (Left Circumflex) constituting 18.5% of single vessel disease respectively. The findings are similar to the results of Robert M Califf et al and Koju R et al.16,17 The vessel involved in single vessel disease were LAD (47.6%), RCA (35.2%) and LCx (17.2%) in the study by Robert M Califf et al and LAD (43.7%), RCA (37.5%) and LCx (21.9%) in the study by Koju R et al. In our study, there were 28 patients who showed negative for myocardial perfusion imaging. They were taken for coronary angiogram in spite of normal MPI as the pre-test likelihood of ischemic heart disease was high and the clinical signs and symptoms were suggestive of ischemic heart disease.

There were 06 false negative cases (normal myocardial perfusion imaging but positive angiographic finding) in the study. Of the 06 cases, 03 were single vessel disease involving RCA and the other 03 cases were triple vessel disease involving all three vessels namely LAD, RCA and LCx. Therefore, myocardial perfusion imaging is more likely to produce false negative results in patients having inferior wall ischemia (RCA territory of myocardium) and triple vessel disease.16

However, in the setting of false
negative result in triple vessel disease, though the perfusion imaging may be normal, there is decreased left ventricular ejection fraction (LVEF) which is unlikely for a normal myocardium. Low LVEF is associated with transient ischemic dilatation of left ventricle and increased tracer uptake by lungs which are indirect markers for ischemic heart disease with left ventricular dysfunction.\textsuperscript{18-20} Since assessment of LVEF by myocardial perfusion imaging and tracer uptake by lungs are not under the scope of the present study, no further emphasis is made.

The present study carried a sensitivity of 88.5\% and specificity of 89.3\% for myocardial perfusion imaging in diagnosing stable ischemic heart disease. Further, the positive predictive value (PPV) was 93.9\% and negative predictive value (NPV) was 80.7\%, making myocardial perfusion imaging a reliable non-invasive investigation for diagnosing stable ischemic heart disease (Table 3).

**Conclusion**

The results conclude that MPI using 99mTc sestamibi is a reliable non-invasive investigation to diagnose stable ischemic heart disease. Though it cannot replace coronary angiogram which is considered a gold standard in detecting ischemic heart disease, the high sensitivity and specificity of MPI makes it a useful and reliable screening procedure. Patients having high suspicion of stable ischemic heart disease may be subjected to MPI initially and if detected to have a reversible perfusion defect which implies a viable myocardium supplied by a stenosed coronary vessel, coronary angiogram may be performed with subsequent Angioplasty.

By making use of MPI as a gateway investigation to coronary angiogram, patients who are unwilling for angiogram can be evaluated with good sensitivity apart from evading some of the ill effects and complications of coronary angiogram.

Though the present study is not powered to make any recommendations, the results clearly indicate the need for further studies powered to make recommendations over the use of MPI as a screening investigation to coronary angiogram in detecting stable ischemic heart disease.

**References**


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- Lower risk of hypog vs conventional basal analogues, lispro mix and BHI
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- Most trusted modern premix insulin worldwide that fits into patient’s life

NovoMix™ 30 (biphasic insulin aspart I.P. 30/70)
simply life ready 24/7
Association of Mean Platelet Volume with Acute Ischemic Cerebrovascular Accident Among Patients with Type 2 Diabetes Mellitus: A Hospital-Based Study

Priyanka Patil1*, Arathi Darshan2, Saroja AO3, VA Kothiwale4

Abstract

Objective: To study the association of MPV (mean platelet volume) and acute ischemic stroke in patients of type 2 diabetes mellitus (DM).

Methods: This was a 1-year cross-sectional hospital-based study involving 79 patients presented with acute ischemic stroke. Among them, 25 were diabetic and 54 were nondiabetic. Demographic data and history of the patients were recorded. Investigations such as haemoglobin estimation, platelet count, MPV, HbA1c, imaging studies were conducted and evaluated for acute ischemic brain stroke. All the patients underwent neurological examination according to National Institute of Health Stroke Scale (NIHSS) at the time of admission and MPV was noted. Outcome of stroke was assessed during discharge by modified Rankin morbidity (MRM) score. SPSS 20 was used to analyse the data.

Results: Among 79 them, 25 patients (31.6%) had history of diabetes which formed the diabetic subset and the remaining 54 (68.35%) were considered in non-diabetic subset. MPV in patients with DM was significantly high (10.16 ± 0.89 fL) compared to nondiabetic patients (8.25 ± 0.91 fL; p<0.001). The mean NIHSS scores were significantly high in patients with diabetes compared to nondiabetic patients (20.38±3.19 vs. 17.76±3.74; p=0.006). Also, the mean MRM scores were significantly high in diabetics than that of nondiabetics (4.12 ± 0.66 vs. 3.00 ± 0.61; p<0.001). History of stroke was present in 12% of patients with DM compared to 1.85% of the non-diabetic patients (p=0.091).

Conclusions: Acute ischemic stroke in diabetic patients is significantly associated with raised MPV level, which is likely to be severe with high morbidity and mortality. Hence, MPV is an easily available blood parameter, which defines platelet reactivity and proves to be a good predictor of severity and outcome of stroke in diabetics. Also, higher percentile of patients showed history of recurrent stroke in diabetics as compared to non-diabetics in whom the MPV was considerably raised compared to other diabetic stroke cases.

Introduction

Stroke is a major cause for death and acquired disability in world population after myocardial infarction. Majority of the strokes are ischemic (80%) while others result from primary haemorrhage either intracerebral or into subarachnoid space.1 Acute ischemic stroke is more common than haemorrhagic stroke and is a result of thrombosis or embolism. Various risk factors involved for stroke include hypertension, cigarette smoking, hyperlipidaemia, and diabetes mellitus.2 Among these, risk factors, DM, and ischemic stroke often ascends together.3 Platelets play a vital role in normal haemostatic process. The mean platelet volume (MPV) is the mostly used laboratory marker of platelet function and activation. Increased platelet reactivity has emphasized to play an important role in developing various vascular complications.4 Particularly, the patients with DM show increased platelet activity. The factors that contribute to this increased platelet activity are not clearly elucidated; however, metabolic abnormalities such as insulin resistance, hyperglycaemia, hyperlipidaemia, and conditions such as oxidative stress, endothelial dysfunction and inflammation have been presumed.5 Studies also have stated that high MPV acts as a risk factor for several vascular complications of DM, which include thromboembolism, myocardial infarction and stroke.6-9

Furthermore, an increase in MPV is associated independently with stroke and increased levels of MPV have been found in acute ischemic stroke patients than in normal subjects. The patients with highest quintile of MPV had a >2 fold risk of severe stroke than those with lower quintiles.10 These findings postulate that, the increase of MPV, specifically in diabetic patients might have a critical role for genesis or worsening of acute ischemic stroke. This prompted us to describe association between MPV and acute ischemic cerebrovascular events, which may serve as a valuable indicator for outcome of the event. MPV, being a cheap and easily available blood parameter, helps to prognosticate stroke both in diabetics and non-diabetics. The objective of this study was to study the association between MPV and acute ischemic stroke in patients with type 2 DM (outcome).

Material and Methods

Study design

This 1-year cross-sectional hospital-
Based study (January 2014 to December 2014) was conducted at the Department of General Medicine and Department of Neurology. The ethical clearance was obtained from Ethics and Research Committee. Patients screened based on selection criteria were informed about the nature of the study. In case of comatose patients, the relatives/caretakers were informed about the study. The patients/caregivers expressing their willingness to contribute in the study were enrolled after obtaining a written informed consent.

### Selection criteria

This study included acute ischemic brain stroke patients with or without prior history of DM. Exclusion criteria included patients who had anaemia with haemoglobin levels <12 gm% in men and 10 gm% in women, coronary artery disease, diagnosed with any other malignancy, immune thrombocytopenia purpura, acute poststreptococcal glomerulonephritis, renal failure, valvular heart disease, cyanotic congenital heart disease, and deep vein thrombosis.

Based on inverse sampling method, all the patients who presented with acute ischemic stroke fulfilling the selection criteria were involved in the study till sample size of patients with acute ischaemic stroke having history of type 2 DM was 25.

### Data collection

Demographic data such as age and sex were recorded. History of other comorbid conditions including hypertension, DM, previous stroke, personal history such as habits of alcohol consumption, and smoking, were noted. A thorough physical examination was conducted for vitals (respiratory rate, pulse rate, and blood pressure) followed by systemic examination. The diagnosis of stroke was entertained after fulfilling WHO definition of stroke by the patient. The ischemic nature of stroke was

### Table 1: Baseline characteristics of the study population

<table>
<thead>
<tr>
<th>Findings</th>
<th>Group A (Diabetic, n (%))</th>
<th>Group B, (Non-diabetic) n (%)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>18 (72 %)</td>
<td>37 (68.52 %)</td>
<td>0.754</td>
</tr>
<tr>
<td>Female</td>
<td>7 (28 %)</td>
<td>17 (31.48 %)</td>
<td></td>
</tr>
<tr>
<td>Age-wise distribution</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>30 or less</td>
<td>0</td>
<td>2 (3.70 %)</td>
<td>0.351</td>
</tr>
<tr>
<td>30-40</td>
<td>1 (4 %)</td>
<td>6 (11.11 %)</td>
<td></td>
</tr>
<tr>
<td>41-50</td>
<td>4 (16 %)</td>
<td>11 (20.37 %)</td>
<td></td>
</tr>
<tr>
<td>51-60</td>
<td>5 (20 %)</td>
<td>11 (20.37 %)</td>
<td></td>
</tr>
<tr>
<td>61-70</td>
<td>8 (32 %)</td>
<td>11 (20.37 %)</td>
<td></td>
</tr>
<tr>
<td>71-80</td>
<td>7 (28 %)</td>
<td>16 (66.67 %)</td>
<td></td>
</tr>
<tr>
<td>81-90</td>
<td>0</td>
<td>4 (7.14 %)</td>
<td></td>
</tr>
<tr>
<td>Previous history of stroke</td>
<td>3 (12 %)</td>
<td>1 (1.85 %)</td>
<td>0.091</td>
</tr>
<tr>
<td>Hypertension</td>
<td>5 (20 %)</td>
<td>10 (18.52 %)</td>
<td>0.551</td>
</tr>
<tr>
<td>Arterial supply</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACA</td>
<td>2 (8 %)</td>
<td>5 (9.26 %)</td>
<td>0.890</td>
</tr>
<tr>
<td>ACA/MCA</td>
<td>2 (8 %)</td>
<td>4 (7.14 %)</td>
<td></td>
</tr>
<tr>
<td>MCA</td>
<td>17 (68 %)</td>
<td>31 (57.41 %)</td>
<td></td>
</tr>
<tr>
<td>MCA/PCA</td>
<td>1 (4 %)</td>
<td>6 (11.11 %)</td>
<td></td>
</tr>
<tr>
<td>PCA</td>
<td>3 (12 %)</td>
<td>8 (14.81 %)</td>
<td></td>
</tr>
<tr>
<td>Circulation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anterior</td>
<td>21 (84 %)</td>
<td>40 (74.07 %)</td>
<td>0.328</td>
</tr>
<tr>
<td>Posterior</td>
<td>4 (16 %)</td>
<td>14 (25.93 %)</td>
<td></td>
</tr>
<tr>
<td>Severe</td>
<td>9 (36 %)</td>
<td>7 (12.96 %)</td>
<td></td>
</tr>
<tr>
<td>Outcome based on NIHSS</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Minor stroke</td>
<td>0</td>
<td>1 (1.85 %)</td>
<td>0.095</td>
</tr>
<tr>
<td>Moderate stroke</td>
<td>3 (12 %)</td>
<td>9 (16.67 %)</td>
<td></td>
</tr>
<tr>
<td>Moderate to severe</td>
<td>13 (52 %)</td>
<td>37 (68.52 %)</td>
<td></td>
</tr>
<tr>
<td>Severe</td>
<td>9 (36 %)</td>
<td>7 (12.96 %)</td>
<td></td>
</tr>
<tr>
<td>Outcome based on MRM scores</td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Slightly disability</td>
<td>0</td>
<td>8 (14.81 %)</td>
<td></td>
</tr>
<tr>
<td>Moderate disability</td>
<td>3 (12 %)</td>
<td>40 (74.07 %)</td>
<td></td>
</tr>
<tr>
<td>Moderate to severe disability</td>
<td>17 (68 %)</td>
<td>4 (7.14 %)</td>
<td></td>
</tr>
<tr>
<td>Severe disability</td>
<td>4 (16 %)</td>
<td>2 (3.70 %)</td>
<td></td>
</tr>
<tr>
<td>Death</td>
<td>1 (4 %)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>MPV (fl)</td>
<td>9.5 or less</td>
<td>49 (90.74 %)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>9.5 or less</td>
<td>49 (90.74 %)</td>
<td></td>
</tr>
</tbody>
</table>
| ACA, Anterior cerebral artery; MCA, Middle cerebral artery; PCA, Posterior cerebral artery; NIHSS, National institute of health stroke scale; MPV, Mean Platelet volume; MRM, Modified Rankin Morbidity score

### Table 2: The comparison of baseline clinical characteristics between the diabetic and non-diabetic subsets

<table>
<thead>
<tr>
<th>Findings</th>
<th>Diabetic, n (%)</th>
<th>Non-diabetic, n (%)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>62.04±10.88</td>
<td>58.11±16.75</td>
<td>0.217</td>
</tr>
<tr>
<td>Mean blood pressure</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic (mmHg)</td>
<td>160.37±15.78</td>
<td>161.60±12.81</td>
<td>0.714</td>
</tr>
<tr>
<td>Diastolic (mmHg)</td>
<td>94.07±7.90</td>
<td>95.60±5.07</td>
<td>0.305</td>
</tr>
<tr>
<td>Hemoglobin (gm%)</td>
<td>13.86±1.06</td>
<td>13.87±1.64</td>
<td>0.968</td>
</tr>
<tr>
<td>Platelet count (lakhs/m3)</td>
<td>2.61±0.51</td>
<td>2.76±0.64</td>
<td>0.290</td>
</tr>
<tr>
<td>NIHSS</td>
<td>20.08±3.19</td>
<td>17.76±3.74</td>
<td>0.006</td>
</tr>
<tr>
<td>MPV</td>
<td>10.16±0.89</td>
<td>8.25±0.91</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>MRM scores</td>
<td>4.12±0.66</td>
<td>3±0.61</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
| NIHSS, National Institute of Health Stroke Scale; MPV, Mean platelet volume; MRM, Modified Rankin Morbidity Score

### Table 3: Association of MPV with different parameters studied

<table>
<thead>
<tr>
<th>Parameters</th>
<th>MPV (fl)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration (years)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5 or less</td>
<td>11 (73.33 %)</td>
<td>4 (26.67 %)</td>
</tr>
<tr>
<td>&gt; 5</td>
<td>7 (70 %)</td>
<td>3 (30 %)</td>
</tr>
<tr>
<td>Treatment</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oral</td>
<td>12 (75 %)</td>
<td>4 (25 %)</td>
</tr>
<tr>
<td>Insulin</td>
<td>5 (62.50 %)</td>
<td>3 (37.50 %)</td>
</tr>
<tr>
<td>Unknown</td>
<td>1 (100 %)</td>
<td>-</td>
</tr>
<tr>
<td>HbA1c ≤ 7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>7.1 to 8.5</td>
<td>4 (80 %)</td>
<td>1 (20 %)</td>
</tr>
<tr>
<td>&gt; 8.5</td>
<td>13 (72.22 %)</td>
<td>5 (27.78 %)</td>
</tr>
<tr>
<td>Previous stroke</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Present</td>
<td>2 (66.67 %)</td>
<td>1 (33.33 %)</td>
</tr>
<tr>
<td>Absent</td>
<td>16 (72.73 %)</td>
<td>6 (27.27 %)</td>
</tr>
<tr>
<td>Hypertension</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Present</td>
<td>4 (80 %)</td>
<td>1 (20 %)</td>
</tr>
<tr>
<td>Absent</td>
<td>14 (70 %)</td>
<td>6 (30 %)</td>
</tr>
<tr>
<td>NIHSS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Moderate</td>
<td>3 (100 %)</td>
<td>0</td>
</tr>
<tr>
<td>Moderate to severe</td>
<td>8 (61.54 %)</td>
<td>5 (38.46 %)</td>
</tr>
<tr>
<td>Severe</td>
<td>7 (77.78 %)</td>
<td>2 (22.22 %)</td>
</tr>
<tr>
<td>MRM score</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Moderate disability</td>
<td>2 (66.67 %)</td>
<td>1 (33.33 %)</td>
</tr>
<tr>
<td>Moderate to severe disability</td>
<td>12 (70.59 %)</td>
<td>5 (29.41 %)</td>
</tr>
<tr>
<td>Severe</td>
<td>3 (75 %)</td>
<td>1 (25 %)</td>
</tr>
<tr>
<td>Death</td>
<td>1 (100 %)</td>
<td>0</td>
</tr>
</tbody>
</table>
| NIHSS, National Institute of Health Stroke Scale; MPV, Mean platelet volume; MRM, Modified Rankin Morbidity Score; HbA1c, glycated hemoglobin
established by computed tomographic/magnetic resonance imaging scan. Evaluation of stroke severity was carried out based on National Institute of Health Stroke Scale (NIHSS). All the outcomes were noted on a predesigned as well as pretested proforma. Clinical investigations such as haemoglobin estimation, platelet count, MPV, HbA1c, imaging studies (Magnetic resonance imaging or computed tomography scan of brain) were conducted and evaluated for acute ischemic brain stroke.

**Estimation of mean platelet volume**

Under all aseptic conditions, 2 mL of blood sample drawn from antecubital vein of the patient at the time of admission was collected in ethylenediaminetetraacetic acid (EDTA) vials and transported for analysis to laboratory. The MPV was estimated on Beckman and Coulter LH 780 haematology analyser. The MPV value of ≥ 9.5 fL was considered as raised.

**Data analysis**

The data obtained was coded in a Microsoft Excel Worksheet. SPSS statistics software version 20.0 was used to analyse the pooled data. The categorical data was expressed in terms of rates, ratios, and proportions and compared using chi-square test or Fisher’s exact test. The continuous data was expressed as mean ± standard deviation (SD) and compared using independent sample t-test or Fisher’s exact test. The continuous data was expressed as mean ± standard deviation (SD) and compared using independent sample t-test. In case of more than two means, one-way ANOVA was used to compare the data. A p ≤ 0.05 was considered as statistically significant.

**Results**

A total of 79 patients presented with acute ischemic stroke during the study period. Among them, 25 patients (31.6%) had history of diabetes, which formed the diabetic subset and the remaining 54 (68.35%) were considered in nondiabetic subset. The baseline study characteristics of the diabetic set and nondiabetic set are presented in Table 1. No significant difference was found between the diabetic subset and nondiabetic subset regarding sex, age, hypertension, arterial supply and type of circulation (p=0.005). However, severity of stroke (MMR) and MPV was found statistically significant between the diabetic and nondiabetic set. Also, history of previous stroke was present in 12% of the patients with DM compared to 1.85% of the non-diabetic patients (p=0.091). Out of 25 diabetic patients, 3 cases were reported to have alarmingly high values of MPV who had history of recurrent stroke. Though the sample size was not sufficient to predict anything strongly.

The mean age of diabetic set was 62.04±10.88 years, whereas that of nondiabetic set was 58.11±16.75 years. The comparison of baseline clinical characteristics between diabetic and nondiabetic subset is provided in Table 2. No significant difference was observed between the diabetic and nondiabetic subset regarding mean age, mean systolic and diastolic blood pressure, NIHSS score, haemoglobin, and platelet count. However, MPV (10.16±0.89 fL vs. 8.25±0.91 fL; p≤0.001) and MRM scores (4.12±0.66 vs. 3±0.61; p≤0.001) were found statistically significant between two subsets.

Among the diabetic patients, no statistical association was observed between MPV and duration of DM, treatment modality, HbA1c, prior history of stroke, hypertension, NIHSS score and MRM score (Table 3).

The mean MPV level in diabetic subset with duration >5 years was 10.29±1.4 fL as compared to 10.07±0.80 fL with duration >5 years or less. However, the difference observed was not significant (p=0.585). The mean MPV levels among the diabetic subset who were on treatment with insulin was 10.36±1.09 fL as compared to 9.98±0.75 fL who received OHA’s (p=0.404). The mean MPV in diabetic population with HbA1c levels ≤7 was 9.75±0.35 fL, 7.01 to 8.50 was 9.98±0.74 fL, and >8.50 was 10.39±1.00 fL. However, the difference was not significant (p=0.678).

**Discussion**

Acute ischemic stroke is a condition that is frequently associated with DM. It is known that DM may contribute to systemic as well as intracranial atherosclerotic disease. This augmented risk has been related to pathophysiological changes observed in the cerebral vessels of diabetic patients.11 Correlating and prognosticating the effect of hyperglycaemia on stroke and its outcome is need of the hour.

As mentioned earlier, platelets with increased size/volume are more reactive. Platelet volume is estimated at the level of progenitor cell. Recent studies stated that cytokines—interleukin-3 (IL-3) or interleukin-6 (IL-6), influence the megakaryocyte ploidy and leads to the production of more reactive and larger platelets.12 Thus, it is rational to speculate that a proinflammatory state followed by cerebrovascular event may consequence in higher MPV and pro-thrombotic event. This provided a platform to associate MPV to a cohort of diabetic stroke and also to compare it to non-diabetic stroke to assess the severity of stroke (NIHSS) and predict the outcome of stroke (MMR score).

The male sex has been listed as the major risk factor for stroke.13 In this study, a male predilection was observed. Although the difference was not significant, age is the most nonmodifiable risk factor for stroke. In the study, the mean age among diabetic patients was 62.04 ± 10.88 years compared to 58.11 ±16.75 years in nondiabetic patients. Likewise, a study by Shah et al.14 to assess the role of MPV in ischemic stroke also reported mean age as 58 years. These observations showed that acute ischemic stroke in this study was common in elderly age group.

It is postulated that higher MPV may predispose to the occurrence of ischemic strokes, which is proved by other research workers.14 In present study, the majority of diabetic patients had raised MPV levels as compared to nondiabetic patients. Correspondingly, the mean MPV was significantly high in patients with history of DM as compared to nondiabetics. These findings confirm the positive association between MPV and acute ischemic stroke in patients with DM. The positive association observed between ischemic stroke with MPV in diabetic patients was independent of treatment of diabetes (p=0.404), duration of diabetes (p=0.585), glycaemic control (p=0.678), and hypertension (p=0.564). There is lack of data to comment on these findings, as this study is first of its kind to study acute ischemic stroke in diabetic patients and study its association with MPV.

Similar results were reported by PROGRESS collaborative group. In this study, stroke rates were greater among individuals with higher measurements of MPV. The study reported that for each 1-fL increase in MPV was associated with 12% increase in relative risk of stroke. Hence, MPV
is known as an independent risk factor of stroke among high-risk individuals. The measurement of MPV may also add useful prognostic information for clinicians in the management of patients with cerebrovascular disease. The association between MPV with both inflammation and thrombosis has also become a pinpoint of interest in last few decades. Studies reported that MPV levels are significantly high in acute ischemic stroke patients. In this study, 12% of the patients with DM presented with history of stroke compared to 1.85% of the nondiabetic patients. Among these diabetic patients, all 12% of patients had history of recurrent stroke in those MPV was highly raised and thus, associating the raised MPV to recurrence of stroke. However, in this study, owing to a lesser sample size, there was no significant association between history of stroke and raised levels of MPV (p=0.645). This observation is in conformity with bulk of other published reports. 

The patients with high MPV (>11.01 fl) had 1.5 times greater vascular mortality risk than those with low MPV (<8.7 fl) value. Also, a significant relation was found between patients with high MPV and ischemic heart disease. Similarly, the current study indicated several other implications regarding severity of stroke and outcome. The severity of stroke is likely to be severe in diabetics based on NIHSS scores (20.38 ± 3.19 vs. 17.76 ± 3.74; p=0.006) and are likely to have higher mortality and morbidity based on MRM scores (4.12 ± 0.66 vs. 3.00 ± 0.61; p<0.001). Likewise, a prospective study conducted by Shah et al. also testified that patients with higher MPV had worse outcome at the end of 1 week, as measured by MRM score. The similar finding has been stated in former studies. 

Moreover, it has been proposed that patients with large platelets are more susceptible to risk factors such as diabetes and obesity, and therefore have an increased risk of acute ischemic stroke. Diabetic patients are known to have higher incidence of myocardial infarction and stroke. Also, presence of high MPV in diabetics might augment the risk of thrombotic complications. It has also observed that diabetics with retinopathy and other complications have higher MPV than those without this complications. Presence of significantly higher MPV in impaired fasting glucose patients as compared to nondiabetic subjects is also reported in the literature. 

Altogether, this is a first study to associate MPV in diabetic stroke and nondiabetic strokes with a positive outcome. Thus, stating MPV was highly raised in diabetic strokes than in nondiabetic strokes and has bad prognosis and worst outcome. 

**Conclusion**

Diabetes being a procoagulant state, patients are at risk of any thrombotic event. MPV a valuable predictor of platelet reactivity is a simple test available in panel of hemograms. Based on findings, the current study lights there is a positive association between MPV and acute ischemic stroke in patients with DM. Also, acute ischemic stroke in diabetic patients with raised MPV is likely to be severe (as assessed by NIHSS score) and may results in high morbidity and mortality (as assessed by MRM). In order to correlate MPV to predict recurrence of stroke, a larger sample size of diabetic strokes has to be considered. 

**Acknowledgments**

Both authors have contributed equally in the development of manuscript

**References**

Preventive Health Practices among Doctors in Delhi

Tanu Anand¹*, Shekhar Grover², Rajesh Kumar³, Naveen Prabhu⁴, GK Ingle⁵

Abstract

Introduction: With times, increasing attention is being given to doctor’s own health as it is known to influence their patient care. Little is known about preventive health practices among them.

Objective: To assess preventive health practices among doctors in Delhi.

Material and Methods: It was a cross-sectional study undertaken amongst the doctors working in selected hospitals, dispensaries and private clinics in Delhi. A self-administered questionnaire containing items for assessment of preventive health and self-care practices was used to collect the data.

Results: Out of the total 160 participants, there were 118 males (73.8%) and 42 (26.2%) females. The mean age of the participants was 29.9±7.4 years. There were 55 doctors (34.4%) who were suffering from chronic diseases like vision problems, dental problems, hypertension and diabetes. Nearly half of the doctors (n=74; 46.2%) did not have any for health insurance. Majority of the doctors (n=65; 40.6%) were obese. The knowledge regarding preventive health guidelines regarding all of the tests asked for, was low among the study participants. As far as preventive health practices were concerned, only 8.8% (14) had checked their blood pressure according to recommended guidelines while none of them had their lipid profile done. While there were 9 female doctors (21.4%) who had done their self breast examination in last six months, there was only 1 participant who had undergone pap test. With respect to self-care practices when the physicians last fell ill, majority had self-managed themselves (n=108; 67.5%)

Conclusions: Preventive health care practices among the doctors are low. There an urgent need for them to follow good health care practices which they in turn can advocate to their patients.

Introduction

Medicine is a demanding profession, making doctors prone to sedentary lifestyles, mounting stress levels and risk of exposure to some deadly infections at their workplace. Further, many a times they have to neglect their own health in favour of their numerous professional obligations.¹ Even though mortality data show that compared with the general population doctors have a significantly lower mortality ratio²,⁴, illnesses experienced by doctors include all the expected categories for the population at large: cardiovascular disease (4%–15%), respiratory illness (10%–21%), musculoskeletal problems (9%–38%), cancer (2%–3%) and psychiatric illness (3%–10%).³⁴⁵⁶ Thus, evidently doctors have similar rates of acute and chronic illnesses and have the same preventive health needs as the general community.³

Increasing attention is being paid to physician health as it has been recognized that health of the physicians impacts the health behaviors of the patients they treat.⁷ In addition, doctors have to maintain their health not only for their personal well being but also for continued and optimal performance when treating their patients.⁸ However, doctors tend to adopt self-reliant view when it comes to taking care of their own health.⁹ This may lead to poorer health outcomes as patients in the health system due to under- and over-treatment and a failure to utilise their own referral networks when in crisis.⁸

Medical literature on health maintenance behavior of doctors from different settings have revealed few data on doctors undertaking preventive health activities for themselves, even for those procedures or tests with evidence of efficacy.¹⁰ Further, they face the challenge of incorporating healthy preventive habits which could prevent the progression of chronic diseases, in their busy work schedule.¹¹

Not much is known about the knowledge and preventive health practices among doctors from Asia including India despite the fact that many patients look up to them for medical advice.⁹ Therefore, the present study was undertaken with objective to assess preventive health practices among doctors in Delhi.

Material and Methods

Study settings and participants

It was a cross-sectional study conducted in Delhi, the capital of India covering government health facilities (providing services to general population) and private practitioners. The health care services in Delhi are provided by a number of agencies like Municipal Corporation of Delhi, New Delhi Municipal Corporation, and Delhi Government Health Services which cater to the general population, and some like the Railways, Directorate General of health Services, Central Government Health Services, and Employees State Insurance cater only to specific population groups.¹¹ There are 34 allopathic hospitals (having 50 or more beds) and 251 dispensaries in Delhi which are under the government of Delhi.¹¹,¹²

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Sampling and Sample size

Stratified random sampling was used to draw sample of hospitals and dispensaries. For the current study, Delhi was divided as per 11 revenue districts and from each district one hospital and two dispensaries under government of Delhi were randomly selected using random number table. The list of hospitals and dispensaries were prepared separately district wise and each health facility was given a distinct number. In case there was only hospital in the district, that hospital was chosen as it is. Therefore, a total of 11 hospitals and 22 dispensaries were selected.

Taking 50% as the expected prevalence rate of preventive practices followed by doctors in a previous study at a 95% confidence level the required sample size was calculated as 100 to yield prevalence estimate with 10% precision. Design effect was taken as 1.5. Therefore, a sample size of 150 was estimated. However, 160 doctors were interviewed.

Inclusion and Exclusion Criteria

All the doctors posted in the medical, surgical and gynaecological Out Patient Department (OPD) of the selected hospital at the time of survey were considered eligible for inclusion in the study. In case if more than 3 doctors were present in any of the 3 OPD’s, the first three consecutive consenting doctors from each OPD were interviewed. All the doctors posted in the selected dispensaries and one private practitioner (PP) (only general physicians) each from the nearby area of the selected dispensaries were included in the study. Interns and undergraduate students were excluded from the study. Doctors who did not give consent to participate in the study were also excluded from the study.

Study Period

Data was conducted during the period from Jan 2015 to Dec 2015.

Study tool

A pre-tested, semi-structured, self-administered questionnaire was used for data collection. The questionnaire was divided into three sections: Section I containing items regarding identification such as age, gender; educational qualifications; work experience; status of health insurance; personal and family history of any chronic diseases. Section II consisted of knowledge of physician items regarding recommended frequency of various anthropometric, clinical and biochemical tests. Section III contained items regarding assessment of preventive health and self-care practices among the doctors like the frequency of undergoing clinical, biochemical and anthropometric tests, immunization status, etc. The reasons for not undergoing tests according to recommended frequency were also explored. The study tool was developed after thorough review of preventive health guidelines for adults formulated by US Preventive Task Force 2012 and other collaborative associations.13,14

A measuring tape (non-stretchable) was used for measuring the height to nearest centimeter. A portable weighing scale with a capacity of 150 kg and which measures weight to nearest 500 g was employed for measuring the weight of the study participants.

Analysis of Items

The knowledge items were categorized as ‘correct’ if the participant indicated recommendations of various tests in adults as follows:

Blood Pressure

Routine blood pressure measurement for every two years in patients with systolic blood pressure < 120 mmHg and diastolic blood pressure < 80 mmHg and every year for systolic blood pressure 120-139 and diastolic blood pressure 80-89 mm Hg.

Weight or Body Mass Index

Every year.

Breast Self Examination

At least every month beginning from 19 to 65+. 

Lipid Profile

A fasting lipoprotein profile (total cholesterol, LDL-C, HDL-C, and TG) in all adults over the age of 20 once every 5 years.

Blood Sugar

Screening for type 2 diabetes in asymptomatic adults with sustained blood pressure (either treated or untreated) greater than 135/80 mm Hg or age more than 45 years at 3 year intervals should be done.

Pap test

Screening for cervical cancer in women ages 21 to 65 years with cytology (Pap smear) every 3 years.

Vision tests

Adult should undergo an eye examination every 2-3 years.15

Stool for Occult blood

At the age of 50 years, the test is to be done every year.

Hemoglobin estimation:

Routine screening of asymptomatic pregnant women.

Dental Screening

Routine screening for dental and periodontal diseases every 6 months.16

Study Methods

After seeking permission from the competent authorities, the selected hospitals, dispensaries and private clinics were visited by the investigators. All the selected doctors were contacted personally and after taking their informed consent, performans were administered and data was collected there and then only. The performa could be filled in 5 minutes.

The anthropometric measurements were taken by the investigator at the time of collecting the completely filled questionnaire from the participant, as per “Step 2 – Physical Measures” described in WHO STEP wise approach to NCD surveillance.17

Statistical analysis

Data collected was entered in MS office excel and analyzed using Epi-info 2005 software of world health organization and SPSS version 16.0 (SPSS Inc., 233 South Wacker Drive, 11th Floor, Chicago, IL 60606–6412). The results were presented in proportions and any difference between two proportions in relation to particular factor was assessed by Chi-square (or Fischer exact test if expected frequency in any of the cell was < 5) and was considered significant if probability of error was < 5%.

Ethical Considerations

Informed written consent was taken from all the participants and privacy and confidentiality of information so provided by them was assured. The study was approved by the Departmental Ethics Committee of the research institution.

Results

Out of the total 165 doctors sampled for the study, 5 private practitioners refused to participate in the study.
Table 1: Knowledge regarding preventive health guidelines among the study participants (n=160) according to gender

<table>
<thead>
<tr>
<th>Tests</th>
<th>Males N=118 (%)</th>
<th>Females N=42 (%)</th>
<th>Total N=160 (%)</th>
<th>Chi square, p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight/BMI index*</td>
<td>16 (13.6)</td>
<td>1 (2.4)</td>
<td>17 (10.6)</td>
<td>0.04*</td>
</tr>
<tr>
<td>Blood pressure</td>
<td>8 (6.8)</td>
<td>7 (16.7)</td>
<td>15 (9.4)</td>
<td>2.49, 0.11</td>
</tr>
<tr>
<td>Lipid profile*</td>
<td>0 (0)</td>
<td>1 (2.4)</td>
<td>1 (0.6)</td>
<td>0.26</td>
</tr>
<tr>
<td>Blood sugar</td>
<td>31 (26.3)</td>
<td>12 (28.6)</td>
<td>43 (26.9)</td>
<td>0.007, 0.93</td>
</tr>
<tr>
<td>Pap test*</td>
<td>3 (2.5)</td>
<td>7 (17.1)</td>
<td>6 (3.8)</td>
<td>0.19</td>
</tr>
<tr>
<td>Breast self examination</td>
<td>11 (9.3)</td>
<td>10 (23.8)</td>
<td>21 (13.1)</td>
<td>4.50, 0.03*</td>
</tr>
<tr>
<td>Haemoglobin estimation</td>
<td>44 (37.3)</td>
<td>8 (19.1)</td>
<td>52 (32.5)</td>
<td>3.90, 0.04*</td>
</tr>
<tr>
<td>Vision tests</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>-</td>
</tr>
<tr>
<td>Dental tests</td>
<td>29 (24.6)</td>
<td>9 (21.4)</td>
<td>38 (23.8)</td>
<td>0.04, 0.84</td>
</tr>
<tr>
<td>Stool for occult blood</td>
<td>0 (0)</td>
<td>1 (2.4)</td>
<td>1 (0.6)</td>
<td>0.26</td>
</tr>
</tbody>
</table>

*p value <0.05; *Fisher exact test applied

Table 2: Preventive health practices among the study participants (n=160)

<table>
<thead>
<tr>
<th>Practices</th>
<th>Males N=118 (%)</th>
<th>Females N=42 (%)</th>
<th>Total N=160 (%)</th>
<th>Chi square, p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frequency of undergoing following tests according to recommendations</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Weight/BMI*</td>
<td>10 (8.5)</td>
<td>2 (4.8)</td>
<td>12 (7.6)</td>
<td>0.73</td>
</tr>
<tr>
<td>- Blood Pressure</td>
<td>10 (8.5)</td>
<td>4 (9.5)</td>
<td>14 (8.8)</td>
<td>0.76</td>
</tr>
<tr>
<td>- Lipid Profile</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>-</td>
</tr>
<tr>
<td>- Blood Sugar (n=56)#</td>
<td>44 (100)</td>
<td>12 (100)</td>
<td>56 (100)</td>
<td>-</td>
</tr>
<tr>
<td>- Pap test (n=15)#</td>
<td>3 (2.5)</td>
<td>1 (2.4)</td>
<td>4 (2.5)</td>
<td>0.01, 0.91</td>
</tr>
<tr>
<td>- Breast Self Exam</td>
<td>3 (2.5)</td>
<td>6 (14.3)</td>
<td>9 (5.6)</td>
<td>-</td>
</tr>
<tr>
<td>Self-care practices when last fell ill</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Did nothing</td>
<td>5 (4.3)</td>
<td>0 (0)</td>
<td>5 (3.2)</td>
<td>-</td>
</tr>
<tr>
<td>- Self managed</td>
<td>79 (66.9)</td>
<td>29 (69.0)</td>
<td>108 (67.5)</td>
<td>-</td>
</tr>
<tr>
<td>- Consulted another physician on phone</td>
<td>6 (5.1)</td>
<td>5 (11.9)</td>
<td>11 (6.8)</td>
<td>-</td>
</tr>
<tr>
<td>- Consulted another physician in person</td>
<td>28 (23.7)</td>
<td>8 (19.0)</td>
<td>36 (22.5)</td>
<td>-</td>
</tr>
<tr>
<td>Completely immunized for:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Hepatitis B*</td>
<td>111 (94.9)</td>
<td>39 (92.1)</td>
<td>150 (93.8)</td>
<td>0.72</td>
</tr>
<tr>
<td>- Tetanus*</td>
<td>112 (94.9)</td>
<td>41 (97.6)</td>
<td>153 (95.6)</td>
<td>0.68</td>
</tr>
<tr>
<td>- Typhoid</td>
<td>43 (36.4)</td>
<td>18 (42.9)</td>
<td>61 (38.1)</td>
<td>0.54, 0.46</td>
</tr>
</tbody>
</table>

*p value <0.05; *Fisher Exact Test applied; #Participants with Family History of Diabetes; SN=Number of women who were married

Fig. 1: Reasons for not following recommended preventive health guidelines

Therefore, a total of 160 doctors participated with 73.8% (n=118) being male and 26.2% (n=42) female doctors. Of these, 99 (61.9%) were working in hospitals, 44 (27.5%) were working in dispensaries and 17 (10.6%) were private practitioners. The mean age of the study group was 29.9±7.4 years (Range=23-61 years). Majority of doctors were less than 40 years old (n=142; 88.8%). Nearly one-third of the doctors (n=58; 36.3%) had post graduate qualifications.

Health profile of the study participants

Out of the total, 105 (65.6%) did not have personal medical history of chronic diseases. There were only 2 doctors (1.2%) who were classified as underweight according to BMI whereas 28.8% (n=46) and 29.7% (n=49) were normal and overweight respectively. Majority of the doctors (n=65; 40.6%) were obese. While 33 doctors out of 55 (60%) were suffering from refractive errors, 14 (25.4%) reported to have dental problems. There were 8 doctors (14.5%) who were hypertensive and 4 (7.3%) were diabetic. Only 53.8% (n=86) participants had health insurance.

Knowledge regarding preventive health guidelines

There were 111 doctors (69.4%) who reported to have received training in preventive health examination with majority having received it during their graduation (n=100/111; 90.1%). The knowledge regarding preventive health guidelines regarding all of the tests asked for, was low among the study participants. The knowledge was lowest for the recommended periodicity of vision tests (0%), stool for occult blood (0.6%) and lipid profile (0.6%). Significantly higher proportion of male doctors had knowledge about recommended guidelines for periodicity in relation to weight measurement (n=16; 13.4%) and haemoglobin estimation (n=44; 37.3%) (p=0.04) in adults, whereas higher proportion of female doctors (n=10; 23.8) were aware about recommended frequency of doing self breast examination (SBE) among females (p=0.03) (Table 1).

Preventive health and self-care practices among the physicians

Only 7.5% (n=12) were measuring their weight according to the recommended guidelines while there only 14 physicians (8.8%) who had got their blood pressure measured on 2 yearly basis (recommended guideline). None of the study participant had undergone lipid profile according to recommendations. There were 56 doctors who had risk factors for diabetes and consequently all had undergone sugar testing for themselves on 3 yearly basis. While only 1 (6.7%) out of 15 married women doctors had undergone pap test, there were only 9
female doctors (21.4%) who were doing SBE on monthly basis (Table 2).

With respect to self-care practices when the physicians last fell ill, majority had self-managed themselves (n=108; 67.5%) while 22.5% (n=36) had consulted another physician in person. More than 90% of the doctors were immunized against tetanus and hepatitis B. However, only two fifths (n=61; 38.1%) had received typhoid vaccination (Table 2).

Reasons for not following recommended guidelines

There were 127 doctors (79.4%) who perceived that they were not following the preventive health guidelines. The most common reason reported by 61.4% physicians for this was ‘no felt need unless the symptoms develop’. There were 47 doctors (37%) who cited lack of time as the reason for not following the preventive health practices (Figure 1).

Discussion

Disease pattern among doctors include all the expected categories as for the general population at large and hence have same preventive health needs as general community.14,19 However, doctors appear to be reluctant patients who look after their health in a haphazard way.9 Due to paucity of data in the country regarding health maintenance practices among the doctors, the present study was undertaken. This group of population was also chosen because they have access to excellent healthcare as well as higher than average educational and socio-economic status. Thus, the health related preventive practices are less likely to be confounded by such factors.20

Nearly one third of the participants (34.4%) were suffering from chronic diseases in the current study. In another study done by Davidson et al.21 in 2003, among 358 Australian doctors, 44% reported to have been suffering from chronic problems. The lower percentage of chronic diseases among the doctors in our study was probably due to the fact that majority of the doctors were less than 40 years (88.8%). The most common chronic morbidity reported by the physicians was vision problem. Observations made by several workers in different part of the world indicate that the prevalence of vision problems is higher among those engaged in professional courses like medicine due to intensive near work associated with it.22

A large proportion of doctors in our study were found to be overweight and obese. The findings are slightly higher than those reported by Sharma et al23 in 2013 among 100 health professionals in Delhi and a study done among 2499 young physicians in South India.18 The results point towards increasing trends of obesity among doctors in India. However, this needs to explored further with a much large scale research on this population. The sedentary lifestyles and extremely stressful work schedules bring the physicians at risk of various lifestyle disorders and therefore, there an urgent need for them to follow good health care practices which, in turn, can advocate to their patients.

Recognition of the escalating costs and burden of chronic disease has led to an increasing research to identify effective approaches to prevention.24 Management of behavioural risk factors in general practice according to standardized preventive guidelines has proven to be a worthwhile strategy. However, it requires knowledge and skills on the part of the practitioners to deliver the services. The current study highlighted low knowledge about preventive health guidelines among the physicians despite the fact that majority had reported to have received training regarding the same. The results are in line with those documented by Meyers et al. in 1997 in Kansas.25 This calls for broad training and professional development strategies that may be needed to be developed.

As per the Knowledge, Attitude, Behaviour (KAB) model, behaviour and practices of the people are dependent on their knowledge and attitudes.26 Consequently, the preventive health practices amongst the doctors were far from recommended guidelines. While only 8.8% had got their blood pressure checked in last two years, none of them had their lipid profile done according to recommendations. This is in stark contrast to one study which showed that 93% of GPs had checked their blood pressure and 64% had checked their cholesterol level in the previous 3 years in Australia.23 Preventive cancer screening practices were also quite low among the women doctors in the current study. This implies an urgent need to motivate the physicians to undergo preventive health care practices considering their susceptibility to whole range of diseases that affect the general population as well.

The most common reason for not following the recommended preventive health guidelines by the doctors themselves was ‘no felt need unless the symptoms develop’. Physicians commonly rely on denial and avoidance when faced with personal medical problems.1 The prevalent idea in the medical profession is that physicians are never ill, and, if they do fall ill, they should silently work through their illness and put patient care above all else.27

Self treatment and self prescribing among doctors is common and a pattern that is established very early in their careers.28 Two thirds of the study respondents in our study reported to have self-treated themselves when they felt last ill. The findings corroborate with those done among Chinese doctors in 20089 and among general practitioners and consultants in UK in 1999.2 Busy schedules make it difficult for the physicians to arrange time for self-care and schedule appointments for themselves.29 Further, it is a common sociological sequence across all cultures: when people need help for their medical condition, they first try to take care of it by themselves, then ask the advice of their friends, and then try home remedies and finally will seek help and make an appointment for professional evaluation and care.29

Immunization coverage with respect to hepatitis B and tetanus toxoid was quite high. These results are far higher than survey data available from different countries where in the coverage of two vaccines have been variable (49-87%).3

Strengths and limitations

One of the greatest strength of the study is the fact that it is the first study of its kind in the country that extensively studied the preventive health practices among the doctors. Further, effort has been made in selecting representative and sufficient sample in the study design. But, the doctors have been selected from government health organization only. Therefore, the findings may not be generalizable to other work settings in and outside Delhi. The
recommended preventive health guidelines’ knowledge and practices among the doctors have been assessed using objective criteria. However, other factors under preventive health like nutrition, physical activity etc. have not been studied at all.

To conclude, despite limitations, the study highlighted the crucial gaps in the knowledge of the physicians regarding preventive health guidelines. This is critical, since it is known that physicians are ideally placed to offer preventive health counselling to their patients that in turn can prevent chronic diseases among them. Therefore, lack of knowledge regarding the same could be hampering the management of behavioural risk factors among their patients. Further, poor knowledge translates into practices not conducive to health promotion among doctors themselves as was evidently seen in the current study. Thus, there is a need to strengthen the training and broad professional development strategies of the physicians. They also need to be motivated to follow good health care practices which they advocate to their clients.

References

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Dr. P.C. Manoria, E-S’103, Arera Colony, Bhopal M.P. 462016 Mob. No.: 98930 42229, E-mail: pmanoria@rediffmail.com
SNP in KCNQ1 Gene is Associated with Susceptibility to Diabetic Nephropathy in Subjects with Type 2 Diabetes in India

Surendra Kumar¹, Vinod Kumar Aswal², RP Agrawal³, Mir Quoseena⁴, Chinmayi Jillellamudi⁵, Suman Kapur⁶, Nitesh Chandra Toshan⁷

Abstract

Objective: Diabetic nephropathy (DN) remains the most common cause of end-stage renal disease (ESRD) as the burden of diabetes increases worldwide. Only 25 to 40% of patients with type 2 diabetes mellitus (T2DM) develop diabetic nephropathy irrespective of glycemic control so there should be a specific genetic basis for the development of diabetic nephropathy.

Method: We have collected venous blood samples from 50 cases (Diabetic nephropathy) and 20 controls (T2DM without nephropathy) diagnosed by spot urine albumin creatinine ratio (ACR). DNA was isolated from processed samples. PCR study and sequencing was done to detect polymorphism of rs2237897 in KCNQ1 gene.

Result: Statistically significant difference was found when the allelic frequencies between the two groups were compared (p=0.03), with the C allele having a 2.4 fold higher risk of having diabetic nephropathy (risk ratio, RR) = 1.16, 95%CI of RR = 1.01 to 1.3, Odds Ratio (OR) = 2.4; 95% CI of OR = 1.06 to 4.6). Chi-square analysis showed a significant difference in genotype frequency of rs2237897 (x² = 4.63, p=0.03) in Diabetic nephropathy subjects, compared with that of controls.

Conclusion: This study suggested that, KCNQ1 being an established type 2 diabetes gene, genetic variation in this gene may contribute to susceptibility to diabetic nephropathy and the C allele is the risk allele for diabetic nephropathy, which is different from Japanese population where the T allele was the risk allele.

Introduction

Diabetes mellitus (DM) refers to a group of common metabolic disorders that share the phenotype of hyperglycemia. Several distinct types of DM are caused by a complex interaction of genetics and environmental factors.¹

Complications from diabetes can be classified as microvascular or macrovascular. Microvascular complications include nervous system damage (neuropathy), renal system damage (nephropathy) and eye damage (retinopathy).²

Diabetic nephropathy is an increasingly growing complication of diabetes that occurs in 20% to 40% of all diabetics. In the entire world, DN is the primary single cause of end-stage Renal disease (ESRD). Both type 1 and type 2 diabetes can lead to nephropathy with a higher propensity to develop into type 1 diabetes, but the number of cases of DN are more in type 2 due to the high prevalence of type 2 diabetes.³

Diabetic nephropathy is a chronic disorder typically characterized by progressive albuminuria and a decline in renal function. Based on the levels of urine albumin excretion, in a didactic manner, DN has two phases: incipient nephropathy or the microalbuminuria phase and clinical nephropathy or the proteinuria phase. Microalbuminuria is considered a risk factor for DN progression.⁴

Many environmental factors have been established as contributing to the development of DN while the role of others has yet to be clearly understood.⁵

Research has focused on seeking potential genetic alterations associated with CKD and ESRD. In fact, genetic evidence has been found in case-control association and linkage studies, and more recently using genome-wide scan (GWS). These studies support the assumption that onset, progression, and severity of DN can be in part attributed to genetic factors.⁶,⁷

The studies of Japanese and East Asian population also showed that in addition to KCNQ1 being an established type 2 diabetes gene, genetic variation in this gene may contribute to susceptibility to diabetic nephropathy.⁷,⁸

In epithelial tissues from organs such as lung, stomach, cochlea, intestine, and kidney, where salt and water transport is crucial for proper function, a lack of functional KCNQ1 channel expression has been found to have severe implications.⁹,¹⁰

In the kidney, KCNQ1 has been shown to assemble with KCNE1, the β subunit of the potassium channel, forming a potassium channel complex localized to the brush border of the mid to late proximal tubule.¹¹,¹² Moreover, it has been shown to play a role in the Na+ secretion at the proximal tubule by maintaining a driving force for Na+ transport across the membrane.¹³

These observations suggest the possibility that KCNQ1 may be a candidate for conferring susceptibility to diabetic nephropathy. SNP typing of DNA samples of the subjects showed that among the reported...
SNPs, rs2237897 was most commonly associated with DN in Japanese and Chinese study so we choose this site for our study.

**Aims and Objectives**

In this study, our aim is to find out the association of single nucleotide polymorphisms (SNPs) of rs2237897 within a KCNQ1 gene with diabetic nephropathy subjects with type 2 diabetes in Indian population.

**Material and Methods**

This study was conducted jointly by a tertiary care hospital and Genetic center. Blood samples of 50 cases (Diabetic nephropathy) and 20 controls (T2DM without nephropathy) were collected for analysis. Among 50 samples, DNA was isolated from 39 only as rest 11 samples are lysed.

Informed consent was taken beforehand, procedure and motive of the study were explained to the patients. Ethical committee approval was taken for study.

Patients with type 2 diabetes mellitus of age more than 30 years with Microalbuminuria or Macroalbuminuria included as cases and without diabetic nephropathy as controls. Patients with chronic kidney disease of etiology other than diabetes, pregnant females, patients having co-morbid condition except hypertension were excluded from the study.

Each patient was subjected to detailed history and complete general physical examination. Detailed history about age, sex, weight, duration of diabetes were noted and spot urine Albumin/creatinine ratio was done to detect microalbuminuria.

Genomic DNA was extracted from venous blood, drawn from subjects, by the Guanidine Thiocyanate (GTC) procedure (Sambrook et al 1989 and Hammond et al. 1996) and dissolved in water. Polymerase chain reaction (PCR) primers were designed for Restriction fragment length polymorphism (RFLP) analysis of rs2237897 using National Center for Biotechnology Information (NCBI) primers and subsequent restriction digestion with appropriate restriction enzymes was carried out using a standard protocol to genotype the polymorphic sites. (Kapur et al., 2007).

Genotype distributions were examined for a significant departure from Hardy–Weinberg equilibrium by v2-test. A trend test was performed to determine any increase in risk with an increase in the number of risk allele (Schoojans 1993). The risk of rs2237897 polymorphism was calculated by odds ratios (ORs) and 95% confidence intervals (CIs), for genotypes in both control and case groups. An odds ratio (OR) is a measure of association between an exposure and an outcome. The OR represents the odds that an outcome will occur given a particular exposure, compared to the odds of the outcome occurring in the absence of that exposure. In statistics, a confidence interval (CI) is a type of interval estimation, computed from the statistics of the observed data, that might contain the true value of an unknown population parameter. The interval has an associated confidence level that, loosely speaking, quantifies the level of confidence that the parameter lies in the interval. The chi-square test was used for comparison of genotype frequencies in the studied groups; A chi-square statistic is one way to show a relationship between two categorical variables. In statistics, there are two types of variables: numerical (countable) variables and non-numerical (categorical) variables. The chi-squared statistic is a single number that tells you how much difference exists between your observed counts and the counts you would expect if there were no relationship at all in the population. Fisher’s exact test is a statistical significance test used in the analysis of contingency tables. Although in practice it is employed when sample sizes are small, it is valid for all sample sizes. Fisher’s exact test was used for comparison of allelic frequencies in this study.

**Results**

The Figure 1 shows that both the cases and the control groups were more or less similar with reference to distribution of the study population, according to age most of the patients both in control and study group were in the age group of 51-70 yrs (58% of cases, 60% of controls). The mean age in diabetic nephropathy cases was 60.54±11.02 years while the mean age in controls was 57.75±7.73 years.

Figure 2 shows that out of total 50 cases, 22 (56%) were females and 28 (44%) were males. Male and female ratio in diabetic nephropathy patients was (1:1.27).
The genotype distribution and allele frequencies of the polymorphic site rs2237897 were studied in the groups. The genotype frequencies of rs2237897 for CC, CT and TT are 0.77, 0.20 and 0.03 for cases and 0.55, 0.4, and 0.05 for controls, respectively (Table 1, Figure 3).

The allelic frequencies of rs2237897 for C and T in two different groups were 75% and 25%, respectively in controls, and 87% and 13%, respectively in Diabetic nephropathy subjects, with the C allele being more frequent in Diabetic nephropathy patients than in the control population (Table 1, Figure 4).

The highly significant association in the frequency of the C allele between cases and control subjects, giving an odds ratio of 2.4, (CI 95%, 1.1 to 5.4) was found in the Diabetic nephropathy group. Chi-square analysis showed a significant difference in genotype frequency of rs2237897 (χ² = 4.67, p=0.03) in Diabetic nephropathy patients, compared with the control population (Table 1, Figure 3).

A statistically significant difference was also found when the allelic frequencies between the two groups were compared (Chi-square = 4.68, p=0.03) with the C allele having a 2.4 fold higher risk of having Diabetic Nephropathy (risk ratio, RR) = 1.4, 95% CI of RR = 1.1 to 1.9, Odds Ratio (OR) = 2.4; 95% CI of OR = 1.1 to 5.4) (Table 2, Figure 4).

Discussion

Diabetes mellitus (DM) refers to a group of common metabolic disorders that share the phenotype of hyperglycemia. Several distinct types of DM are caused by a complex interaction of genetics and environmental factors. A large proportion of people with diabetes will develop microvascular complications. Diabetic nephropathy is a chronic disorder typically characterized by progressive albuminuria and a decline in renal function.

Research has focused to find out potential genetic alterations associated with Chronic Kidney Disease and ESRD in type 2 diabetic patients. In fact, genetic evidence has been found in case-control association and linkage studies, and more recently using genome-wide scan (GWS). These studies support the assumption that onset, progression, and severity of DN can be in part attributed to genetic factors.

To identify the role of variants in candidate genes for contribution to diabetic nephropathy risk, usually compares the frequency of the variant between cases and controls, i.e. Whether the variant is associated with the disease. Association studies offer a potentially powerful approach to identifying genetic variants that influence susceptibility to disease.

The KCNQ1 gene is associated with type 2 diabetes and the expression of KCNQ1 could be observed in the human kidney. In the kidney, KCNQ1 has been shown to assemble with KCNE1, the β subunit of the potassium channel, forming a potassium channel complex localized to the brush border of the mid to late proximal tubule, moreover, it has been shown to play a role in the Na⁺ secretion at the proximal tubule by maintaining a driving force for Na⁺ transport across the membrane.

These observations suggest the possibility that variants in the KCNQ1 gene may be a candidate for conferring susceptibility to diabetic nephropathy. To test this hypothesis, we focused on KCNQ1 as a candidate gene for diabetic nephropathy and investigating the association between the single nucleotide polymorphisms (SNPs) within KCNQ1 and diabetic nephropathy in type 2 diabetes.

The genotype distribution and allele frequencies of the polymorphic site in the groups studied are shown in Tables 1 and 2. The genotype frequency of rs2237897 for CC, CT and TT are 0.77, 0.20 and 0.03 for cases and 0.55, 0.4, and 0.05 for controls, respectively (Table 1, Figure 3).

The highly significant association in the frequency of the C allele between cases and control subjects, giving an odds ratio of 2.4, (CI 95%, 1.1 to 5.4) was found in the Diabetic nephropathy group (Table 2).

Comparison of genotype frequencies showed a statistically significant difference between the studied groups (p=0.03).

In a similar study done by Ohshige et al (2010) in Japan, genotyped 33 SNPs in KCNQ1 using 754 type 2 diabetic patients with overt nephropathy and 558 control subjects (an initial study),
and we further examined the association of a candidate SNP using three other independent Japanese populations and found that Combined analysis by a meta-analysis revealed that the T allele of rs2237897 was significantly associated with susceptibility to diabetic nephropathy in Japanese subjects with type 2 diabetes (odds ratio 1.22 [95% CI 1.10-1.34], P = 3.1 x 10 (-4), corrected P = 0.01).

A study done by X.L. Lim et al. 2012 included a total of 752 Chinese patients with type 2 diabetes. Albuminuria was determined by ACR using spot urine samples, and renal function was approximated using estimated GFR. Genotyping was performed using invader and Taqman assays as appropriate. Multivariate regression analyses were used to analyze the associations between SNPs and renal traits.

Significant associations were detected between rs2283228 and macroalbuminuria (p < 0.001, corrected p < 0.01), as well as log (e) ACR (p = 0.004, corrected p = 0.036) after multiple hypothesis testing and adjustment for potential confounding. A trend of increasing OR was observed with increasing severity of diabetic nephropathy (low and high microalbuminuria, macroalbuminuria). rs2237897, previously implicated in the earlier Japanese study, was also associated with macroalbuminuria, but this finding did not remain significant after correction for multiple testing. Meta-analyses of the Chinese and Japanese studies revealed both SNPs to be significantly associated with microalbuminuria.

In our study done in India, we also found that the frequencies of rs2237897 were consistently higher in the nephropathy groups than in the control groups and the frequency of C allele is higher, so in our study C allele was the risk allele for diabetic nephropathy, which is different from the T allele of Japanese study. This difference will be most probably due to different ethnicity, race and genetic composition of different geographical area.

**Conclusions**

Together with the previous Japanese study and East Asians study, our findings also support the hypothesis that, in addition to KCNQ1 being an established type 2 diabetes gene, genetic variation in this gene may contribute to susceptibility to diabetic nephropathy and KCNQ1 may be a good candidate marker for diabetic nephropathy in the future, but this is a small study so larger studies will be required to establish as a marker of DN.

**Competing Interests**

The authors of this study have no personal or financial conflicting interests that bias the work of this study.

**References**

Effects of Canagliflozin on Abnormal Liver Function Tests in Patients of Type 2 Diabetes with Non-Alcoholic Fatty Liver Disease

Ashish Gautam¹, Prabhat Kumar Agrawal¹*, Jitender Doneria², Ashwini Nigam¹

Abstract

Introduction: Canagliflozin, a second line OHA is well known to reduce weight. Patients of type 2 diabetes with non-alcoholic fatty liver disease (NAFLD) frequently have abnormal liver functions. We evaluated role of canagliflozin in reducing weight and improving liver function tests (LFT) in type 2 diabetes with NAFLD.

Aim: Effects of canagliflozin on abnormal liver function tests in patients of type 2 diabetes with non-alcoholic fatty liver disease.

Methods: We selected type 2 diabetes patients who were having comorbid NAFLD with abnormal LFT. Subjects were prescribed canagliflozin in dose of 100mg/day for 6 months. Dose adjustments of other drugs (oral hypoglycemics agents and insulins) was done to monitor glycemic target. Effects of canagliflozin was observed on LFT, vitals and HbA1c. It was an observational study. Subjects who developed major side effects were excluded and managed.

Results: One subject was lost to follow up during study and 31 completed the study successfully. Average HbA1c and weight differences were -0.46% and -1.86% respectively. Average ALT reduction was 36 U/L; t= -9.153623, p is < 0.00001. Average AST reduction was 19.0 U/L; t= -8.153660; p is <0.00001. Average GGT reduction was 5.87 U/L; t= -3.286677, p=0.002588. Average ALP reduction was 1.68 U/L; t= -1.295661. p=0.204973. Serum Bilirubin was elevated by 0.04%; t=0.912, p=0.368. With 0.46% reduction in HbA1c there is 37.5% reduction in ALT levels (R=0.1424) and with 1.86% weight reduction there is 37.5% ALT reduction (R=0.3448).

Conclusions: Canagliflozin controls HbA1c and reduce weight in type 2 diabetes. It also significantly improves LFT in co-morbid NAFLD.

Introduction

Background

Non-alcoholic fatty liver disease (NAFLD) is considered as the hepatic manifestation of the metabolic syndrome – a condition related to type 2 diabetes, insulin resistance, hypertension, central obesity, and hyperlipidemia (low high-density lipoprotein cholesterol, hypertriglyceridemia). NAFLD is presumed to be the most common cause of chronic liver disease in western countries. Depending on the populations studied, estimates of current prevalence range from 5% to 30%¹. India has the largest number of people with type 2 diabetes in the world and with increasing obesity and type 2 diabetes, there is a miserable possibility of prevalence of NAFLD increasing further.²

Rational for this Study

Treatment for type 2 diabetes and NAFLD has several similarities. Life style modification, Weight reduction, Alcohol and Tobacco abstinence, Anti-Oxidants, Metformin, Thiazolidinediones “and” Liraglutide are the mainstay treatment for both conditions. Till date, the only FDA-approved agents that in controlled studies have shown to significantly improve liver histology in patients of type 2 diabetes with NAFLD are Pioglitazone³ and Liraglutide⁴.

Canagliflozin, a Sodium-glucose co-transporter 2 (SGLT2) inhibitors is a new oral hypoglycemic agent (OHA) which controls blood sugar by producing glycosuria.⁵ Besides managing sugar the drug is proved to significantly reduce the weight among obese patients with type 2 diabetes⁶ and improves insulin sensitivity.

Objective of this Study

To evaluate Canagliflozin as first or second line in the treatment of type 2 diabetes with NAFLD and quantify its effects in improving LFT in above clinical setting.

Material and Methods

Study Type

Post marketing Observational study of pleotropic effects of Canagliflozin. Study design was made as per guidelines laid in STROBE STATEMENT.

Study Design and Subjects Selection

Study was conducted at Sarojini Naidu Medical College, Agra, India from August 2015 to July 2016. Subjects were selected from General Medicine OPD and Diabetes specialty clinic. During the above period, all patients with type 2 diabetes who were attending the above clinic were evaluated clinically for eligibility. Patients with type 2 diabetes, with NAFLD and abnormal liver function tests (LFT) were considered eligible to be enrolled for the study. 32 subjects of type 2 diabetes, having clinical suspicion of NAFLD were extensively investigated by means of pathological tests and radiological scans to confirm the diagnosis and enrolled further.

All patients were investigated for liver functions including Alanine aminotransferase (ALT or SGPT) and Aspartate aminotransferase (AST or SGOT), total serum Bilirubin, alkaline

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with NAFLD and type 2 diabetes with normal LFT were also excluded. Weight, vitals and LFT were observed before start of the study and repeated just after completion of observation period.

Procedure

Subjects who were on OHA or Insulin were prescribed Canagliflozin 100 mg daily with dose adjustments of other drugs to maintain glycemic targets and monitoring of possible side effects. Patients were informed about the beneficial effects of Canagliflozin for their better sugar control and weight reduction as well. Its side effects were also explained in detail. Canagliflozin used was available commercially. Self-monitoring of blood sugar was done by subjects to monitor blood sugar fluctuations and HbA1c was done in the mid of observation period to maintain glycemic targets. Frequency of subject’s visits were individualized as per the blood sugar levels. Total observation period was 6 months. Other necessary investigations were done during observation period as on required basis to prevent any complication or side effects and to monitor rapid deterioration of liver functions. Minor side effects were managed as on required. Subjects who developed major side effects were excluded immediately and managed.

Study Endpoints and Statistical Analysis

Change in the averages of subject’s Weight, HbA1c, AST, ALT, Bilirubin, GGT “and” ALP were observed before and after the observation period. Subjects who completed the follow up observation period of 6 months were considered eligible to be included in observation. Marked decrease or increase in blood sugar values, marked changes in HbA1c levels, rapid deterioration in liver function or vults of subject or development of any known or unknown fatal side effect of Canagliflozin developed during observation period were considered to exclude subjects immediately from the study. Repeated measure student’s t test was used to calculate statistical difference in LFT values before and after observation period and its significance. Pearson’s correlation coefficient calculator was used to evaluate relationship between HbA1c and Weight with LFT changes before and after observation period. All calculations and graphs generated using SPSS version 16 statistical calculator.

Results

Demographic and Clinical Profile

Clinical characteristics and pathological data are presented in table 2. One subject was excluded during observation period due to development of recurrent urinary tract infection and genital candidiasis. Twenty out of 21 new subjects and all 11 old subjects (total 31) completed the observation period with minimal side effects. Ratio of males and females was 2:1.1.

Average age of females was 44-8 years, whereas of males was 47-3 years (overall average age was 46-54 years; SD 10-58). HbA1c reduced by -0.46%, whereas average weights loss was 1.56 Kg before start and after completion of study.

Changes in LFT: (Students t test)

Changes in LFT displayed in table 3. Average reduction in ALT was 35-9 U/L; t = -9.153623; p < 0.00001. Average reduction in ALT was 19-0 U/L; t = -8.153600; p < 0.00001. There was 7-82% reduction in GGT level; t = -3.286677; p = 0.002588. There was 2-01% reduction in ALP levels; t = -1.295661; p = 0.204973; the result was not significant at p ≤ 0.05. There was 3-41% rise in serum bilirubin levels; t = 0.912519; p = 0.368771; the result was not significant at p ≤ 0.05.

Relationship between HbA1c reduction and changes in LFT

Presented in Table 4 and Fig. 2 the relationship between changes in HbA1c

Table 1: Modalities used to confirm NAFLD (combination of two or more)13

<table>
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<th>Procedure</th>
<th>Medical and family history and history of alcohol intake</th>
<th>General physical examination to evaluate for risk factors, BMI, and waist-hip ratio</th>
<th>Test serum liver aminotransferases</th>
<th>Imaging evaluation: ultrasound</th>
<th>Serology to exclude viral hepatitis: HBsAg, HCV Ab</th>
<th>Fasting blood sugar, lipid profile, HbA1c</th>
<th>Screening for insulin resistance</th>
<th>Rule out other chronic liver diseases: optional/additional lab tests (Hereditary hemochromatosis, Wilson’s disease, alpha-1-antitrypsin deficiency, polycystic ovary syndrome, Autoimmune liver diseases (ANA, ASMA, AMA, anti-LKM Ab)</th>
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Fig. 1: BMI changes before and after study duration
and LFT before and after the study. With 0.46% reduction in HbA1c there was statistical significant reduction in ALT, AST, GGT “and” ALP levels, where as insignificant rise in bilirubin levels. But the strength of association between HbA1c and variables of LFT was weak. Relationship between Weight Loss and Changes in LFT

Presented in Table 5 and Figure 3 the relationship between weight loss and LFT before and after the study. With 1.86% weight loss there was statistical significant reduction in ALT, AST, GGT “and” ALP levels where as insignificant rise in bilirubin levels. But the strength of association between weight loss and variables of LFT was weak.

**Relationship between weight loss and HbA1c**

With a 1.86% reduction in weight of subjects there was 0.46% reduction in HbA1c levels. The relationship was statistically significant but the association between the two variables was weak. (R=0.2344). The relation between the two variable is presented in Figure 4.

**DISCUSSION**

Lebovitz HE et al in their report that involved more than 5000 subjects of type 2 diabetes found 5.6% subjects with raised ALT level between 1 to 2.5 times the upper limits of normal. Further evaluation revealed that 98% of these asymptomatic subjects with mild raised ALT have fatty liver disease and chronic hepatitis. Among all liver disease NAFLD is the most prevalent among type 2 diabetes patients.

Canagliflozin besides control the blood sugar level also reduces the weight of patients of type 2 diabetes. In this study we demonstrated that the weight reduction by Canagliflozin improves the LFT. The weight reduction was due to its glycosuric mechanism of reducing blood sugar. Besides glycosuria, osmotic diuresis, a mild but usual side effect of Canagliflozin also reduce the weight. In a double blind placebo controlled study by Leiter LA et al on 1450 patients demonstrated that with 100, 300 mg strength of Canagliflozin, there was significant -4.1% and -4.2% reduction in body weight respectively. The above study also proved effective and sustained reduction of HbA1c by Canagliflozin at 104 weeks. Reductions from baseline in HbA1C were -0.65% and -0.74% respectively. Our observation period was 6 months and also number of subjects were less but a sustained loss of weight of 1.86% was significant. Also, the HbA1c reduction was 0.46% from the baseline. Till date there is no evidence-based approved therapeutic drug available for managing or reversing NAFLD. Lifestyle change in the form of weight reduction and dietary modification is critical in any attempt to reverse the course of NAFLD. In the clinical setting of type 2 diabetes with NAFLD, Canagliflozin contribute to...
manage both the conditions by effective and statistically significant weight reduction. Weight reduction is also presumed to be due to osmotic diuresis or reduction in visceral fat mass and hepatic fat that has been proved in experimental studies on animal. Suzuki M et al also demonstrated that weight reduction was due to urinary glucose excretion and relative increase in fatty acid oxidation as compared to carbohydrate oxidation. The latter mechanism prevents hepatic fat accumulation and reduction in inflammation in hepatic adipose tissue. 14

As per the present literature, less than one third of patients having proven NAFLD have elevated LFT. In our study improvement in LFT was observed with weight reduction with slight increase in bilirubin level. In a landmark study done by John B. Dixon et al patients with biopsy proven NAFLD and NASH has Significant improvement in liver histopathology with weight loss. Significant improvement in all parameters of LFT and HbA1c was also observed in this study. 15 Study on type 2 diabetic mouse by Tahara A. et al demonstrated significant improvement in hepatic steatosis along with improvement in glycemic control and reduction in obesity with use of other SGLT2 inhibitor. 16 In a double blind randomized phase 3 placebo control trial, Cefalu WT et al demonstrated that Canagliflozin was well tolerated then metformin and provides greater and better HbA1c reduction than glimepiride. 17 In a study by Nakano S et al, over obese mouse found markedly lowered both ALT (76%) and AST (48%) in a 4 weak therapy with SGLT 2 inhibitor. 18 In another trial by Okhi T et al, SGLT 2 inhibitors were found to be more effective in reducing weight and normalization of ALT levels then Incretin based therapy. 19 Gautam. A et al in a controlled study on 30 cases and 32 comparators found remarkable weight reduction with use of Canagliflozin among patients of type 2 diabetes, having pioglitazone associated pedal edema. Thus, a co-prescription of Canagliflozin with pioglitazone can be promising results in NAFLD. 20 These findings support the use of Canagliflozin as a viable treatment option for patients who do not achieve sufficient glycemic control with metformin therapy. These evidences are putting firm strength for addition of Canagliflozin to the current treatment regimen of type 2 diabetes patients with NAFLD and deranged LFT, with simultaneous dose adjustment of previous OHA, not only favorably improves the HbA1c level but also helps in weight reduction. This also improves LFT significantly, with insignificant rise in serum bilirubin levels. Canagliflozin may have direct effect on improvement in liver function besides its indirect effect due to improvement in HbA1c levels and weight reduction.

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7. Fauci A S and others, Harrison’s principles of internal
Introduction

Global Diabetes has risen by 45% worldwide from 1990 to 2013 as per a study funded by the Bill and Melinda Gates Foundation. The prevalence of Type 2 Diabetes Mellitus has been increased over recent decades, reaching worldwide epidemic. Hence, for any country, it requires a higher portion of expenditure on medical care and other economic resources. DPP-4 Inhibitors offer effective but expensive choice especially for a country like India where the financial burden of a disease and its treatment is born by patient’s themselves. DPP-4 (Dipeptidyl peptidase-4) inhibitors are classified as class 1, class 2 and class 3 based on their interaction with a selected inclusion criterion. Teneligliptin, which is being used for nearly a decade (Vildagliptin and Saxagliptin) bind with a selected inclusion criterion.

Teneligliptin, An Economic and Effective DPP-4 Inhibitor for the Management of Type-2 Diabetes Mellitus: A Comparative Study

Prabhat Agrawal1*, Ashish Gautam1, Nikhil Pursnani2, PK Maheshwari3

Abstract

Context: Increasing diabetic burden worldwide is creating an alarming situation for the management and development of economic resources for its’ treatment. Progressive nature of the disease requires allocation of a higher proportion of expenditure on health care initiative of any country.

Aim: Present study is designed with an aim to determine the effectiveness of cost-effective DPP-4 inhibitor, Teneligliptin, over the other agent of the same class.

Material and Method: The study was carried out in Postgraduate Department of Medicine, S.N. Medical College, Agra and 112 patients were selected as subjects with a selected inclusion criterion.

Statistical Analysis used: Independent student’s t-test was applied to compare the means. Mean standard deviation was calculated for quantitative data. All p values were two-tailed and values p<0.05 were considered statistically significant

Result: There was no significant difference in the levels of blood sugar or glycosylated hemoglobin (HbA1c) before and after the treatment of Teneligliptin.

Conclusion: Teneligliptin offered an efficient second line treatment for the management of type-2 Diabetes Mellitus at a reduced average price of INR 39 per day, when compared to other DPP-4 inhibitors.
to S1 and S2 and are considered as fundamental/basic inhibitors. Class 2 (Alogliptin and Linagliptin) bind to the additional site of S1, S2 and S1’ and may produce more DPP-4 inhibition than class 1, Linagliptin additionally binds to the S2’ subsite. Class 3 inhibitors (Sitagliptin and Teneligliptin) binds to S1, S2 and additional site of S2 extensive and produce more extensive DPP-4 inhibition.4,5

Teneligliptin is a third-generation gliptin, which offers a pharmacodynamic advantage with unique “J-shaped anchor-lock domain” which signifies for its potent and long duration of action. It also offers a pharmacokinetic advantage with a long half-life of 26.9 hours and a convenient once-daily administration as an oral unit dosage form. It has a dual mode of elimination via renal and hepatic which sheds the burden of its clearance and can be preferred choice for the treatment of the patient with renal and mild to moderate hepatic impairment. Owing to its effects on vascular function, Teneligliptin shows benefits in improvement of endothelial function, left the ventricular function, lipid levels, and least chances of hypoglycemia and neutral effect to body weight. Teneligliptin has been approved in Japan, Korea, Argentina, India and currently undergoing phase 1 trials in the USA and phase 2 trials in Europe.4,5

This study is designed with an aim to evaluate the efficacy of the use of Teneligliptin in comparison to other agents like Vildagliptin, Sitagliptin, Linagliptin, Saxagliptin as the second line agent with conventional oral hypoglycemic and to review the economic aspect of the treatment.8

### Materials and Method

The present study was carried out in the Postgraduate Department of Medicine, S.N. Medical College, Agra, India from September 2016 to March 2017. This study was approved by the institutional ethical review board.

Subjects were selected from the out-patient department of medicine and diabetic outdoor of S.N. Medical College, Agra, India, a tertiary care center.

Patients who were taking Glitins (Vildagliptin, Sitagliptin, Linagliptin, Saxagliptin) along with the conventional antihyperglycemic agents like Metformin, Sulphonylurea, Pioglitazone, Voglibose and Insulin whose level blood sugar was controlled or nearly controlled; were selected as the subjects for the study. An informed consent was signed from all the patients before participating in the study.

Subjects were chosen so as to shift from expensive Gliptin (Vildagliptin, Sitagliptin, Linagliptin, Saxagliptin) to low cost (Teneligliptin) because of their own affordability issue.9 Inclusion and exclusion criteria were laid.

#### Inclusion criteria
1. Diagnosed cases of Type 2 Diabetes Mellitus.
2. Patients between 25 to 80 years of both sexes.
3. Blood sugar level or glycosylated hemoglobin (HbA1C) is nearly controlled or controlled i.e., less than 7.

#### Exclusion criteria
1. Patients who were taking conventional oral antihyperglycemic agents and had controlled blood sugar i.e., HbA1C more than 7.
2. Patients with a comorbid history of cerebrovascular accident, ischaemic heart disease or other debilitating conditions.
4. Patients with hepatic or renal dysfunction.

Study subjects included 41 Females and 71 males. The average age of subjects was 44.13 ± 8.7 years. Sex distribution of BMI among subjects were females 25.3 ±3.3 whereas, males 24.6 ± 3.2. An average duration of...
diabetes was since 8.4±4.2 years and the subjects taking DPP-4 inhibitor for diabetes was since 20±7 months.

The subjects enrolled for the study were properly instructed not to change or add any new drug and not to take any Ayurvedic, Homeopathic or Unani Medicines during this phase. Patients were also advised not to change lifestyle or dietary pattern.

Glycosylated hemoglobin (HbA1C) was measured for all the subjects before and after starting the use of Teneligliptin; spectrophotometrically by turbidimetric immune-inhibition (Olympus AU60, Beckman-Coulter, USA).

Statistical Analysis

All statistical analysis was done by using SPSS version 20 (SPSS Inc., Chicago, USA). Independent student’s t-test was applied to compare the means. Mean standard deviation was calculated for quantitative data. All p values were two-tailed and values p<0.05 were considered statistically significant.

Results

Total 132 subjects were screened for this study after which 112 were selected after adequate consent. Twelve subjects were excluded due to their variable grades of abnormal renal function tests, 8 subjects didn’t give consent to include in the study.

Statistically, there was no significant difference between the previous DPP-4 inhibitors (Sitagliptin, Linagliptin, Vildagliptin, Saxagliptin) and Teneligliptin with respect to the level of HbA1c at a confidence interval of 95%. Teneligliptin was equally potent to any other available DPP-4 inhibitor in terms of efficacy in maintaining HbA1c (Table 1).

Among the 112 subjects the frequency of choice of DPP-4 inhibitors, 29 were using Sitagliptin, 23 were using Vildagliptin, 32 were using Linagliptin and 28 were using Saxagliptin to control blood glucose (Figure 1). It was ensured that each subject was taking same DPP-4 inhibitor for last 3 months (Figure 1).

There was no significant difference in the levels of % HbA1c when other DPP-4 inhibitors were changed to Teneligliptin, when evaluated on total 112 sample size (Table 2). The average cost per day for DPP-4 inhibitors before Teneligliptin was INR 47.75, whereas it was reduced to INR 9 per day after switching to Teneligliptin. Thus, the average price was reduced by INR 38.75 (39) for DPP4 inhibitors (Figure 2).

Discussion

Teneligliptin has proved potential DPP-4 inhibitor promise in stabilizing glycemic fluctuations throughout the day and consequently suppressing the progression of diabetic complications.10

A head to head trial published by Tushar B. Chudiwal on 116 patients comparing effects of teneligliptin to vildagliptin. Results show a 17.9% reduction in HbA1c with vildagliptin as compared to teneligliptin which shows 18.9% reduction in DPP4i naive patients at the end of three months.11 Similar results were observed in our study where difference in HbA1c reduction between them is insignificant. In another study it was reported that gliptins (DPP-4 inhibitor) have slight lesser HbA1c lowering potential when compared to active glucose lowering agent like metformin. Though the former was reported of having better gastrointestinal tolerability.4 In a study by Gupta CN et al, concluded that Teneligliptin significantly improves glycemic control in Indian patients with T2DM when prescribed as an add-on to one or more other commonly prescribed antidiabetic drugs, even in patients of rural India.12 In the present study it is evident that teneligliptin shows insignificant difference between in glucose lowering potential when compared to other DPP-4 inhibitors the difference lies in the economic burden.

Teneligliptin provides more economic choice of treatment than other gliptins.

Conclusion

The study presents Teneligliptin, a DPP-4 inhibitor as an effective, antihyperglycemic second line agent with the use of other conventional antidiabetic agents. Along with it, Teneligliptin also offers low-cost treatment at an average reduced daily price of INR 39, when compared to other DPP-4 inhibitors. Since it is a hospital-based study which involves convenient sampling, and also the sample size is small, precaution needs to be taken before generalizing this finding to the general population.

References

5. Ramanathan, Balamarugan. DPP-4 Inhibitors in the Management of Type 2 Diabetes Mellitus.
In Hypertension,

Zilarbi™
Azilsartan Medoxomil 40/80 mg Tablets

Drop in BP, as it should be...

In newly diagnosed T2DM patients

Right from the start

Glipsov™
Teneligliptin 20 mg Tablets

Aspire beyond Just Control

Emcure Pharmaceuticals Ltd.
Survey No. 255/2, Phase-I, M.I.D.C., Hinjewadi, Pune-411057 • Tel: +91 20 39821000 • www.emcure.com
von Willebrand Factor: A Tool to Predict Severity and Prognosis in Liver Disease

Mayank Jain, Joy Vargese, Deepti Sachan, Jayanthi Venkataraman

Abstract
Von Willebrand factor (vWF) is an adhesive and multimeric glycoprotein that has a central role in primary haemostasis. vWF levels correlate with thrombosis risk and inversely with bleeding risk within the apparently healthy population. Recently, numerous publications in Indian and western literature have focused on its role in liver diseases like acute liver failure, chronic liver disease, non-cirrhotic portal hypertension and tropical infections e.g. dengue. The present review encapsulates the recent advances in this aspect.

Introduction
Von Willebrand factor (vWF) is an adhesive and multimeric glycoprotein that found its historical origin in 1924, when the Finnish physician Erik von Willebrand first reported a family with a serious hereditary bleeding amongst consanguineous families.

Molecular Structure
vWF gene was cloned in 1985 using endothelial cell cDNA libraries. The gene is located on the short arm of chromosome 12 at the locus 12p13.3 and spans 178 kilobases. The human vWF gene contains 52 exons and the exon 28 is the largest, its length is 1.4 kb.

Analysis of the amino acid sequence shows four distinct domains that are each repeated from two to four times. There are three A-domains, three B-domains, two C-domains and four D-domains. The D1-D3 domains exhibit a binding site for factor VIII (FVIII), heparin and P selectin. The A1 domain is the only known binding site for the platelet receptor glycoprotein (GP) Ibα, and contains additional binding site for heparin, sulphated glycolipids and the snake venom botrocetin. The A2 domain contains the cleavage site for the metalloprotease ADAMTS-13. The A3 domain is the binding site for fibrillar collagen type I and III. The C1 domain which comprises the RGD sequence is the binding site for the integrin αIIBβ3.

Functions
vWF has a central role in primary haemostasis. It mediates platelet adhesion to the damaged vascular sub endothelium and thereby promotes platelet aggregation.

vWF is an adhesive plasma glycoprotein that enables haemostatic functions through its binding capability to FVIII, platelet surface glycoproteins and to constituents of connective tissue. It serves as a FVIII stabilizer in the circulation and the vWF-FVIII complex protects FVIII from degradation by activated protein C. Further, it mobilises FVIII to sites of platelet plug and clot formation. vWF by blocking the interaction of FVIII with lipoprotein-related receptors enhances the half life of FVIII in the circulation.

Plasma vWF exists as multimers of various sizes. Ultra-large vWF multimers can be detected transiently in normal plasma. The latter are hyperactive in binding the platelet receptor GPIb-IX-V complex, resulting in spontaneous platelet aggregation and therefore need rapid extraction from plasma of in a healthy individual.

The regulation of size of plasma vWF is by specific proteolytic process referred to as metalloprotease ADAMTS-13. Severe deficiency of ADAMTS-13 activity may result in thrombotic thrombocytopenic purpura (TTP) and mutation in the A2 domain enhances the susceptibility of vWF to cleavage that manifests as von Willebrand Disease (VWD) type 2A.

vWF level correlates with greater risk for thrombosis and inversely with bleeding rates in an apparently healthy population. These risks vary continuously and reciprocally across the normal range of vWF levels, with no clear cut demarcation or cut off between a normal and a pathological risk for these adverse events.

vWF in liver disease

Acute liver failure
Hugenholtz et al assessed levels and functionality of von Willebrand factor (VWF) and ADAMTS13 in the plasma of patients with acute liver injury and acute liver failure (ALI/ALF). The levels of vWF antigen were grossly elevated in these patients. The proportion of high molecular weight vWF multimers were reduced, despite extreme reduction of ADAMTS13 levels. The authors concluded that extreme elevated levels of VWF in plasma of patients with ALI/ALF supported platelet adhesion, despite a relative loss of function of the molecule.

Cirrhosis and portal hypertension
vWF-Ag in recent times is considered as a simple and noninvasive predictor of clinically significant portal hypertension (CSPH). It correlates well with liver function and hepatic venous pressure gradient and independently predicts clinical outcome VITRO score (the VWF-Ag/platelet ratio) is a good tool to diagnose CSH. A vWF-Ag cut-off value at 315% stratifies patients with compensated and decompensated liver cirrhosis.

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Compensated patients had 25% mortality after 53 months if the vWF-Ag was <315% compared to 15 months in patients with vWF-Ag >315% (P < 0.001). Decompensated patients had a mortality of 25% after 7 and 8 months if their vWF-Ag was <315% and >315%, respectively (P = 0.002). In compensated patients with a vWF-Ag >315% median time to decompensation or death was 32 months compared with 59 months in patients with vWF-Ag <315%. vWF-Ag was also similar to Model for End-Stage Liver Disease (MELD) in mortality prediction. Thus, it can be considered to be a valuable biomarker for predicting mortality in cirrhotic patients.15

**Indian contribution**

Eapen et al19,20 reported association of vWF and ADAMTS13 in patients with non cirrhotic portal hypertension (NCIPH). They reported deficiency of ADAMTS13 and presence of ultra large vWF multimers in these patients as well as in those with portopulmonary hypertension.19,20 The same authors have reported that ADAMTS13 deficiency in NCIPH in patients with relatively preserved liver function was probably responsible for morphological changes in NCIPH.21

In a study on patients with ACLF, the same centre22 reported markedly elevated vWF which correlated with organ failure and predicted survival in these patients. The vWF activity and not vWF antigen correlated with liver disease severity (MELD score, ACLF grade) and organ failure (Sequential Organ Failure Assessment [SOFA] score). The authors postulated in this publication that vWF-reducing treatments such as plasma exchange may benefit ACLF patients.

More recently, Eapen et al have proposed ADAMTS13 deficiency as a possible marker for predicting worsening of patients with severe dengue infection.23

**Conclusion**

vWF level correlates with thrombosis risk and inversely with bleeding risk within the apparently healthy population. The impact of abnormalities of vWF on liver disease and its outcome has now been well documented. Research in required to device procedures and treatments that would enable physicians to use this knowledge for the benefit of their patients.

**References**

Reliving 25 years of Experience with Omeprazole in Acid-peptic Diseases

Praveen Sharma

Abstract

Background: Acid-peptic diseases (APDs) are commonly encountered in clinical practice. The identification of proton pump and the subsequent introduction of proton pump inhibitors (PPIs) can be heralded as a milestone in the treatment of APDs. They have been used for the past 25 years with a good track record of safety. Omeprazole is a well-established and most studied drug in the PPI class.

Objectives and methods: This review is an objective overview of the efficacy and safety of PPIs in APDs, with special focus on omeprazole.

Results: The efficacy of omeprazole in gastroesophageal reflux disease (GERD) and peptic ulcer disease (PUD), including those caused by non-steroidal anti-inflammatory drugs (NSAIDs) is well documented. In clinical studies, the newer, more potent PPIs, used at comparable doses, have not shown greater efficacy than omeprazole. The PPIs are in general well-tolerated. Most of the concerns regarding their long-term safety have been unfounded.

Conclusion: Twenty five years after the introduction of omeprazole, the first of the PPIs, omeprazole has still remained a valuable drug in the armamentarium of clinicians.

Introduction

Acid-peptic diseases (APDs) are a group of disorders with overlapping pathogenic mechanisms involving the effects of gastric acid on diminished mucosal defense. These include peptic ulcer disease (PUD) and gastroesophageal reflux disease (GERD). They impair the quality of life and productivity of the afflicted patients and are associated with morbidity and mortality.

This article presents an overview of our current understanding of APDs. An account of proton pump inhibitors (PPIs), which are the most commonly used pharmacotherapy in APDs, as well as an overview of omeprazole, the prototype of PPIs in the management of APDs, defining its role in APDs over 25-years after it was initially introduced for clinical use are presented.

Peptic Ulcer Disease

Peptic ulcer disease is a mucosal defect that extends to or beyond the muscularis mucosa, reaching the submucosa, mostly occurring in the stomach (gastric ulcers) and the proximal duodenum (duodenal ulcers) (Figure 1). The lifetime prevalence of PUD in the general population is reported to be 5–10%. In an epidemiologic study carried out in India, involving 30,216 patients, the prevalence of PUD was found to be 7.8%.

Etiopathogenesis

Infection with the bacteria, Helicobacter pylori (H. pylori) and the use of non-steroidal anti-inflammatory drugs (NSAIDs) or aspirin are the main risk factors of both, gastric and duodenal ulcers. The pathophysiological mechanisms associated with PUD are represented in Figure 2. The acid-peptic microenvironment has a vital role in the mucosal damage due to NSAIDs, as shown in many experimental and clinical studies.

Clinical Features and Diagnosis

A history of episodic epigastric pain, relief of pain after food intake, and nighttime awakening because of pain, with relief following food intake are suggestive of peptic ulcer and help in the diagnosis. Anemia, hematemesis, melena, or heme-positive stool suggests bleeding whereas vomiting suggests obstruction. Anorexia or weight loss indicates cancer; persisting upper abdominal pain radiating to the back indicates penetration; and severe, spreading upper abdominal pain suggests perforation.

Endoscopy is considered as gold standard for the diagnosis of PUD. Detection of H. pylori using histology or rapid urease test serves as a guide to treatment.
dyspepsia, gastritis, gastroenteritis, and gastroesophageal reflux disease are commonly mistaken conditions for peptic ulcer disease.⁴

### Treatment

Treatment of PUD includes eradication of H. pylori in patients with this infection. Administration of histamine (H₂) receptor blockers or PPIs for four weeks leads to healing in most duodenal ulcers. Proton pump inhibitors provide superior acid suppression, healing rates, and symptom relief and therefore recommended as initial therapy for most patients. Meta-analysis of randomized controlled trials comparing PPIs with H₂-blockers reported earlier pain control and better healing rates at four weeks for PPIs.⁵

#### Gastro-esophageal Reflux Disease

Gastroesophageal reflux disease (GERD) refers to mucosal damage caused by the abnormal reflux of gastric contents into the esophagus (Figure 3) or beyond, into the oral cavity (including larynx) or lungs. A common condition seen in both, primary care and gastroenterology clinics, the prevalence of GERD (defined by at least weekly heartburn and/or acid regurgitation) has been reported to be 10%–20% in the Western world and <5% in Asia.⁶,⁷ In a prospective, multi-center study carried out by the Indian Society of Gastroenterology Task Force (n=3,224), 7.6% of Indian subjects were found to have significant GERD symptoms.⁸

#### Etiopathogenesis

Usually, the anti-reflux barrier (the lower esophageal sphincter, the extrinsic crural diaphragm, and the supporting structures of the gastroesophageal flap valve) prevent the reflux of acid into the esophagus. When this barrier is compromised, an increasing numbers of reflux events as well as increasingly abnormal esophageal reflux exposure results. This, as well as the reduced ability of the esophagus to clear and buffer the refluxate are contributory to esophageal mucosal damage.⁹ Based on the presence or absence of esophageal mucosal damage seen on endoscopy, GERD can be classified as non-erosive reflux disease (NERD) or erosive reflux disease (ERD).⁷

#### Clinical features and diagnosis

The clinical features of GERD are summarized in Table 1.⁷ A presumptive diagnosis of GERD is made if the patient presents with typical symptoms of heartburn and regurgitation as well as with a trial of treatment with PPIs.⁷,⁸ Objective testing with upper endoscopy and esophageal pH monitoring may be needed in patients who are not responsive to PPIs, with alarm features, at risk for Barrett’s esophagus.⁷

#### Treatment

Empiric medical therapy with a PPI for 8-weeks is the first-line treatment in GERD to facilitate healing of esophagitis as well as for symptom relief. Maintenance therapy with PPI is recommended for GERD patients who continue to have symptoms after PPI is discontinued, and in patients with complications, including erosive esophagitis and Barrett’s esophagus. PPIs have been shown to be superior to H₂-blockers for symptom relief, healing of esophagitis, as well as preventing relapses in patients with erosive esophagitis and for symptom relief in NERD.⁸

#### Acid-peptic diseases in India

In a cross-sectional study involving 1000 clinicians, which was carried out with the objective of understanding the epidemiology, clinical presentation, and associated overlapping co-morbidities in Indian patients with APDs, it was observed that:²

1. The incidence of GERD was 39.2% and that of PUD was 37.1% (duodenal ulcer: 10.5%, gastric ulcer: 9.9% and peptic ulcer-non-specified: 16.7%).
2. Heartburn, the most common symptom in GERD, was reported in 60.5% patients while epigastric pressure/pain, was the most common symptom of PUD, was noted in 72.3% patients.
3. Amongst patients with GERD, extra-esophageal symptoms were seen in 23% patients, with reflex cough being the most common feature noted in 53% patients.
4. Concomitant lower GI complaints like lower abdominal pain and constipation were reported in 28% GERD patients.
5. Alarm symptoms were seen in 49% GERD patients, with dysphagia being the most common feature.

### Table 1: Symptoms of gastrooesophageal reflux disease²

<table>
<thead>
<tr>
<th>Typical Symptoms</th>
<th>Atypical Symptoms</th>
<th>Extra-esophageal Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heartburn</td>
<td>Epigastric fullness/pressure/pain</td>
<td>Chronic cough</td>
</tr>
<tr>
<td>Acid regurgitation</td>
<td>Dyspepsia</td>
<td>Bronchospasm</td>
</tr>
<tr>
<td></td>
<td>Nausea</td>
<td>Wheezing</td>
</tr>
<tr>
<td></td>
<td>Bloating</td>
<td>Hoarseness</td>
</tr>
<tr>
<td></td>
<td>Belching</td>
<td>Sore throat</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Asthma</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Laryngitis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Dental erosions</td>
</tr>
</tbody>
</table>

*COX-1: Cyclooxygenase-1; PG: Prostaglandin. Based on data from reference 1*
(67%) while among patients with PUD, GI bleeding was the most common alarm symptom, seen in 47.6% patients.

6. The most common overlapping conditions associated with both, GERD and PUD included functional dyspepsia (25.9%), constipation (23.4%) and irritable bowel syndrome (23.4%).

Proton pump inhibitors in the management of acid peptic diseases

Proton pump inhibitors were introduced for clinical practice more than 25 years ago. The identification of hydrogen potassium adenosine triphosphatase (H⁺/K⁺-ATPase) as the proton pump of the parietal cell by Forte and Lee and by Sachs et al may be regarded as a milestone in the management of APDs. The PPIs have been widely used for the management of a variety of APDs and are recognized as the mainstay in the treatment of APDs. These drugs have been consistently demonstrated to be well tolerated, with excellent safety record, and generally superior acid-suppressing capability than prior agents. Proton pump inhibitors are recognized as the first-choice for treatment of esophagitis, NERD, PUD, prevention of NSAID-associated ulcers, Zollinger-Ellison syndrome (ZES), and functional dyspepsia and form an integral part of eradication therapy for *H. pylori*. As PPIs require the expression of H⁺/K⁺ ATPase in the active canaliculi for binding, which occurs in response to a meal, PPIs are usually administered before a meal. They then inhibit acid secretion until replacement pumps can be synthesized (up to 36 hours).

Mechanism of action

Following absorption, PPIs are taken up by the activated gastric parietal cells, where they concentrate within the acidic secretory canaliculi to undergo acid-catalyzed cleavage of a sulfoxide bond to the active sulfenic acid and/or sulfenamide. These compounds then bind covalently to cysteine residues on the hydrogen/potassium ATPase (H⁺/K⁺ ATPase) or the proton pump. The proton pump, that is responsible for the secretion of hydrogen ions into the lumen of the gastric glands and stomach represents the last step in the secretion of gastric acid (Figure 4).

Clinical Uses of Proton Pump Inhibitors

The FDA approved indications for PPIs are listed below:
- Treatment of gastroesophageal reflux disease
- Healing of erosive esophagitis
- Maintenance treatment for healed erosive esophagitis
- Treatment of gastric and duodenal ulcers
- Treatment and prophylaxis for NSAID-induced ulcers
- Treatment of *H. pylori* infection in combination with antibiotics
- Management of pathologic hypersecretory conditions (including Zollinger-Ellison syndrome)

<table>
<thead>
<tr>
<th>Table 2: Proton pump inhibitors</th>
<th>Oral formulations</th>
<th>Intravenous formulation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Omeprazole</td>
<td>10, 20, 40 mg</td>
<td>Yes</td>
</tr>
<tr>
<td>Esomeprazole</td>
<td>20, 40 mg</td>
<td>Yes</td>
</tr>
<tr>
<td>Lansoprazole</td>
<td>15, 30 mg</td>
<td>Yes</td>
</tr>
<tr>
<td>Dexlansoprazole</td>
<td>30, 60 mg</td>
<td>No</td>
</tr>
<tr>
<td>Pantoprazole</td>
<td>20, 40 mg</td>
<td>No</td>
</tr>
<tr>
<td>Rabeprazole</td>
<td>20 mg</td>
<td>No</td>
</tr>
</tbody>
</table>

Table 3: Pharmacokinetic properties of proton pump inhibitors

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Omeprazole</th>
<th>Esomeprazole</th>
<th>Lansoprazole</th>
<th>Pantoprazole</th>
<th>Rabeprazole</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bioavailability (%)</td>
<td>30–40</td>
<td>66–90</td>
<td>80–85</td>
<td>77</td>
<td>52</td>
</tr>
<tr>
<td>Time to peak plasma level tₘₜₜ (hours)</td>
<td>0.5–3.5</td>
<td>1.5</td>
<td>1.7</td>
<td>2–3</td>
<td>2–5</td>
</tr>
<tr>
<td>Protein binding (%)</td>
<td>95</td>
<td>97</td>
<td>97</td>
<td>98</td>
<td>96.3</td>
</tr>
<tr>
<td>Liver metabolism</td>
<td>CYP2C19</td>
<td>CYP2C19</td>
<td>CYP2C19</td>
<td>CYP2C19</td>
<td>CYP2C19</td>
</tr>
<tr>
<td>Primary excretion</td>
<td>Hepatic</td>
<td>Hepatic</td>
<td>Hepatic</td>
<td>Hepatic</td>
<td>Hepatic</td>
</tr>
<tr>
<td>Half-life (hours)</td>
<td>0.5–1</td>
<td>1–1.5</td>
<td>1.6</td>
<td>1–1.9</td>
<td>1–2</td>
</tr>
</tbody>
</table>

Fig. 4: Mechanism of action of proton pump inhibitors – Schematic representation. Ach: Acetylcholine; PGE₂: Prostaglandin E₂; M₁: M₁ muscarinic receptor; Ca²⁺: Calcium ions; ATP: Adenosine triphosphate; cAMP: Cyclic adenosine monophosphate; K⁺: Potassium; H⁺: Hydrogen. (+) represents activation and (–) represents inhibition.
Clinical advantages of PPIs

The PPIs represent the most potent inhibitors of gastric acid secretion as they directly block the final common pathway for acid secretion, the proton pump, unlike the anticholinergics and H₂-blockers. Their superior biochemical effect compared to H₂-blockers is due to their ability to reliably maintain intra-gastric pH >4 for between 15 and 21 hours daily, as compared to only 8 hours for H₂-blockers. The effectiveness of PPIs is also superior with respect to post-prandial and nocturnal intra-gastric pH control. Treatment with PPIs can also be maintained over the long-term without the need for dose escalation. This is in contrast to development of tachyphylaxis with H₂-blockers within 3 to 5 days of regular use, which may reduce their acid-suppressing effect by about one-half. ¹¹

Omeprazole in acid peptic diseases - From bench to bedside - The journey of omeprazole

The discovery of omeprazole was the culmination of the efforts of scientists engaged in a research project initiated at the department of gastrointestinal pharmacology at Hässle in Mölndal, Sweden, in the late 1960s, with the objective of developing an antisecretory drug for use in acid hypersecretory disease states such as PUD. The finding that the substituted benzimidazoles inhibited acid secretion only when the immediate environment was acidic was an indication that these drugs need conversion to their protonated form to exert their action. The first PPI, picoprazole (compound H149/94) was highly effective; however, it was found to cause necrotizing vasculitis in toxicological studies. Omeprazole (compound H168/68) was synthesized in 1979, and was found to be the most powerful inhibitor of stimulated gastric secretion in experimental animals and in human tissue in vitro, without serious toxicity. ¹²

Pharmacological studies demonstrated that omeprazole exhibited a specific binding to the target site and resulted in long-lasting inhibition of acid secretion. It was at the World Congress of Gastroenterology, Stockholm, 1982 that the first clinical results obtained from the use of omeprazole were presented at a satellite symposium titled “Substituted benzimidazole - a new approach to control of gastric secretion”. Following early clinical studies in PUD and ZES, omeprazole was subsequently evaluated in GERD and as a part of H. pylori eradication regimen. ¹² Omeprazole was introduced for clinical practice in 1989. ¹³

Omeprazole in the acute treatment of duodenal ulcer and gastric ulcer

A meta-analysis, which included 30 double-blind prospective trials of omeprazole (20 mg daily) compared with either ranitidine or cimetidine showed an overall therapeutic gain of 15.2% in healing for duodenal ulcer (p <0.001) and 9.9% for gastric ulcer (p = 0.005) after only 2 weeks of treatment. In addition, a greater percentage of patients were also free of symptoms at the first follow-up, when treated with PPIs. ¹⁴ A pooled data analysis from 384 randomized controlled trials (RCTs), which included a total of 44,870 patients concluded that omeprazole was significantly more effective (p = 0.001) than H₂-blockers in achieving ulcer healing, with overall rates of 80.8% and 74.7%, respectively. ¹¹

In patients with PUD (n = 143), who were refractory to high-dose ranitidine (450 mg/day), administration of omeprazole (40 mg/day) resulted in ulcer healing in 94% patients within 2–8 weeks. After healing, 133 patients underwent long-term maintenance treatment with omeprazole, 40 mg daily, for 1–5 years. During maintenance therapy with omeprazole, no endoscopically verified relapses occurred, and no drug-related adverse effects were seen. ¹⁵ In 27 Asian patients with PUD refractory to ranitidine, omeprazole (40 mg/day) resulted in rapid symptom relief from the first day of therapy and healing of ulcers (Figure 5). Maintenance therapy with omeprazole resulted in no relapses and it was well-tolerated. ¹⁶

Omeprazole for prevention of peptic ulcer relapse

Following initial healing of peptic ulcers, maintenance therapy should be considered for patients at high-risk for recurrence, e.g., those with PUD-related complications, recurrences, or H. pylori-negative ulcers. ¹¹

A double-blind, randomized, parallel-group clinical trial compared the efficacy of omeprazole 10 mg and 20 mg given in the morning with ranitidine 150 mg at bet-time in 928 patients with endoscopically proven healed duodenal ulcers, over a 12-month period. More duodenal ulcer patients were maintained in remission with omeprazole 20 mg daily than with omeprazole 10 mg daily or with ranitidine 150 mg at bedtime (Figure 6). ¹⁷

Omeprazole for prevention and treatment of NSAID-induced ulcers

In view of the gastrointestinal toxicity associated with NSAIDs, the American College of Gastroenterology guideline recommends prophylaxis for patients perceived to be at risk for NSAID-induced GI toxicity. The various options for reducing the risk of NSAID-associated GI toxicity include addition of misoprostol or acid antisecretory therapy, the use of a COX-2 selective NSAID, or any combination of...
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Table 4: Omeprazole for NSAID-induced peptic ulcers

<table>
<thead>
<tr>
<th>Investigator(s) and study design</th>
<th>Patients</th>
<th>Treatment</th>
<th>Results</th>
</tr>
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<tbody>
<tr>
<td>Yeomans 18</td>
<td>1,456</td>
<td>Omeprazole, 20 and 40 mg once daily (both studies); Ranitidine, 150 mg twice daily (ASTRONAUT); Misoprostol, 200 μg four times daily (OMNIUM)</td>
<td>Ulcer healing at 8-weeks: Omeprazole (both doses): 77%; Ranitidine: 63%; Misoprostol: 71%</td>
</tr>
<tr>
<td>Hawkey 19</td>
<td>425</td>
<td>Omeprazole, 20 mg once daily; Ranitidine 150 mg at bed-time (ASTRONAUT); Misoprostol, 200 μg twice daily (OMNIUM); Placebo (SCUR, OPPULENT)</td>
<td>SCUR: Fewer patients on omeprazole developed a peptic ulcer (4.7% vs. 16.7%, respectively) or dyspeptic symptoms (8.2% vs. 20.0%) at 3-months; OPPULENT: 3.6% patients on omeprazole vs. 16.5% on placebo developed peptic ulcer at 6-months; OMNIUM: More patients remained in remission during maintenance treatment with omeprazole (61%) than with misoprostol (48%, p = 0.001) at 6-months</td>
</tr>
</tbody>
</table>

NSAIDs: Non-steroidal anti-inflammatory drugs; ASTRONAUT: Acid Suppression Trial: Ranitidine versus Omeprazole for NSAID-Associated Ulcer Treatment; OMNIUM: Omeprazole versus Misoprostol for NSAID-Induced Ulcer Management; SCUR: Scandinavian Collaborative Ulcer Recurrence; OPPULENT: Omeprazole versus Placebo as Prophylaxis of Ulcers and Erosions from NSAID Treatment.

Fig. 7: Proportion of patients in remission of GERD at 12-months (n = 175) 22

of these strategies. 11 Omeprazole has been shown to be effective both, for prevention and treatment of NSAID-associated ulcers and was superior to ranitidine and misoprostol for prevention of peptic ulcer relapse and superior to ranitidine for healing peptic ulcer associated with NSAIDs (Table 4). 18, 19

Omeprazole for H. pylori infection

Omeprazole has been shown to inhibit H. pylori via a urease-independent mechanism, with inhibition of growth seen at a low pH, both in the absence of urea and in a urease-deficient strain of H. pylori. 20 A meta-analysis reported that triple therapies with omeprazole were more effective than comparable regimens containing ranitidine, lansoprazole, or bismuth. Omeprazole also appeared to be successful in triple therapy regimens used in children with H. pylori infection. 21

Omeprazole for GERD with and without esophagitis

In patients with acute GERD with esophagitis, omeprazole was found to be as effective as lansoprazole or pantoprazole in promoting healing and was found to be superior to ranitidine, cimetidine or cisapride in healing of esophagitis and symptom relief. In patients with symptomatic GERD without esophagitis, more patients reported symptom relief after short-term treatment with omeprazole than with ranitidine, cisapride or placebo, and symptoms were more readily prevented by omeprazole than by cimetidine or placebo. Omeprazole was also effective in healing and relieving symptoms of reflux esophagitis in children with esophagitis refractory to histamine H2-receptor antagonists. 21

Omeprazole for maintenance of healing in erosive esophagitis

In a prospective trial by Vigneri et al., involving 175 patients with endoscopically confirmed erosive esophagitis, it was found that after 12 months of maintenance, omeprazole alone (or in combination with cisapride) was significantly superior in maintaining endoscopic remission to ranitidine alone (p<0.001), cisapride alone (p = 0.003), or both ranitidine and cisapride (p = 0.03). The proportion of patients in remission remaining in the five treatment groups at 12 months are shown in Figure 7. 22

Omeprazole for Zollinger-Ellison syndrome

A prospective study was carried out by Maton PN et al., to demonstrate long-term efficacy and safety of omeprazole in patients with Zollinger-Ellison syndrome. It was observed that long-term treatment of up to 4 years with omeprazole was safe, with no evidence of hematologic, biochemical, or gastric toxicity. Furthermore, omeprazole remained effective, with only 23% of patients requiring an increase in dose, and continued to control symptoms in patients who had not been entirely symptom-free despite high doses of H2-receptor antagonists. 23

Omeprazole for functional dyspepsia

Omeprazole (20 mg daily) provided complete symptom relief in patients with dyspeptic symptoms and negative endoscopy when compared with placebo (38% versus 28%, p = 0.002). Among those with ulcer-like and reflux-like dyspepsia, complete symptom relief was seen in 40% and 54% on omeprazole 20 mg, and 35% and 45% on omeprazole 10 mg, respectively, compared with 27% and 23% on placebo (p <0.05). 24

Comparative studies with other PPIs

Several head-to-head trials have
compared the newer PPIs with omeprazole. In general, the results of these trials have shown that the efficacy of the newer PPIs, both, in respect of healing and symptoms relief of PUD and GERD as well as maintaining remission was comparable to omeprazole, when the drugs were used at comparable doses. Though some head-to-head trials comparing esomeprazole (40 mg/day) with omeprazole (20 mg/day) have reported that esomeprazole is superior to omeprazole, the doses are not comparable as per the US Food and Drug Administration’s clinical review, which indicates that esomeprazole 40 mg is pharmacodynamically three-times as effective as omeprazole 20 mg.25

Symptom relief and healing in patients with erosive esophagitis

No differences in symptom relief or healing of esophagitis was seen in a review of 16 head-to-head trials using comparable doses of PPIs. There was no difference between omeprazole, lansoprazole, pantoprazole, and rabeprazole for healing of esophagitis, both, at 4 and 8 weeks.26

In a multicenter study involving 202 patients with erosive or ulcerative GERD, it was found that the healing rates for rabeprazole 20 mg and omeprazole 20 mg were equivalent: 81% after 4 weeks of treatment and >90% after 8 weeks of treatment. Both the PPIs also provided similar relief of heartburn, as measured by frequency and severity of symptoms.26

In a double-blind, randomized, multicenter study involving 286 patients with reflux esophagitis, pantoprazole (40 mg daily) was compared with omeprazole (20 mg daily). The length of time required for symptom relief was similar for the two drugs. The healing rates were comparable at 4- and 8-weeks (Figure 8).27

Prevention of relapse in patients with erosive esophagitis

For maintenance of healed esophagitis, no difference was reported between omeprazole, lansoprazole, and rabeprazole.25

Symptom relief in patients with non-erosive gastroesophageal reflux disease

An analysis of three head-to-head trials involving patients with GERD but without erosive esophagitis on endoscopy revealed no difference between esomeprazole 20 mg and omeprazole 20 mg, pantoprazole 20 mg, or rabeprazole 10 mg.25

Peptic ulcer disease

An analysis of 10 head-to-head trials comparing PPIs in patients with duodenal ulcer revealed no significant difference in healing rates between esomeprazole and rabeprazole (Figure 9).28 Limited comparative data in patients with gastric ulcer revealed no significant difference in healing rates between omeprazole and rabeprazole (Figure 10).25,26 Symptom relief was reported to be better with rabeprazole 20 mg, but not with rabeprazole 10 mg, compared to omeprazole 20 mg daily.25

In healing of NSAID-associated peptic ulcers, no differences were noted between omeprazole, esomeprazole, and lansoprazole. In arthritis patients receiving NSAIDs, a direct comparison of pantoprazole 20 mg, 40 mg, and omeprazole 20 mg daily did not demonstrate statistically significant differences in rates of therapeutic

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Table 5: Long-term safety of PPIs – Concerns and evidence

<table>
<thead>
<tr>
<th>Theoretical concern</th>
<th>Possible mechanism</th>
<th>Clinical evidence</th>
<th>Clinical implication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastrointestinal malignancies</td>
<td>PPI-induced structural and functional changes in the gastric mucosa due to potent acid suppression, which are exaggerated during <em>Helicobacter pylori</em> infection</td>
<td>No clinical data supporting increased risk of gastric or colorectal cancer</td>
<td>PPIs alone are unlikely to be related to gastric and gastrointestinal malignancies.</td>
</tr>
<tr>
<td>Risk of bacterial enteric infections with <em>Clostridium difficile</em>, <em>Salmonella</em> and <em>Campylobacter</em></td>
<td>Long-term PPI-induced hypochlorhydria</td>
<td><em>C. difficile</em> infection: OR 2.10 (95% CI: 1.20–3.50) SIBO: OR 2.28 (95% CI: 1.23–4.21)</td>
<td>Risk is low-to-modest; impact of both, dose and duration of PPI treatment on this association is not clear.</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>Long-term PPI-induced hypochlorhydria</td>
<td>Conflicting data; risk reported in studies possibly due to confounders</td>
<td>Insufficient evidence for causality</td>
</tr>
<tr>
<td>Interstitial nephritis</td>
<td>Idiosyncratic, rare effect</td>
<td>Increased risk has been shown; causal relationship established.</td>
<td>In such cases, it is advised to withdraw the PPI and avoid re-exposure. After PPI withdrawal and corticosteroid therapy, almost all patients recovered a normal renal function.</td>
</tr>
<tr>
<td>Nutrient absorption</td>
<td>Long-term PPI-induced hypochlorhydria</td>
<td>No consistent effects on calcium or iron absorption have been reported. There is evidence to support interference with vitamin B₆ absorption.</td>
<td>Low evidence of causality</td>
</tr>
<tr>
<td>Bone fractures</td>
<td>Reduction in BMD and osteoporosis</td>
<td>PPI use has not been shown to be associated with accelerated bone mineral density loss or osteoporosis; bone fractures not consistently seen in clinical studies</td>
<td>Prevalence of bone fractures in older adults is low; in patients with risk factors for osteoporotic changes*, calcium and vitamin D supplementation is required*</td>
</tr>
<tr>
<td>Hypomagnesemia</td>
<td>By inhibiting intestinal transport of magnesium</td>
<td>May occur in patients with CKD on diuretic therapy</td>
<td>Monitoring for magnesium levels needs to be considered in at risk patients and those suspected to have symptoms potentially due to hypomagnesemia, such as cramps, paresthesias and cardiac arrhythmias.</td>
</tr>
<tr>
<td>Acute myocardial infarction</td>
<td>Not known</td>
<td>No association found in RCTs</td>
<td>More data needed</td>
</tr>
</tbody>
</table>

*Pre-existing osteoporosis, steroid therapy or malabsorption.* In 2010, the US FDA issued warning about possible risk for fracture of the hip, wrist, and spine with PPIs at high dose (more than once daily) or for a long duration (greater than 1 year). PPI: Proton pump inhibitor; FDA: Food and drug administration; OR: Odds ratio; CI: Confidence interval; RCTs: Randomized controlled trials; SIBO: Small intestinal bacterial overgrowth; BMD: Bone mineral density.

Conclusion

Proton pump inhibitors have revolutionized the treatment of acid-peptic diseases. They have been used for the past 25 years with a good track record of safety. Omeprazole is a well-established and most studied drug in the PPI class. Its effectiveness in the treatment of all acid-related diseases is well documented. Newer PPIs administered at comparable doses are similar in efficacy to omeprazole in GERD, PUD and NSAID-related peptic ulcers. In patients with ulcers associated with long-term non-steroidal, anti-inflammatory drug use, omeprazole has demonstrated superior efficacy than ranitidine and misoprostol for healing and maintaining remission in PUD. Thus, after 25 years of its introduction for clinical use, omeprazole still remains a valuable therapy for acid-peptic diseases.

References


Renin-Angiotensin System Gene Polymorphisms and Hypertension

Priyanka Shankarishan¹, Prasanta Kumar Borah², Jagadish Mahanta ³

Abstract
Hypertension has emerged as a major public health problem in developing countries including India. Hypertension, a major cardiovascular risk factor is recognized as a multi-factorial trait resulting from the interaction of various environmental and genetic factors. The genetic contribution is speculated to make up about 30% to 40% of the variation in blood pressure. Identification of variant genes that contribute to the development of hypertension is complicated by the fact that the two entities that determine blood pressure, namely cardiac output and peripheral resistance, are controlled by other intermediary phenotypes, including the autonomic nervous system, vasopressor/vasodepressor hormones, the structure of the cardiovascular system, body fluid volume, renal function and many others. Identification of genes controlling the variations in blood pressure, can define primary physiological mechanisms causing this trait, thereby clarifying disease pathogenesis, establishing molecular diagnostics and developing a novel mechanism to prevent premature death of people at risk of developing hypertension and perhaps new therapy for hypertension.

No single genetic variant has emerged from linkage or association analysis as consistently related to blood pressure level or definitive risk category (i.e. Hypertensive versus normotensive) in every sample and in all population. However, polymorphisms in candidate genes encoding proteins influencing renal tubular sodium transport, either directly or indirectly through effects on intra-renal hemodynamics, have been associated with differences in blood pressure level. Considering the importance of genetics on hypertension and the diversity of the related genes, evaluation of these genes and the study of new genes are necessary. It is hoped that by deducting related genes for essential hypertension in individual, will help in prevention of potential patients. We will be able to diagnose those at risk and develop new treatments for these patients.

Introduction
Hypertension has emerged as a major public health problem in India and in many developing countries. It is reported to be the fourth contributor to premature death in developed countries and the seventh in developing countries.¹ Hypertension, a major cardiovascular risk factor is recognized as a multi-factorial trait resulting from the interaction of various environmental and genetic factors. The genetic contribution is speculated to make up about 30% to 40% of the variation in blood pressure.²

Identification of variant genes that contribute to the development of hypertension is complicated by the fact that the two entities that determine blood pressure, namely cardiac output and peripheral resistance, are controlled by other intermediary phenotypes, including the autonomic nervous system, vasopressor/vasodepressor hormones, the structure of the cardiovascular system, body fluid volume, renal function and many others. Identification of genes controlling the...

Fig. 1: The RAAS pathway
Hypertension and the Renin – Angiotensin System

The Renin angiotensin system (RAS) is a coordinated hormonal cascade in the control of cardiovascular, renal, and adrenal function that governs fluid and electrolyte balance and arterial pressure (Figure 1). Since role of RAS is involved in BP regulation, the genes that encode the components of RAS have been suggested to be promising candidate for understanding the pathophysiology of hypertension. Particularly, polymorphisms in genes of the renin-angiotensin-aldosterone system namely angiotensinogen, angiotensin-converting enzyme (ACE), angiotensin II type I receptor and aldosterone synthase, have been prominent. The end product of the renin-angiotensin cascade, angiotensin II, enhances renal tubular sodium reabsorption both directly and indirectly via stimulation of aldosterone synthase and release. Polymorphisms in two of these genes, namely angiotensinogen and ACE, have been associated with functional differences in the encoded gene products with measures of “sodium sensitivity”, as measured by blood pressure response to changes in sodium intake.

Genes of the Renin – Angiotensin System

Angiotensinogen

Given the strong correlation of plasma angiotensinogen levels and blood pressure, angiotensinogen (AGT) is one of the frequently studied genes which is located on 1q42 to 43, and comprises of five exons and four introns, spanning 13 kb. Angiotensinogen is a key protein in the renin–angiotensin system, which influences vascular tone, renal sodium reabsorption, and blood pressure.

The cleavage of angiotensinogen by renin is the rate-limiting step in the cascade of enzymatic events leading to the generation of angiotensin. Angiotensinogen is also synthesized and present in many tissues in addition to the liver, such as the brain, large arteries, kidneys, and adipocytes. Therefore, modest changes in plasma or tissue angiotensinogen could play a major role in the generation of angiotensin I (Ang I) and in controlling blood pressure.

Angiotensinogen is a moderately abundant 55,000-60,000 Da serum glycoprotein that is the precursor to the angiotensin peptides and is the only known naturally occurring renin substrate. It is synthesized by a variety of cells, most prominently hepatocytes, adipocytes, and astrocytes. Most angiotensinogen is extracellular and is constitutively secreted. Thus, there is apparently no way that an organism can orchestrate rapid changes in angiotensinogen concentration. The angiotensinogen gene is regulated by several hormones (e.g., glucocorticoid and estrogen), and is an acute-phase protein. Angiotensinogen is a member of the serpin gene superfamily, but there is little reason to suppose that this protein is a serine protease inhibitor.

Plasma levels of angiotensinogen (AGT) have received particular attention for several reasons. First, plasma AGT levels and diastolic blood pressures are correlated in some patients, and associations of AGT levels and hypertension have been demonstrated in families. Second, infusion of AGT into sodium-depleted but not sodium repleted rats raises their blood pressures, while administration of antibodies against AGT lowers pressure. Third, transgenic mice expressing high levels of rat AGT have elevated blood pressures. Fourth, human plasma AGT levels are near the Km of renin, so that variations in AGT levels will affect the rate at which renin converts AGT to angiotensin I.

Angiotensinogen (AGT) plays an important role in hydro-mineral balance and the control of blood pressure. Walker et al. (1979) observed a highly significant correlation between plasma AGT concentration and blood pressure in a large cross-sectional epidemiological study. Within the context of a family study, Watt et al. (1992) reported higher plasma AGT levels in young adults with an elevated blood pressure whose parents also had high blood pressure compared with young adults with low blood pressure whose parents also had low blood pressure. Plasma AGT is also reported to be higher in hypertensive subjects and in the offspring of hypertensive parents. In addition, over-expression of the AGT gene causes elevated blood pressure in transgenic mice carrying the rat AGT gene.

Several reports show that the AGT genotype has a moderate but significant effect on plasma AGT concentration. Plasma AGT is elevated 20% in men and women carrying the 235T allele. Bloem et al. (1995) also found that the plasma AGT concentrations of normotensive white American children carrying the 235TT genotype were 13% higher than those with the 235 MM genotype. The mean plasma AGT concentration in African American children was 19% higher than in whites, but the association was not detected because the frequency of M235 was too low to show an association. Indeed, when splitting the 235T allele with another AGT gene polymorphism in African Americans, Bloem et al. (1997) found a significant association with plasma AGT. Busjahn et al., (1997) reported a trend to a co-dominant effect of the 235T AGT allele on plasma AGT concentration in twins, although the variation in the concentration was too great to reach significance. Another study on a large sample of the MONICA Augsburg cohort also found a co-dominant and significant increase in plasma AGT concentration in patients bearing the M235T variant.

The AGT genotype could influence the amounts of AGT mRNA and AGT in tissues. No report has shown a relationship between AGT mRNA and tissue AGT protein concentration, but Morgan et al. (1997) described increased AGT mRNA in the uterine spiral arteries of heterozygous women. These results offered a plausible explanation for the association and linkage of the AGT locus with the occurrence of pregnancy-induced hypertension.

Although several polymorphisms in the AGT region have been identified, much interest has focused on two coding region polymorphisms, M235T and T174M, both in exon 2. More specifically, through case-control studies, many but not all investigators have concluded that the threonine allele (T235) of M235T and the methionine allele (M174) of T174M are associated with elevated risk for hypertension. The M235T mutation changes a nonpolar amino acid to a polar amino acid and thus potentially changes the tertiary structure of the
protein. Because of this, it is likely that such a mutation may also influence protein function.

A collaborative investigation of the AGT gene in siblings from Utah and Paris sharpened these findings by reporting both linkage and association of AGT molecular variants (235T and 174M) with hypertension, suggesting that these AGT polymorphisms may represent markers of an inherited predisposition to essential hypertension in humans. These findings have recently been extended to a Japanese population, where a significant association was also noted between hypertension and the 235T allele, along with a substantial increase in the population frequency of the 235T allele. The probable involvement of the AGT genomic region with blood pressure regulation is strengthened by two reports of an association between proteinuric preeclampsia and AGT polymorphisms: one with the 235T allele,28 the other with a microsatellite polymorphism.29

Several subsequent linkage studies showed a relationship between the AGT locus and high blood pressure. In the United Kingdom, Caulfield et al., (1994)30 showed a strong linkage and association of the AGT gene locus with essential hypertension in a group of 63 white British families, despite the fact that there was no association between hypertension and the 235T variant. A weak linkage was found in 180 hypertensive Mexican Americans patients belonging to 46 large families living in the San Antonio, Texas area.31 However, the AGT locus showed no evidence of linkage to hypertension in a large multi-centric European study involving 630 affected sib pairs, even when patients with severe hypertension were selected.32 The implication of this gene in essential hypertension in Chinese people has also been challenged; there was no evidence of linkage in 310 hypertensive sib pairs from central China.32

The common 235T variant does not affect the Km of renin, and its secretion and metabolism are similar to that of 235M AGT. However, the replacement of a methionine by a threonine residue is not neutral. Cohen et al., (1996)33 showed that 235M and 235T AGT could be readily distinguished by a set of monoclonal antibodies, which allows plasma immuno-genotyping of homozygous or heterozygous patients. Because the 235T variant is not functional per se, it could be a marker for a putative, as yet unknown, functional molecular variant that increases plasma AGT and mediates predisposition to hypertension.

**Angiotensin-converting Enzyme**

Angiotensin-converting enzyme (ACE) is a zinc metallopeptidase widely distributed on the surface of endothelial and epithelial cells. Angiotensinogen is converted to angiotensin I by renin to angiotensin–aldosterone system (RAAS). The human ACE gene is located on chromosome 17q23, and includes 26 exons. The coding sequence codes for a 1306 amino acid protein, including a single peptide. The gene product, ACE, is composed of 2 homologous domains with 2 active sites. The ACE gene product plays an important role in the degradation of bradykinin. Bradykinin acts as a potentiator of nitric oxide (NO) release. NO plays a crucial role in protecting the endothelium from injury. Furthermore, it has been reported that hypertensive effects are mediated in a bradykinin-dependent manner.34 These two actions make ACE inhibition a goal in the treatment of conditions such as high blood pressure, heart failure, diabetic nephropathy, and type 2 diabetes mellitus. Inhibition of ACE (by ACE inhibitors) results in the decreased formation of angiotensin II and decreased metabolism of bradykinin, leading to systemic dilation of the arteries and veins and a decrease in arterial blood pressure. In addition, inhibiting angiotensin II formation diminishes angiotensin II-mediated aldosterone secretion from the renal cortex, leading to a decrease in water and sodium reabsorption and a reduction in extracellular volume.

The ACE gene encodes 2 isoforms, namely, the somatic form (sACE), with a molecular mass of 170 kDa which is expressed in somatic tissues mainly in the lung, including vascular endothelial cells and epithelial kidney cells and the germinal form or the testicular form (tACE) with a molecular mass of 100 kDa is expressed in germinal cells in the testis.35

The ACE gene, first described by Rigat et al., (1990)36 has an insertion/deletion (I/D) polymorphism in intron 16. The group published an important report that provided the impetus to further study polymorphisms in this gene. They found a polymorphism involving the presence (insertion, I) or absence (deletion, D) of a 287-bp sequence of DNA in intron 16 of the gene. Mean ACE activity levels in DD carriers were approximately twice that found in II genotype individuals. Subjects with the ID genotype had intermediate levels indicating codominancy. The I/D polymorphism accounted for approximately half (47%) of the observed variance in ACE levels in this study group. Later studies showed that the involvement of the I/D polymorphism is not limited to ACE levels in plasma, and is also detected in tissue ACE levels.37,38 The ACE I/D polymorphism were initially detected by restriction fragment length polymorphism (RFLP) analysis.36 The first polymorphic chain reaction (PCR)-based detection of this polymorphism was reported by Rigat et al., (1992)39 who used a set of primers flanking the insertion sequence. Family based studies performed by Shanmugam et al., (1993)40 however, showed the possibility of mistyping I/D heterozygotes with this PCR method. Preferential amplification of the shorter D allele may cause the misclassification of approximately 4 to 5% of ID genotypes to DD. An additional PCR amplification reaction was, therefore, formulated for the confirmation of DD genotypes obtained in the first standard PCR, including a new sense primer that is insertion-specific.40

Various published reports suggest an association or linkage of the D allele of the ACE gene with myocardial infarction41 (Cambien et al., 1992), essential hypertension,42 left ventricular hypertrophy,43 renal insufficiency44 and high fasting blood sugar levels.45 However, some other investigators have found no association between ACE I/D polymorphism and hypertension.46 Inter-ethnic variations in the frequency of allelic forms of certain genes have been suggested as one of the reasons for such discrepancies.47 This is particularly true for the ACE gene, since wide inter-ethnic allelic variations have been
African-American, Chinese, and in the ACE gene is associated with genotype of the I/D polymorphism. Studies have shown that the DD discord exists, whereas the I allele has been associated with high endurance.

Since its identification, several studies have shown that the DD genotype of the I/D polymorphism in the ACE gene is associated with hypertension and other cardiovascular risk factors. Significant association of hypertension with D allele of the ACE gene has been documented in the African-American, Chinese, and Japanese populations. However, many other studies have failed to detect such an association. Genetic and environmental heterogeneity among different ethnic groups may account for this inconsistent result.

In a linkage study, Jeunemaitre et al., (1992) found no evidence to support linkage between the ACE locus and essential hypertension. Likewise, in the Dutch Hypertension and Offspring Study, Schmidt et al., (1993) failed to find a significant association between the I/D polymorphism and blood pressure status in subjects with high or low blood pressure and in their offspring. This lack of association was repeatedly found in later studies.

Several other studies, however, reported a positive association between the D allele and high blood pressure.

**Angiotensin II Type I Receptor**

The renin-angiotensin system comprises a cascade of enzymatic reactions, which results in the production of angiotensin II from the angiotensinogen substrate. The physiological effects of angiotensin II are mediated by a final common pathway, through angiotensin II binding to specific receptors located on the cell membrane. Two isoforms of endothelial receptors for angiotensin II are known so far: AT1 and AT2 using ligand binding studies. Most of their physiological effects are mediated by the activation of AT1-subtype receptors. The receptors belong to the super-family of the G-protein-coupled receptors, and, in the case of AT1 receptors (AT1R), coupling occurs via Gq proteins. Consequently, stimulation of AT1 receptors activates phospholipase C, increases the levels of diacylglycerol (DAG) and inositol triphosphate (IP3), elevates the intracellular Ca²⁺ concentration, and activates several kinases, modulating cell functions. Angiotensin II acts as a mitogen in vascular smooth muscle cells by activating several signaling pathways, such as that of phospholipase C, phospholipase A₂, and phospholipase D, as well as by activating a large number of kinases, such as tyrosine kinases, mitogen-activated protein kinases (MAPKs), c-src kinase, Janus-associated tyrosine kinase, and receptors with tyrosine-kinase activity. Angiotensin II also stimulates transcription factors, such as the activating protein, signal transduction and transcription activators (STATs), and the nuclear factor kappa B (NFkB). Several studies have reported that the proliferative effects of angiotensin II are mediated by the activation of AT1 receptors.

Cloning of cDNA of the AT1 receptor provided the identification of a polymorphism in the nontranslated region 3’ (A1166C), corresponding to an A to C transversion (adenine replaced by cytosine) in the position of the nucleotide 1166 of the mRNA sequence, resulting in 1 heterozygous (AC) and 2 homozygous (CC and AA) genotypes. The A allele that lacks the enzyme-restriction site is designated as the larger fragment whereas the C allele, which has an enzyme restriction site at nucleotide position 1166, is designated as the smaller fragment. The human AT1R gene, which mediates the major cardiovascular effects of angiotensin II, was cloned in 1992 and was present as a single-copy gene on human chromosome 3q 21-25 and spans about 60 kb including five exons and four introns. Exon sizes range from 59 to 2014 bp. Exon 5 is the largest and the only coding exon, while the first four exons encode a 59 untranslated region (UTR). AGTR1 is expressed in different organs including the heart, skeletal muscle, brain, human liver, lung, and adrenal gland. This receptor is included in the guanyl nucleotide binding protein (G-protein) coupled receptor super-family for which the intracellular messengers are phospholipase, calcium, and protein kinase. In humans, the AT, receptor is present predominantly in vascular smooth muscle cells, and the AT2 receptor is present in the uterus, brain, and adrenal medulla. Both subtypes are also expressed in the adrenal cortex and kidney. The AT1 receptor, through which are exerted most of the actions of Ang II, is a G-protein-coupled receptor spanning seven transmembrane domains, and the cDNA and gene encoding human AT, have been cloned.

AT1R may be an important target for control of angiotensin II-dependent hypertension, as supported by the results of three studies. First, AT1R antagonists were shown to be effective antihypertensive agents. Second, a genome-wide scan suggested that the AT1R locus is the most significant contributor to hypertension in Finnish populations. Third, polymorphisms of the AT1R gene have been associated with hypertension.

Although substitution of cytosine for adenine at position 1166 (A1166C) in the AT1R gene was associated with susceptibility to essential hypertension in French and Finnish populations, this finding was not confirmed in other ethnic groups, and thus these differences may be due to an ethnic variation. Paillard et al., (1999) found that AT1R sites on platelets are of limited density and that there is no effect of the genotype on receptor number or affinity. It also affects responses to losartan and angiotensin II. It has also been suggested that the A1166C polymorphism may be involved in the regulation of the expression of AT1R. Weak but significant linkage disequilibrium with a polymorphism in the promoter region of the AT1R gene and AT1R/A1166C has also been reported. Interethnic differences in cardiovascular diseases indicate the need to examine the association of AT1R gene polymorphism and hypertension in other populations.

The silent A1166C SNP in the AT1R gene has been associated with the severe form of essential hypertension, and in particular in drug-resistant hypertensive patients taking two or more antihypertensive drugs. The C allele was particularly over represented.
in Caucasian hypertensive subjects with a strong family history and it was also significantly more frequent in women with pregnancy-induced hypertension. A significant interaction between ACE I/D and AT1R +1166C polymorphisms in terms of influence on BP variation has been reported, although their linkage mechanism remains unclear. Henskens et al., (2003) confirmed an association of both these polymorphisms with BP in healthy normotensive subjects, although synergistic effects did not seem to be present. A higher prevalence of the AT1R CC genotype was found in Chinese hypertensive patients than in a control population whereas the +1166A/C genotype distribution did not differ between hypertensive and normotensive subjects from Japan. Tiret et al., (1998) showed a higher prevalence of C allele among female hypertensive patients than in control subjects but no such difference was observed in men. Szombathy et al., (1998) did not find any difference for this polymorphism in the AT1R gene between normotensive control subjects and subjects with resistant essential hypertension but high values of systolic BP were associated with the C allele in older overweight patients.

Lajemi et al., (2001) found that the 1166C allele in the AT1R gene influences the relationship between age and arterial pulse valve velocity in the additive effect with the -135A/G SNP in the AT1R gene. The C allele was also associated with aortic in both normotensive and hypertensive subjects but Girerd et al., (1998) did not find such a correlation with vascular hypertrophy in subjects with no evidence of cardiovascular disease. Takami et al., (1998) also reported an association between the C allele and left ventricular mass index, but in normotensive subjects without hypertrophic cardiomyopathy. These results are not in accordance with the studies of Hamon et al., (1997) and Ishanov et al., (1998) Hamon et al., (1997) observed that the subjects homozygous for the AT1R CC genotype had a significantly lower ejection fraction than those with the A allele.

**Conclusion**

According to experiments and researches, genetic factors are involved in the process of hypertension including pathogenesis, diagnosis, treatment, and prevention of hypertension. Considering the importance of genetic hypertension and the diversity of the related genes, evaluation of these genes and the study of new genes are necessary. It is hoped that by deducing related genes for essential hypertension, we be better able to diagnose those at risk and develop new treatments for these patients.

**Acknowledgement**

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**References**


Undergraduate Medical Teaching: Time to integrate?

Ravikirti¹, Sadhana Sharma²

Abstract
Traditionally, the undergraduate medical curriculum is taught as separate subjects. The basic sciences are taught in the beginning while clinical subjects are taught in the later years. However, now there is a greater emphasis on teaching in an integrated fashion to achieve the larger goals of the curriculum. This article describes the various types and steps of integration, its advantages and the challenges in its implementation.

Introduction

Abraham Flexner submitted a report on medical education to the Carnegie Foundation for advancement of teaching in 1910.¹ The Flexner report, as it is popularly known, was a landmark in the history of medical education in North America. It paved the way for the standard model of undergraduate medical teaching where basic sciences are taught in the first half of the course and clinical subjects in the later years. Hundred years later, the Foundation has called for the need to move away from ossified curricular structures to a system where the doctors in training can constantly integrate all aspects of their knowledge, skills and values.² Similar sentiments are echoed by the Medical Council of India in its document ‘Vision 2015’ when it talks of its plan to “facilitate horizontal and vertical integration between disciplines, bridge the gaps between theory and practice, between hospital based medicine and community medicine”.³

Worldwide, we see today a move away from fragmented teaching of medical disciplines to a more integrated curriculum. Integration can be defined as the organisation of teaching matter to interrelate or unify subjects frequently taught in separate academic courses or departments.⁴ Practically, most undergraduate courses will find themselves somewhere on a continuum that has on one extreme a completely fragmented curriculum where different departments deliver their teaching without any consideration for other departments and on the other extreme a model where different disciplines work in unison to facilitate concept building and acquisition of skills by the learner. This continuum has been described by Harden as the eleven steps on the integration ladder (Table 1).

Models of Integration: Horizontal versus Vertical⁶

Horizontal integration refers to integration across subjects that are usually taught separately but simultaneously. They may be unified into one inter-disciplinary block. For example, anatomy, physiology and biochemistry may be combined into one block of basic sciences. It helps by reducing redundancy in content and assessment and frees up more time for self learning.

Vertical integration implies integration across time. It attempts to transcend the conventional barrier between basic and clinical sciences. The student is exposed to both basic and clinical subjects throughout the course. The curriculum may consist of a larger proportion of basic sciences in the beginning. The importance, in terms of time and resource allocation, of the clinical subjects may increase as the student progresses through the course. The idea is to provide earlier clinical exposure and a better opportunity to correlate theory with practice. There is evidence to suggest that concepts are best grasped when they are learnt in the context in which they will be used.⁷

Integration may be done in both horizontal and vertical models (Table 2).

Table 1: Eleven Steps on the integration ladder⁴
1. Isolation – The teachers teach their subject without any consideration for what is being taught in other subjects.
2. Awareness – The teachers are aware of what is being taught in other disciplines but there is no conscious effort to integrate.
3. Harmonization – There is cross-disciplinary communication among teachers with an effort to adapt.
4. Nesting – Teachers try to allude to topics from other subjects to enrich the teaching of their own subject. The individual disciplines recognize the broader curricular outcomes and relate their own teaching to these.
5. Temporal coordination - The timetable is adjusted so that related topics from different subjects are taught around the same time.
6. Sharing - Two disciplines plan and jointly implement a teaching programme. For example, the departments of paediatrics and community medicine may jointly run a programme in community child health.
7. Correlation - An integrated teaching session is introduced in addition to the subject-based teaching. This session brings together areas of interest common to each of the subjects.
8. Complementary programming – There is both subject-based and integrated teaching. The integrated sessions represent a major feature of the curriculum.
9. Multidisciplinary – Themes transcending subject boundaries are identified and taught by experts from different disciplines. For example, in the module on thyroid, physiology may teach thyroid hormone synthesis and its regulation, pathology the underlying disease processes, pharmacology the action of anti-thyroid drugs, surgery the management of goitre, and medicine the clinical manifestations and management of thyroid disease.
10. Inter-disciplinary – There is a higher level of integration, with the content of all or most subjects combined into a new programme. There may be no reference to individual disciplines or subjects, and subjects are not identified as such in the timetable.
11. Trans-disciplinary - The curriculum focuses on the learner’s process of constructing meaning from information and experience.

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horizontal and vertical dimensions. This is known as spiral integration. In this model, basic and clinical sciences interact throughout the course with common themes uniting the two. There is enhanced reinforcement as topics are revisited with increasing levels of complexity. The learner relates new learning with previous learning and gains in competence with successive encounters. Ideally, themes like clinical methods, ethics, and health promotion run through all stages of the curriculum. A similar model is followed in the University of Dundee. The students learn about normal structures and functions using a system-based approach in the first phase. The spiral is broadened in phase two to include abnormal structure and function. The same systems are revisited in phase three from a clinical perspective but making correlations with the previously acquired knowledge. Finally, in the fourth spiral, theory is put into practice during internship.

Some Practical Considerations

Moving from the conventional model of delivering undergraduate medical education to integrated teaching can be a daunting task. To begin with, there is the inevitable resistance to change. Integration breaches and often demolishes the boundaries between disciplines. Teachers may find this difficult as they often have a sense of belongingness to their respective disciplines. Furthermore, it requires a lot of inter-departmental planning and coordination, even more so at the outset when the entire curriculum has to be reviewed and recast in the new model.

A good starting point can be curricular mapping. The desired competencies (knowledge, skills, attitudes) should be well defined considering the larger goals of the curriculum. The content of the curriculum, i.e. the syllabus, should facilitate the acquisition of these competencies. Next steps in curricular mapping are outlining how this syllabus is to be taught (teaching methods, learning resources) and preparing a suitable teaching schedule. Finally, appropriate methods and timings of assessment need to be decided.

Based on their experience in implementing an integrated curriculum, Malik and Malik have emphasized the need to create curriculum development groups with appropriate representation from foundation as well as clinical sciences. They have also stressed upon the importance of teachers making references to contents of other teaching sessions in order to link and build upon what has been taught by teachers from other disciplines.

The journey up the integration ladder is challenging but exciting. An appetite for change, careful planning and an excellent interdisciplinary coordination are the most important prerequisites of success.

References

Cerebral Venous Thrombosis in Papillary Carcinoma Thyroid

Mugundhan Krishnan¹, Balamurugan N², Thiruvarutchelvan K³, Sivakumar S³

CVT is an uncommon and frequently unrecognized type of stroke that affects approximately 5 people per million annually and accounts for 0.5% to 1% of all strokes.² Predisposing causes of CVT are multiple. The risk factors for venous thrombosis in general are linked classically to the Virchow triad of stasis of the blood, changes in the vessel wall, and changes in the composition of the blood. Risk factors are usually divided into acquired risks (eg, surgery, trauma, pregnancy, puerperium, antiphospholipid syndrome, cancer, exogenous hormones) and genetic risks (inherited thrombophilia). In the ISCVT, 7.4% of cases of CVT were associated with cancer, particularly in patients with hematologic malignancies. Potential mechanisms for an association of cancer with CVT include direct tumor compression, tumor invasion of cerebral sinuses, or the hypercoagulable state associated with cancer.³⁴

A 40 years old female was admitted in the emergency ward with history of serial seizures (GTCS), 6 episodes in the past 2 days. The patient was diagnosed to have papillary carcinoma of thyroid with neck nodal metastasis. Post contrast axial and coronal reformation of CT Neck shows metastatic neck nodes of thyroid CA compressing right IJV (Figures 1, 2, 3). She underwent total thyroidectomy with bilateral modified radical neck dissection in the recent past. On examination patient’s vitals were stable. Fundus examination showed bilateral papilledema. Patient was conscious, oriented and without any focal neurological deficits. She was evaluated with routine blood investigations including serum electrolytes, which were within normal limits. MRI Brain with MRV showed features suggestive of thrombosis in right transverse, sigmoid sinus and superior sagittal sinus thrombosis (Figures 4, 5). Diagnosis of cerebral venous thrombosis in papillary carcinoma thyroid with nodal metastasis was made. Patient was started on antiedema measures, antiepileptics and low molecular weight heparin. Seizures controlled. Patient was discharged on oral anticoagulants with monitoring of coagulation parameters. His thrombophilic and vasculitic workup was negative.

The possible mechanisms by which cerebral venous thrombosis in papillary carcinoma thyroid with nodal metastasis is thrombus formation due to venous stasis following occlusion of internal jugular vein by neck nodes, prothrombotic state associated with malignancies and direct invasion by the the tumour.³⁵ Hypercoagulability is a well known paraneoplastic...
syndrome associated with several solid and hematologic malignancies.1,6 Classically, tumors of the endocrine system have not been associated with hypercoagulability states. We present a patient who developed a coagulopathy in the setting of papillary carcinoma of thyroid.

References

Coronary AV Fistula
Rajeev Bhardwaj

A one month child was admitted in department of pediatrics of our college with fever. He was found to have continuous murmur at apex and was referred to us for echocardiography. Echocardiography showed patent foramen ovale. There was suggestion of dilatation of right coronary. On color Doppler, there was continuous color flow into the right ventricle (Figure 1) suggestive of coronary AV fistula (CAVF)

CAVF involves a sizable communication between a coronary artery, bypassing the myocardial capillary bed and entering either a chamber of the heart (coronary-cameral fistula) or any segment of the systemic or pulmonary circulation (coronary arteriovenous fistula).1 CAVF are thought to arise due to the persistence of embryological sinusoidal connections that allow direct communication between the coronary artery and a cardiac chamber or great vessel.2 It is the most commonly encountered congenital coronary artery anomaly during cardiac catheterisation with a reported incidence of approximately 0.1–0.2%.3 Most coronary artery fistulas are small, do not cause any symptoms, and are clinically undetectable until echocardiography or coronary arteriography is performed for an unrelated cause. However, the larger fistulae can cause coronary artery steal phenomenon, which leads to ischemia of the segment of the myocardium perfused by the coronary artery and so may require, closure by surgery or transcatheter technique. 

The most common finding on physical examination in patients with CAVF is the presence of a continuous murmur, which is commonly heard over the left sternal border and the apex. Transthoracic echocardiography with colour Doppler flow mapping is a useful initial investigation, which may demonstrate aneurysmal dilatation of the feeding coronary artery as well as dilatation of the receiving chamber. Coronary angiography is considered the “gold standard” imaging modality for diagnosis of CAVF and definition of coronary artery structure and flow. Newer imaging techniques, such as multidetector CT and MRI provide useful additional information and may be used as an adjunct to coronary angiography.

References
A Curious Case of Afebrile Dengue

Wasim Khot1, Nitin Gupta1, Saurav Khatiwada2, Alpesh Goyal2, Rojaleen Das3, Megha Brijwal4, Aashish Choudhary4, Neeraj Nischal5, Lalit Dar6, Ashutosh Biswas7

Abstract
A 50-year-old male presented to us with features of diabetic ketoacidosis which was managed with adequate hydration and insulin therapy. His routine laboratory investigation revealed transaminitis, acute kidney injury and pancytopenia. Further evaluation for hematological and biochemical derangements uncovered positive dengue test (NS1 antigen and polymerase chain reaction assay). Patient distictively reported no history of fever and remained afebrile during the course of illness. We report this case to highlight the possibility of afebrile dengue in endemic areas.

Case Report
A 50-year-old male, nursing orderly at our hospital presented to us with complaints of fatigue for a few hours while on duty. He was a known diabetic, secondary to chronic calcific pancreatitis, on oral anti-diabetic drugs since last 12 years. He was advised insulin on multiple visits previously but he never complied. He was hemodynamically stable at the time of presentation but was found to have uncontrolled sugars (>700 mg/dl) and high anion gap metabolic acidosis. With a diagnosis of diabetic ketoacidosis (DKA), he was managed with intravenous fluids and insulin. His sugars were corrected within 24 hours of presentation and he was switched to subcutaneous insulin. On routine investigation, he was found to have pancytopenia, elevated liver enzymes and deranged kidney function (Table 1). His urine routine showed 3-9 pus cells/high power field but the cultures were sterile. Chest X-ray was clear. Procalcitonin levels were less than 0.5 ng/ml. Vitamin B12 and folic acid levels were normal. His platelet count fell to 12,000/ cu.mm in two days of admission.

The blood samples were sent for testing dengue NS1 antigen (Panbio Dengue Early ELISA, Standard Diagnostics Inc., Korea) which came out to be positive. This was confirmed with a reverse transcription polymerase chain reaction (RT-PCR) test for dengue virus (FTD Dengue/Chik, Fast Track Diagnostics, Luxembourg) in the same blood sample. On the sixth day of illness, his blood sample was tested for anti-dengue IgM antibodies (Dengue IgM Capture ELISA, NIV, Pune, India) which was also reported positive (Table 2).

His hospital stay was however complicated with hospital acquired pneumonia due to methicillin resistant Staphylococcus aureus (MRSA) which was managed with intravenous vancomycin (Figure 1). His complete blood count, liver function tests and kidney function tests returned to normal by ninth day of the illness.

Discussion
Dengue is an acute febrile illness, endemic to most parts of the Indian subcontinent, frequently striking as outbreaks.1 Although, majority of patients with dengue are asymptomatic, fever is the commonest presentation in symptomatic patients. It typically presents with an acute onset high grade fever, myalgia and retro-orbital pain.2 However, the febrile response may be masked in certain conditions like diabetes, old age and other immune-compromised states.3 Here, we present a case of afebrile dengue with severe manifestations in a diabetic patient with uncontrolled sugars.

Since, DKA is usually precipitated

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Table 1: Laboratory parameters of the patient with reference values

<table>
<thead>
<tr>
<th>Laboratory parameters</th>
<th>At admission</th>
<th>At discharge</th>
<th>Reference values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemoglobin (g/dl)</td>
<td>9.7</td>
<td>8</td>
<td>12-15</td>
</tr>
<tr>
<td>Hematocrit (%)</td>
<td>28.2</td>
<td>21.8</td>
<td>40-50</td>
</tr>
<tr>
<td>Total leucocyte count (/mm³)</td>
<td>2500 (N66, L25, M8)</td>
<td>4700 (N84, L7, M9)</td>
<td>4000-11000</td>
</tr>
<tr>
<td>Platelet count (/mm³)</td>
<td>50,000</td>
<td>1,82,000</td>
<td>150000-400000</td>
</tr>
<tr>
<td>Total bilirubin (mg/dl)</td>
<td>0.5</td>
<td>1.1</td>
<td>0.8-1</td>
</tr>
<tr>
<td>Aspartate transaminase/Alanine transaminase (IU/l)</td>
<td>132/62</td>
<td>30/12</td>
<td>Up to 50</td>
</tr>
<tr>
<td>Urea/ Creatinine (mg/dl)</td>
<td>81/1.2</td>
<td>20/0.6</td>
<td>0-40/0-1</td>
</tr>
</tbody>
</table>

Abbreviations: g/dl- gram per deciliter, mm³- cubic millimeter, mg/dl- milligram per deciliter, IU/L- International units per liter
by an infection in the urinary or respiratory tract, the patient was evaluated for both. He had no localized symptoms for either and his routine urine examination and chest X-ray were normal, at the time of presentation. There was no evidence of sepsis at the time of evaluation, with patient being hemodynamically stable and reports showing normal serum procalcitonin. As the patient presented during the ongoing outbreak of dengue, he was evaluated for dengue and was found to be positive.

Classically, dengue is suspected in patients with high grade fever with or without haemorrhagic manifestations and features of plasma leakage. However, it has been observed in certain reports that some patients may not mount a febrile response but have other clinical, biochemical and hematological features consistent with dengue. In a series of children with mild symptomatic dengue from Thailand, over 20% of the children were afebrile but had other symptoms. It has been observed in few studies that the mononuclear cells of diabetic patients secrete less inflammatory cytokines (IL-1 and IL-6) and consequently may not mount fever in response to infections. It is possible that the febrile response could have been blunted due to the presence of concurrent diabetic keto-acidosis. Dengue fever is associated with multiple organ involvement including hepatic and renal dysfunction. Transaminitis is a very common manifestation of dengue fever with frequencies as high as 90% reported in the published literature. Aspartate transaminase (AST) is commonly more elevated than alanine transaminase (ALT) in dengue as AST is also secreted from other sources besides liver (myocytes, cardiac myocytes). While, AKI is reported in about 0.8 to 14% of dengue patients, its etiopathogenesis is still uncertain with no single superior hypothesis. Both, leucopenia and thrombocytopenia have been used in differentiating dengue from other febrile illnesses, especially in adults. The presence of these features, in the setting of dengue outbreak, prompted us to evaluate the patient for dengue. The presence of dengue NS1 antigen in the first five days and seroconversion to IgM positivity on the sixth day led us to the diagnosis of dengue. Detection of dengue RNA by RT-PCR further confirmed our diagnosis.

Therefore, in an endemic area, dengue should always be kept as an important differential diagnosis in patients with leucopenia and severe thrombocytopenia, even in absence of fever, especially during period of outbreak. We present this case to highlight the possibility of afebrile dengue in immunosuppressed patients.

### References


### Table 2: Dengue tests done on different days of illness

<table>
<thead>
<tr>
<th>Test</th>
<th>Day of illness</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>NS1</td>
<td>3</td>
<td>Positive</td>
</tr>
<tr>
<td>Reverse transcriptase polymerase chain reaction assay</td>
<td>3</td>
<td>Positive</td>
</tr>
<tr>
<td>IgM capture Enzyme linked immunosorbent assay</td>
<td>6</td>
<td>Positive</td>
</tr>
</tbody>
</table>

Table 2: Dengue tests done on different days of illness
Neurofibromatosis Type 1 Associated with Hashimoto’s Thyroiditis

S Sakthi Selva Kumar¹, S Palaniandavan², MV Bhargavi², A Selva Gambeer¹, G Nithyalakshmi¹

Abstract
Hashimoto’s thyroiditis is a common form of chronic autoimmune thyroid disease (AITD) and it often coexists with other autoimmune diseases, but Hashimoto’s thyroiditis associated with an autosomal dominant neurofibromatosis type 1 is exceedingly rare. A 30-year-old woman presented with complaints of headache for 1 year on and off. Physical examination revealed nodular swelling in the neck, cafe-au-lait spots, and neurofibromas covering the entire surface of her body. Her thyroid hormones were within normal limits. Thyroid ultrasound revealed mild altered heterogeneous echo texture, multiple nodules of varying sizes, with hyper vascularity and ultrasound-guided fine needle aspiration cytology revealed lymphocytic infiltration of the gland, suggesting Hashimoto’s thyroiditis. High levels of autoimmune antibodies such as antithyroglobulin and antimitosomal antibodies confirmed the diagnosis. When encountering a patient with Neurofibromatosis type 1, the possibility of associated autoimmune diseases should be considered. So further studies of such patients having combination of neurofibromatosis type 1 and autoimmune thyroiditis will certainly provide better understanding of this link in the near future.

Introduction
Hashimoto’s thyroiditis or goitrous autoimmune thyroiditis is a common form of chronic autoimmune thyroid disease (AITD). It occurs in 2% of the general population and is ten times more frequent in women than in men especially older women.¹ Neurofibromatosis type 1 (NF1) is an autosomal dominant neurocutaneous disorder, characterized by neurofibromas, cafe-au-lait spots, axillary and inguinal freckling, and Lisch nodules in the eye. NF1 is caused by mutation of the NF1 gene on chromosome 17q11.2. The NF1 gene encodes for neurofibromin, which acts as a tumor suppressor protein. NF1 associated with autoimmune diseases is rare. A review of the literature reveals that Hashimoto’s thyroiditis associated with NF1 is extremely rare, and only few cases have been reported so far.²,³ We present a case of Hashimoto’s thyroiditis incidentally detected in a patient with neurofibromatosis type.

Case Report
A 30-year-old woman presented with complaints of headache for one year on and off associated with neck pain. She also complained of feeling lethargic with occasional breathlessness, weight gain and unable to tolerate cold places. Her family history revealed consanguineous marriage of her parents, and her father also had similar skin lesions all over the body. Physical examination revealed a large firm swelling with multinodular appearance in the front of the neck which moved with deglutition (Figure 1). Neurofibromas over the entire surface of her body, cafe-au-lait macules and axillary skin fold freckling were found.

Complete blood count, serum biochemistry, and urine analysis were normal. Our patient had serum levels of total thyroxine (T4) at 2.5 μg/dL (normal 4.5-12 μg/dl), triiodothyronine (T3) at 66.3 ng/mL (normal 80-180 ng/dL), and thyroid stimulating hormone (TSH) levels of 7.8 IU/mL (normal 0.35 to 5.5 ^U/mL). Thyroid ultrasound (US) revealed both lobes of thyroid showing mild altered heterogeneous echo texture with multiple nodules of varying sizes, largest being 0.8*0.6cm in right lobe and 0.7*0.6 cm noted in left lobe, with hyper vascularity not associated with lymphadenopathy. An ultrasound-guided fine needle aspiration cytology (FNAC) was carried out which showed follicular epithelial cells in singles and few cohesive clusters in acinar pattern with some of the follicular cells showing Hurtle cell change with plenty of lymphocytes and occasional plasma cells in a background.
of abundant colloid. The findings suggested the diagnosis of Hashimoto’s thyroiditis. Antithyroglobulin levels were 618 IU/mL (normal range <100 IU/mL), and anti-microsomal antibodies were >900 IU/mL (normal range was <35 IU/mL), confirming the diagnosis. US abdomen, ECG, Echocardiographic findings were normal.

Discussion

Hashimoto’s thyroiditis has been shown to coexist with other autoimmune diseases such as type 1 diabetes, celiac disease, rheumatoid arthritis, multiple sclerosis, and vitiligo and with autoimmune polyendocrine syndrome type 2 (APS-2), which has two or more of following: Addison’s disease (always present), AITD, and/or type 1 diabetes,4 in the same patient. However, association of Hashimoto’s thyroiditis with neurofibromatosis 1 is very rare, since each of them follows a different pathophysiology. A comprehensive search of published literature revealed two more instances where NF1 was associated with autoimmune diseases, especially with vitiligo and autoimmune thyroiditis.2,3

NF1 (von Recklinghausen disease) is an autosomal dominant multisystem disorder, which affects approximately 1 in 3500 people. In 1987, seven cardinal diagnostic criteria for NF1 were established.5 If any two of the following seven criteria are met, a diagnosis of NF1 is made: (a) two or more neurofibromas on or under the skin or one plexiform neurofibroma, (b) freckling of the groin or the axilla (arm pit), (c) six or more cafe-au-lait spots measuring 5 mm in the greatest diameter in prepubescent individuals and over 15 mm in the greatest diameter in post pubescent individuals, (d) skeletal abnormalities such as sphenoid dysplasia or thinning of the cortex of the long bones of the body, (e) two or more Lisch nodules (hamartomas of the iris), (f) optic glioma, or (g) a first-degree relative with NF1. These diagnostic criteria are highly specific to adults with NF1.

Clinical presentation of neurofibromatosis and Noonan syndrome often overlaps and recent studies have implicated a mutation in NF1 gene in the etiology of NFNS.

Our patient presented with neurofibromas all over the surface of her body, multiple large cafe-au-lait spots, and axillary freckling along with a positive family history. The pathophysiology involves a mutation in NF1 gene, which encodes for a tumor suppressor protein neurofibromin, located on chromosome 17q11.2. Abnormal production of neurofibromin suppresses expression of fas-ligand, preventing apoptosis of CD4+ T-cells, which may contribute to the development of autoimmunity.6 It is hypothesized that such a mechanism may have led to Hashimoto’s in our patient.

A growing number of cases reporting an association between neurofibromatosis type 1 and autoimmune thyroiditis point to a possible link between these etiologically different diseases. A comprehensive study using the published data from the reported cases may elucidate a veritable connection.

Conclusion

Neurofibromatosis type 1 is a common heritable neurocutaneous disorder and is rarely associated with Hashimoto’s thyroiditis. It is pertinent for a physician diagnosing neurofibromatosis type 1 to be aware of the possibility of coexisting autoimmune diseases owing to increased reports of such association. More extensive studies are required to establish whether this association with neurofibromatosis type 1 is coincidental or a link in pathogenesis does exist.

References

HIV – Old Foe with a New Face

Sumeet Prakash Mirgh¹, Vikas A Mishra², Rishit Harbada³, Jehangir S Sorabjee³

Abstract

We report a case of a middle aged seropositive male, virologically well suppressed on second line ART (Anti-Retroviral therapy) who presented with a subacute history of neurological symptoms. On imaging and CSF (cerebrospinal fluid) evaluation, he was found to have CD8 encephalitis - a new, rare but treatable entity. To the best of our knowledge, no case has been reported from India.

Introduction

Spectrum of HAND (HIV-associated Neurocognitive disorders) varies from asymptomatic neurocognitive impairment to Minor neurocognitive dysfunction to HIV-associated dementia. It is the most common CNS complication of HIV. CD8 encephalitis is a new form of CNS immune reconstitution inflammatory syndrome (IRIS) characterized by CD8+ T-cell infiltration into the brain without high viral burden in the CNS or typical IRIS presentation. CD8 cells in CSF and post-gadolinium T1 perivascular contrast enhancement are diagnostic. Very few cases have been reported.

Case

A 55 year old right handed businessman, known case of retroviral disease presented to us in July 2014 with a three month history of increased sleepiness, episodic involuntary facial movements, memory disturbance and slurring of speech. He was diagnosed HIV-1 ten years back and started on an AZT/3TC/NVP regimen (Zidovudine, Lamivudine, Nevirapine). Four years later, he developed Pneumocystis-Carinii pneumonia wherein his CD4 counts decreased >50% and viral load increased to >7,00,000 copies per ml.

Hence, he was shifted to second line ART - TDF/FTC/ATV(r) (Tenofovir, Emtricitabine, Boosted Atazanavir). He was virologically well suppressed on the second regimen for five years.

On admission, his Mini Mental Status Examination (MMSE) score was 19 with impaired recall and calculation. CNS examination revealed a bilateral upper motor neuron facial nerve involvement, prominent jaw jerk, grade four power in all limbs with spasticity, hyperreflexia, bilateral ankle clonus and bilateral Babinski’s sign. The patient had spastic dysthria with intermittent facial tics.

He was investigated as shown in tables and figures below. In view of MRI findings and stable CD4 count, special CSF investigations were done as in Table 4. Investigations revealed a significantly elevated CD8 cell count in CSF along with elevated CNS HIV viral load in the presence of suppressed plasma viral load. CNS immune dysregulation was thus evidenced by the disproportionate presence of CD8 cells in the CSF. Hence, he was given intravenous pulse methylprednisolone 500 mg for five days and ART regimen changed to ABC/3TC/DRV(r) (Abacavir, Lamivudine, Boosted Darunavir) to improve CNS penetration. His facial tics and drowsiness improved within two weeks followed by gradual improvement in memory (MMSE – 26) and spasticity over next eight weeks. At 1 year follow-up, he is stable without any neurological deterioration.

Discussion

CD8 encephalitis is characterized by a massively diffuse but predominantly perivascular infiltration of polyclonal CD8+ lymphocytes. Four causes have been identified: trivial infection in well controlled patients, CNS IRIS, virological escape and HAART interruption. There is a transient disequilibrium between HIV and brain immunity evidenced by the presence of numerous perivascular CD8 lymphocytes, reactive astrocytosis and microgial activation. The inconstant and weak HIV-1 p24 antigen immunostaining on brain biopsies confirmed that microglial activation was not due to underlying viral replication.

Mascolini’s group of fourteen HIV patients had a median age of 41, HIV infection for 10 years duration, median CD4 - 493 and median plasma viral load 117 copies. The condition presented subacutely in almost 50% which included epilepsy, headache, intermittent facial tics.
A close differential of CD8 encephalitis is ADEM (Acute Disseminated Encephalomyelitis). In CD8 encephalitis, T2-FLAIR hyperintensities are more diffuse and poorly delineated than large and multiple lesions in ADEM, but the principal differences are the gadolinium-enhanced lesions. In CD8 encephalitis, they are thinner than 2 mm and could be missed if a post-contrast T1 spin echo-sequence with magnetization transfer is not performed. These faint enhancements follow perivascular spaces with a linear/punctate shape amidst the FLAIR hyperintensities whereas in ADEM, the enhancement is peripheral with a ring/incomplete ring-shaped form. Our case had bilateral hyperintensities on T2-FLAIR and perivascular enhancement on post-contrast sequence which were diagnostic.

CSF pleocytosis in these patients comprised >90% lymphocytes which were mainly CD8 lymphocytes expressing the CCR5 phenotype. The mean CSF HIV viral load was 5,949 copies/ml in one study and 2,236 copies/ml in second without any role of blood CD8 count. Our case had a CSF HIV viral load of 11,157 copies/ml and disproportionately increased CSF CD8 cells.

In certain cases, the inflammation after HIV infection may overshoot its objective thereby becoming self-sustaining. Corticosteroids block this phenomenon. One study showed a mean survival time of 8 years whereas other reported considerable improvement with steroids in one-third patients over a median follow up of four years. Patients were treated with intravenous methylprednisolone followed by a tapering dose of prednisone (1 mg/kg for 2 months followed by a reduction of 5 mg every 2 weeks) for a median period of 6 months as proposed in ADEM. Our patient responded to methylprednisolone and is stable on follow up despite no long term oral steroids being administered.

**Conclusion**

The triad of subacute diffuse severe encephalitis, CD8-cells in CSF and a diffuse leukoencephalopathy with restricted diffusion and perivascular contrast enhancement on imaging has been suggested as the diagnostic triad for CD8 encephalitis. Clinicians should recognize this as it is treatable by corticosteroids and ART modification.

**Abbreviations**

3TC – Lamivudine; ADEM – Acute Disseminated Encephalo-Myelitis; ART – AntiRetroviral Therapy; ATV (r) - Atazanavir boosted with ritonavir; AZT – Zidovudine; CNS – Central Nervous System; CSF - Cerebrospinal fluid; CPE – CNS Penetration Effectiveness score; FLAIR - Fluid Attenuated Inversion Recovery Sequence; FTC – Emtricitabine; HAART - Highly Activated AntiRetroviral Therapy; HAND - HIV Associated Neurocognitive Disorders; HIV - Human Immunodeficiency Virus; IRIS - Immune Reconstitution Inflammatory Syndrome; MMSE - Mini Mental Status Examination; MRI - Magnetic Resonance Imaging; NVP – Nevirapine; TDF - Tenofovir

**References**

1. Smurzynski M, Wu K, Letendre S, Robertson K, Bosch

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**Table 3: CSF routine and special investigations on admission**

<table>
<thead>
<tr>
<th>Test</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pressure (mm H2O)</td>
<td>100</td>
</tr>
<tr>
<td>Proteins (mg/dl)</td>
<td>91</td>
</tr>
<tr>
<td>Glucose (mg/dl)</td>
<td>50</td>
</tr>
<tr>
<td>Leukocytes (cells per microlitre)</td>
<td>30 (lymphocytes - 70%)</td>
</tr>
</tbody>
</table>

**Table 4: Special CSF investigations to diagnose CD8 encephalitis**

Special CSF investigations: Values

1. CSF CD4: 13.06 % (0.8 cell/mm³)
2. CSF CD8: 75.45 % (4.9 cell/mm³)
3. CSF CD4: CD8 ratio (Normal: 1.48 – 2.26): 0.17
4. CSF HIV viral load (copies/ml): 11,157 (corresponding Plasma Viral load: 200 copies/ml and CD4 count: 525 for comparison)

**Table 5: CPE scores of different ARV drugs**

<table>
<thead>
<tr>
<th>Drug class</th>
<th>Drug name</th>
<th>CPE score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nucleoside reverse transcriptase inhibitors</td>
<td>Zidovudine, Abacavir, Emtricitabine</td>
<td>4, 3, 2, 1</td>
</tr>
<tr>
<td>Nonnucleoside reverse transcriptase inhibitors</td>
<td>Nevirapine, Delavirdine, Efavirenz</td>
<td>4, 3, 2, 1</td>
</tr>
<tr>
<td>Protease inhibitors</td>
<td>Indinavir/r, Darunavir/r, Fosamprenavir/r, Lopinavir/r</td>
<td>4, 3, 2, 1</td>
</tr>
<tr>
<td>Entry/fusion inhibitors</td>
<td>Maraviroc, Enfuvirtide</td>
<td>4, 3, 2, 1</td>
</tr>
</tbody>
</table>

**Fig. 1:** T2 Weighted Axial image showing hyperintensities in bilateral periventricular white matter. Arrows show the periventricular hyperintensities more prominent on the frontal horns (frontal vertical arrows)
Severe Hyponatremia as an Uncommon Presenting Feature of Pituitary Macroadenoma

CL Nawal¹, Radhey Shyam Chejara², PD Meena³, Swapnil Jain⁴, Sebastian Marker⁴, Vinay Tuteja⁴

Abstract
Hyponatremia is a common electrolyte disturbance, but less commonly utilized and require a thorough evaluation to unmask etiology. It has variety of causes and is rarely due to hypopituitarism. Hyponatremia is a very early complication of pituitary tumor. Here, we report a case, who presented to us with hyponatremia and eventually thorough work-up led us to a diagnosis of Non-functioning pituitary macroadenoma.

Introduction
Hyponatremia is serum sodium level of <135 mEq/L. It can lead to symptoms like decreased ability to think, irritability, lethargy, headache, nausea, and poor balance.¹ Severe symptoms include confusion, seizures, and coma.² The cause of hyponatremia is classified according to person’s fluid status into hypo-, eu- and hypervolemic hyponatremia. Hypovolemic hyponatremia can result from diarrhoea, vomiting, diuretics and sweating. Euvolemic hyponatremia is seen in polydypsia, hypothyroidism, adrenal insufficiency and SIADH. Hypervolemic hyponatremia is seen in congestive heart failure, liver cirrhosis and renal failure. Pituitary macroadenomas³ (>10 mm) are the most common cause of hypopituitarism, and in the majority of cases they are non-secretory adenomas.⁴ A pituitary adenoma usually presents with bitemporal hemianopia due to compression of optic chiasma. Other symptoms are headache, psychiatric symptoms like depression, anxiety, or symptoms due to hyper-pituitarism if secretory adenoma is present. Secondary adrenal insufficiency can occur due to a pituitary tumor and thus result in hyponatremia.

Case Report
Our case was a 60 year old right handed male, resident of Nagore (Rajasthan, India), retired postmaster, who presented with chief complaints of multiple episodes of vomiting since 15 months, episodes of giddiness, blackouts, fatigue and lethargy since 4 months, and single episode of loss of consciousness 1 month back. Vomiting was non-bilious, non-projectile, 1 to 2 episodes per day, associated with nausea and relieved by medications. Giddiness was associated with episodes of blackouts. There was an episode of loss of consciousness which lasted a few minutes, without any premonitory symptoms, involuntary movements or confusion after the episode. No history of headache, neck pain, altered sense of smell, visual symptoms, facial numbness or weakness, decreased hearing, loss of taste or altered taste, difficulty in swallowing, breathing. No history of trauma, unknown bite, vaccination, muscular weakness, fever, diarrhea or severe vomiting. He was non-alcoholic, non-smoker, vegetarian with normal bowel and bladder habit without any history of diabetes, hypertension, or any significant drug history.

On general physical examination,
was afebrile (98.2 °F), hypotensive (90/60 mmHg), had tachycardia (120 beats per minute), with normal respiratory rate (16 breaths per minute). Conjunctivae and tongue were dry with reduced skin turgor. Axillary and pubic hair were sparse. There was no palor, icterus, cyanosis, clubbing, lymphadenopathy or pedal edema. On nervous system examination, higher mental functions were normal, visual field reduced on confrontation test, plantar response was extensor bilaterally, with normal power at all joints and normal deep tendon reflexes. Examination of sensory system, cerebellar signs, cranium spine and other cranial nerve were normal. Differential diagnosis kept were metabolic encephalopathy, vertebo-basilar insufficiency, chronic meningitis and vestibular disorders.

In routine investigations, complete blood count, liver and renal functions were normal (Hemoglobin-11.3 g/dL; Total leucocyte count- 8,540/cumm; Platelet- 1.42 lacs/mL; Total bilirubin- 1.1 mg/dL; SGOT/PT- 34/18 U/L; ALP-113 U/L; LDH- 432 U/L; Urea-16mg/dL; Creatinine- 0.93 mg/dL). However, uric acid was raised (7.9 mg/dL). Amongst electrolytes, there was hyponatremia (112 mEq/L) with normal potassium (4.6 mEq/L) and chloride (88 mEq/L). Calcium (7.9 mg/dL) and phosphate (4.6 mg/dL) were normal. Random blood sugar was 62mg/dL. Arterial blood gas analysis was normal (pH- 7.45, pCO2- 26.8, pO2- 104, HCO3- 22.5, SO2- 98.4%). Serum and urine osmolality were also normal (288.5 and 373 mosm/L respectively). To find cause for loss of sodium in urine (224 mEq/L), other pituitary hormones were almost normal (TSH- 0.82 μU/mL; LH- 1.26 mIU/mL; FSH- 5.06 mIU/mL; Prolactin- 5.03 ng/mL and FT3- 1.63 ng/dL, FT4-0.47 ng/dL indicated mild hypothyroidism. These investigations indicated a non secretory pituitary tumor. So, MRI Brain with Sellar Cuts with contrast was obtained, which revealed 28 x 24 mm sellar and suprasellar mass which was not differentiable from pituitary and caused upward deviation of diaphragmatic sella with compression of optic chiasma. Visual Acuity in-RIGHT EYE was, Distant-6/36, after correction-6/18; and in LEFT EYE- Distant- 6/9, after correction-6/6. Perimetry revealed bitemporal constriction of visual fields. Thus a final diagnosis of Non functioning pituitary macroadenoma with secondary adrenal insufficiency with hyponatraemia resulting in metabolic encephalopathy was kept. Patient was discharged in stable condition on Tab. Levothyroxin, Tab.Dexamethasone and Tab. Fludrocortisone. Patient was advised for surgery by neurosurgery department and is under regular follow up.

**Discussion**

Hyponatremia is often present in patients with intracranial pathology or those recovering from neurosurgery. Syndrome of inappropriate anti-diuretic hormone secretion (SIADH) and cerebral salt wasting syndrome (CSWS) are the main causes. Apart from these two, pituitary mass leading to secondary hypoadrenalism and hypothyroidism can also lead to hyponatremia. Distinguishing these conditions is important as management is different for each of them. Hyponatremia in SIADH is caused by excessive ADH resulting in free water reabsorption. Mechanism of natriuresis in this condition is attributed to an increase in the glomerular filtration rate or a reduction in the tubular reabsorption of sodium. Diagnosis of SIADH is made in the presence of a plasma osmolality <275 mOsm/Kg with urine osmolality >100 mOsm/kg, clinical euvoalaemia and an elevated urinary sodium excretion in the presence of a normal salt and water intake. Hypothyroidism, hypoadrenalism and diuretic use must be excluded prior to making a diagnosis of SIADH.

Cerebral Salt Wasting Syndrome (CSWS) results from excessive natriuresis in patients with intracranial disease. The mechanism underlying this natriuresis is unknown but has been proposed to involve the release of natriuretic factors (atrial natriuretic peptide, brain natriuretic peptide, c-type natriuretic peptide and ouabain-like peptide) together with decreased sympathetic input to the kidney. Cortisol is an inhibitor of ADH secretion, thus secondary hypoadrenalism due to pituitary non secretory macroadenoma, results in increased ADH secretion and consequently there is decreased excretion of water by the kidney and hyponatremia. Our patient was a classical example of secondary hypoadrenalism leading to hyponatremia which is suspected less often.

**Conclusion**

Hyponatremia is a very important diagnostic tool, which, if evaluated completely, can unmask serious underlying etiology, allowing us to manage properly and without delay.

**References**

Sudden Renal Failure in a Scleroderma Patient: A Clinical Dilemma

Rathindranath Sarkar¹, Rudrajit Paul², Indranil Thakur³, Sanjay Chatterjee⁴, Shyamaprasad Singh⁵

Abstract
Scleroderma is a connective tissue disease which may present with renal crisis. But sometimes, acute renal failure in scleroderma may be due to a second pathology. We here present a case of a 35 year old woman with systemic sclerosis, who presented with acute renal failure. She was started treatment as a case of scleroderma renal crisis. But her condition continued to deteriorate and she also developed some cutaneous vasculitic lesions. Finally, serology and kidney biopsy established the renal lesion as stage IV lupus nephritis. She responded to immunosuppressive regimen for lupus with rapid improvement of kidney function. Such overlap of scleroderma with lupus is very rarely reported.

Introduction
Scleroderma is a multi-systemic connective tissue disorder which can cause acute renal failure. The condition is called scleroderma renal crisis and it often has a poor prognosis.¹ Thus, development of renal failure in a patient of scleroderma is often an adverse prognostic marker and requires immediate management.

However, acute renal failure in scleroderma patients can also be caused by other overlapping disorders. Timely differentiation of the etiology in such cases is vitally important as the management of these other disorders with renal failure is widely different from scleroderma renal crisis. We here present such a case of renal failure in a scleroderma patient, which presented to us as a clinical dilemma.

The Case Report
A 35 year old woman was admitted with rapidly progressive dyspnea and anasarca for 15 days. She had progressive oliguria and at the time of admission, her urine output was 200 ml/day. She also had intermittent fever and arthritis of small joints. In the past, this woman had been diagnosed as diffuse systemic sclerosis (dSSC) but except for NSAIDs for her arthritis, she was not receiving any therapy. She had occasional episodes of Raynaud’s phenomena but did not take any treatment for it. At the time of admission, she was receiving some herbal treatment.

On examination, the patient was found to have a pulse rate of 120/minute and blood pressure of 180/96 mm of Hg in both the arms. Her hands showed digital gangrene with pseudoclubbing (Figure 1) and there was skin tightening in the face (Figure 2). She had mild pallor, pedal edema and generalized muscle tenderness. The respiratory rate was 32/minute and SaO₂ was 95% in room air. Examination of the thorax revealed decreased breath sound with percussion dullness in right lower zone, suggestive of pleural effusion.

Initial investigations revealed hemoglobin level of 8.1 gm/dl, total leukocyte count of 13700/cmm (neutrophil 81%) and platelet count of 2.34 lakh/cmm. The ESR was 120 mm in the 1st hour. Blood urea was 154 mg/dl and creatinine 3.2 mg/dl. Serum sodium was normal and potassium level was 5 mEq/L. Peripheral blood smear examination revealed anisocytosis with polychromasia. The reticulocyte count was 6.3 %. Routine urine examination showed protein 2+, plenty of WBCs/hpf and 8-10 RBCs/hpf; there were no casts or crystals. Ultrasonography of kidneys showed only mild intra-renal edema. Repeat serological tests showed Anti-Nuclear factor to be positive (1:640) with a speckled pattern and Anti-Scl-70 to be moderately positive.

The patient was at first diagnosed as a case of scleroderma renal crisis and started on ACE inhibitors (Enalapril 5 mg BD). Also, calcium channel blockers were given for the hypertension. But the condition continued to deteriorate and on the 3rd day, she had complete anuria with severe anasarca. The urea/creatinine on day 3 was 196/4 mg/dl respectively. She was started on hemodialysis.

However, on the 4th day, the patient was noticed to have some skin lesions (Figure 3) on her feet and legs, which...
were diagnosed as cutaneous vasculitis. The next day, she also developed a few similar lesions on her trunk. In view of these lesions, some further tests were done which revealed positive anti ds-DNA (1:160). Complement levels were also low (C3: 60 mg/dl; C4: 6 mg/dl). The patient was immediately given pulse methylprednisolone (1 g for 3 consecutive days) followed by first dose of cyclophosphamide (750 mg/m²). There was rapid decline in the urea/creatinine levels with levels 98/1.5 mg/dl on day 4 after starting methylprednisolone. The edema and pallor also decreased markedly. 24 hour urinary protein came as 4.2 gm. After stabilization, a kidney biopsy was done which revealed WHO class IV Lupus nephritis with activity index 6/24. IgG, IgM, C3 and C1q deposits were found in subendothelial and subepithelial locations. Anti U1-RNP and ANCA were negative. Thus, the next day, she also developed a few similar lesions on her trunk. In view of these lesions, some further tests were done which revealed positive anti ds-DNA (1:160). Complement levels were also low (C3: 60 mg/dl; C4: 6 mg/dl). The patient was immediately given pulse methylprednisolone (1 g for 3 consecutive days) followed by first dose of cyclophosphamide (750 mg/m²). There was rapid decline in the urea/creatinine levels with levels 98/1.5 mg/dl on day 4 after starting methylprednisolone. The edema and pallor also decreased markedly. 24 hour urinary protein came as 4.2 gm. After stabilization, a kidney biopsy was done which revealed WHO class IV Lupus nephritis with activity index 6/24. IgG, IgM, C3 and C1q deposits were found in subendothelial and subepithelial locations. Anti U1-RNP and ANCA were negative. Thus, the case was finally diagnosed as overlap of SLE with class IV nephritis in a case of systemic sclerosis. The patient was started on oral steroids (1 mg/kg) with cyclophosphamide according to NIH protocol. In follow up, she has maintained a stable kidney function. There has been no new skin lesions.

Discussion

The guidelines for management of individual connective tissue disorders (CTD) are now established with a fair degree of consensus. But often clinicians are faced with patients having overlapping features of more than one CTD. While some of these entities (like rhupus or mixed connective tissue disorder) are well defined, some others are often ill defined and may present a diagnostic and therapeutic challenge. Often, for these “overlap” syndromes, there is no particular guideline and management is determined by the presenting features.

Scleroderma (SSC) can sometimes have overlap with other CTDs. Rheumatoid arthritis, Sjogren’s syndrome and myositis have been reported to overlap with SSC. Overlap with SLE is comparatively rare. The autoantibodies found in SSC, like Scl-70, may also appear in other connective tissue disorders like SLE. Hence, only the presence of autoantibodies is not a definitive proof of the presence of a particular CTD. Proper clinical features (like the renal failure in our case) must also be present for diagnosis.

Cases with SSC/SLE overlap has been reported rarely from other parts of the world. A case from China reported a 15 year old boy who had SSC to start with and then developed pleural effusion and polyarthritis. However, renal involvement was not detected. Another case was reported from Canada where SLE/SSC overlap presented with orchitis due to vasculitis. In our case, besides the renal involvement, cutaneous vasculitis was also present. In general, cutaneous vasculitis is not a common feature of SSC. Presence of such lesions should prompt a search for other second concomitant disorders.

In our case, there were certain subtle clues to suggest a diagnosis other than scleroderma renal crisis. The first was the ESR. SSC is the only CTD where the ESR remains normal. Even in renal crisis, it may remain normal. Thus, highly raised ESR in a scleroderma patient may be an indication of some second pathology. The peripheral blood picture was not helpful because fragmented RBCs causing anisocytosis may be found in scleroderma renal crisis (as it is predominantly a microangiopathic crisis) as also in SLE due to haemolytic anemia. Another clue was the urine report. In our patient, significant active sediments and proteinuria were present. But, in scleroderma renal crisis, usually proteinuria is mild as the glomeruli are relatively spared.

Some authors have reported ANCA-associated renal disease in SSC. Hence, a full autoimmune serology must be done in suspected scleroderma renal crisis to rule out secondary disorders. Sometimes, kidney biopsy remains the only way of differentiation. Typically, SSC crisis shows sparing of glomeruli with fibrinoid necrosis of vessels. But, in SLE and other vasculitis, the glomeruli are invariably involved with or without immune deposits.

Coexistence of SLE and scleroderma may present a therapeutic dilemma. Steroids are often used for SLE but that may precipitate a scleroderma renal crisis. Thus, treatments have to be individualized and often, frequent changes of treatment may be needed.

Conclusion

We present this case to sensitize clinicians to this rare overlap syndrome. Elucidation of the exact aetiology of renal failure in such cases is important as the therapy varies widely for scleroderma renal crisis and SLE nephropathy.

References

Better performers have

**Volibo**

No obstructions for GI therapy

**VoliboM**

**Better performers have Volibo**

**No obstructions for GI therapy**

**VoliboM**

Better PPI GI Clinical

Preserve β-cell function
Wilder Penfield-Cerebral Cartographer

Jayant Pai-Dhungat¹, Geeta Gore²

Wilder Graves Penfield (1891-1976) was born in Spokane, Washington on January 26, 1891. He spent most of his early life in Hudson, Wisconsin and studied at Princeton University, where he became all-round scholar athlete and graduated in 1913. Penfield was a slow plodder and accepted the challenges of his ambition; he prepared himself to shape the years to come. He went to Princeton University, New Jersey, where he decided to pursue medicine, the profession of his grandfather and estranged father because it seemed to him the most direct way to “make the world a better place in which to live.” Penfield won the Rhodes scholarship and spent years training at Oxford, Spain, Germany, and New York, before becoming the first neurosurgeon in Montreal.

Although Penfield studied under Harvey Cushing, the father of modern neurosurgery, it was the eminent British physiologist Sir Charles Sherrington who inspired him to become a surgeon. Penfield enrolled in Sherrington’s mammalian physiology course at Merton College, Oxford University in 1914. This 3 year course consisted of Sherrington “exercises”, involving various procedures, like the dissection of the peripheral nerves and spinal cord of animals. Penfield learned to handle living tissues with great care while dissecting them.

Upon completing this course, Penfield finished the clinical part of his medical training at John Hopkins University, and, after graduating in 1918, was interned at Peter Bent Brigham Hospital in Boston, where he did his apprenticeship with Harvey Cushing. Penfield then took his position at the New York Presbyterian Hospital.

In the 1950s, Penfield was trying to treat patients with intractable epilepsy. When the patients experienced an aura, Penfield thought if he could provoke this aura with a mild electric current on the brain, then he would have located the source of the seizure activity; and could remove or destroy that bit of tissue. While patients were fully conscious, under local anesthesia he opened their skulls and tried to pinpoint the source of their epilepsy.

His technique was often successful, but his experimental surgery led him to an even more dramatic discovery. Stimulation anywhere on the cerebral cortex could bring responses of one kind or another. Thus he developed a map of the brain, often portrayed as a cartoon called the motor homunculus (miniature distorted human being). This cartoon character has features drawn according to how much brain space they take up. Therefore, lips and fingers with their high number of nerve endings are larger than arms and legs.

Most interestingly he found that only by stimulating the temporal lobes could he elicit meaningful, integrated responses such as memory, including sound movement, and color. These memories were much more distinct than usual memory, and were often about things unremembered under ordinary circumstances.

Penfield was one of the greatest neurosurgeons of the twentieth century, whose pioneering work revolutionized the discipline. His technique for treating intractable epilepsy, developed with his colleague Herbert Jasper, came to be known as the Montreal Procedure; it was ground-breaking because it applied the principles of neurophysiology to the practice of neurosurgery. Penfield amassed a large body of data, which together constituted the first detailed large scale functional map of the human cerebral cortex.

He devoted much thinking to the mystery of the mind, and continued to contemplate and question whether there is a scientific basis for the existence of the human soul. Penfield died in 1976.

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CORRESPONDENCE

Smoking Intensity and its Relationship with Lung Function and Antioxidants in Healthy Subjects

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Sir,

The gas and tar phases of tobacco are rich in reactive oxygen and nitrogen species and disrupt the respiratory and pulmonary function leading to development of COPD, cancer etc.1 Antioxidants form the first line of defense against oxidative insult. Studies on lung function and oxidant/antioxidant imbalance due to the intensity of smoking in healthy subjects was sparse. Hence, prospective cross-sectional study was undertaken to test the lung function, oxidant and antioxidant imbalance, in healthy smokers focusing on the effect of duration and quantity of smoking. Data was collected from a random sample of 150 smokers (males) who were >40 years of age with a smoking history >10 pack years from rural villages in Chittoor District, Andhra Pradesh. Sample size was established assuming a 95% confidence interval with 3% sampling error. Informed consent was obtained from all the subjects. Spirometry was carried out on individuals with no respiratory problems strictly with an FEV1/forced expiratory volume in 6 s ratio >70%. Information on demographics, smoking status and anthropology were collected. Pack years were calculated as per the standard procedure. Erythrocyte superoxide dismutase, catalase, glutathione S-transferase, glutathione peroxidase and reduced glutathione and plasma malondialdehyde was measured as per the standard procedures.

Study participants had a mean age of 60 years, average number of cigarette/bidi per day 26, average duration of smoking 42 years, average pack years was 46 respectively. FEV1 and FEV1/FVC% were negatively correlated with age and duration of smoking status. Systolic blood pressure exhibited a linear relationship with age and duration of smoking. Pack years was positively correlated with malondialdehyde. Glutathione peroxidase activity negatively correlated with duration of smoking, while reduced glutathione was negatively correlated with number per day and pack years. Pack years had exerted about 23% of the variance in the malondialdehyde level and 10% of the variance in reduced glutathione level. An elevation of one pack year increases 0.6 nmol/ml of malondialdehyde and decreases 0.3 nmol/ml of reduced glutathione level.

The present investigation confirms the role of oxidant and antioxidant imbalance in smokers. Intensity of smoking status elevated the plasma malondialdehyde level and depletion of antioxidant levels. Further, both FEV1% and FEV1/FVC% decreased significantly upon exposure to smoking, indicating the restrictive pattern of disease as against obstructive or mixed as noticed in several studies.2 These observations are in line with our previous work showing declined pulmonary function test parameters in smokers with COPD.3 Even though respiratory function ratio failed to show association either with oxidative stress and antioxidants, exposure to smoking has significantly elevated oxidative stress and decreased antioxidant capacity. Increased malondialdehyde levels and decreased antioxidant levels were observed upon exposure to smoking. Interestingly lung function was positively correlated with malondialdehyde in the study sample. On the other hand malondialdehyde was negatively correlated with reduced glutathione. The correlations observed in the study could be speculated that antioxidant supplementation may ameliorate the deterioration of lung damage. Thus, stoppage of smoking, before any clinically evident respiratory impairment takes place, bears potential scope for preventive programs.

Acknowledgements

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References


Primary Human Parvovirus B19 infection in an HIV patient on Anti-retroviral Therapy

Sumeet P Mirgh1, Vikas A Mishra2, Jehangir S Sorabjee3
1AIIMS, New Delhi; 2GSVM Med College, Kanpur, Uttar Pradesh; 3Head of Department, Bombay Hospital, Mumbai, Maharashtra

Sir,

A propon the case report – “Primary Human ParvovirusB19 infection in an HIV patient on Anti-retroviral therapy” JAPI December 2013, Vol 61, Pg 910. We wish to raise the following points.

The initial finding of anaemia was attributed to Zidovudine, but no mention was made regarding the Mean corpuscular volume (MCV). MCV is almost always increased in any patient on Zidovudine, in fact it is used as a differentiator of the two conditions.1 An exception to this is patients with parvovirus B19 infection results in the correction of anaemia.2 Hence, the MCV serves as a rapid and easy differentiator of the two conditions.

Erythropoietin (EPO) levels in a patient with HIV and most anemias are generally lower for the degree of anaemia and treatment with EPO results in the correction of anaemia. An exception to this is patients with Zidovudine associated anaemia in which EPO levels are high, no EPO levels were done in this case and should generally be done when a Zidovudine associated anaemia is suspected – this is an easily available and simple blood
Post Varicella Zoster: Acute Transverse Myelitis

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Sirs,

Neurologic complications occur in approximately 2 per 10,000 cases of Varicella.1 Common CNS complications of chicken pox are cerebellar ataxia and encephalitis, and rare complications are transverse myelitis, aseptic meningitis, Guillain-Barre syndrome, meningoencephalitis, ventriculitis, optic neuritis, post-hepatic neuralgia, herpes zoster ophthalmicus, delayed contralateral hemiparesis, peripheral motor neuropathy, cerebral angiitis, Reye syndrome and facial paralysis. Here we present a case of ATM, following varicella infection in an adult patient.

Mrs. M, 45 year old female, developed fever followed by vesicular rashes over the body. The rashes were present in different stages of development. A clinical diagnosis of varicella was made. The patient did not receive any specific anti-viral treatment and the lesions healed on their own with scab formation and fever subsided. Five days following this, she developed acute onset urinary retention and was catheterized for the same. Later she developed constipation & numbness of both lower limbs with inability to move them. Over next 24 hours the numbness progressed to the level of upper chest. There was no weakness in upper limbs and no difficulty in breathing. Weakness and numbness didn’t progress any further.

On Examination Vitals were stable. Healed rashes with scabs were present on trunk, arms and legs. On neurological examination, hypotonia was present in bilateral lower limbs. Power was 0/5 in lower limbs at ankle, knee and hip joints. Knee jerk and ankle jerk were absent bilaterally. Abdominal reflex was absent and bilateral plantar were mute. Bilateral upper limbs were normal on examination. Touch, temperature, vibration and proprioception were absent below third dorsal spinal level. Examination of other systems was normal. A clinical diagnosis of post varicella acute transverse myelitis was made.

On investigating her hemogram, KFTs, LFTs, urine (R&M), Chest Xray PAV, ECG were all within normal limits. HIV serology was negative. In CSF: leukocyte count -were 5 cells/mm3; 80% lymphocytes, 20% polymorphs, protein- 231 mg/dl, sugar- 47mg/dl, ADA - negative (ADA =2 IU/l; normal <5). MRI dorsal spine with lumbosacral screening showed spinal cord from D5 to D7 vertebral levels appears bulky in size and hyperintense T2/STIR image. On T1WI it appears iso-intense to remaining spinal cord suggestive of acute transverse myelitis. Serum VZV IgM ELISA - positive 1:256 (cut-off: <1:32 negative; 1:32-1:64 equivocal; 1:128 or higher positive).

The patient was treated with IV methylprednisolone 1 g daily for 5 days, following which oral prednisolone 1 mg/kg for a total of 2 weeks was given, with taper over next 4 weeks. However, the weakness did not improve after 1 week of therapy. So, patient was discharged with urinary catheter in situ, with instructions regarding regular physiotherapy and catheter care. In follow up, patient partially regained sensation to touch and temperature 1 month after the acute episode. Following this, she had gradual improvement in lower limb power such that at 3 months she was able to sit in a wheel chair with support. Power at that time was 3/5 in lower limbs.

The frequency of transverse myelitis during or after Varicella infection is 0.3%.2 The pathogenic bases for neurological complications has been postulated as either direct viral invasion or through an immune-mediated allergic mechanism. The interval between chicken pox and ATM is variable. According to a report, it can occur with the rash or may be delayed for up to 2 weeks.1

No diagnostic test is completely accurate, since VZV cannot usually be isolated from blood or cerebrospinal fluid (CSF) in VZV myelitis and thus the diagnosis remains essentially clinical. There are no established treatment regimens for transverse myelitis following VZV infection. Treatment of ATM is with corticosteroids, and methylprednisolone intravenous has been found to be effective in one study. The use of acyclovir in the literature

References

is not clear, however, in some case reports they have administered 10 mg/kg/dose every 8 hourly for 10 days and revealed it as useful medicine when used in combination with methylprednisolone. Early diagnosis and early start of therapy is useful in preventing prolonged neurological sequelae.

**References**


**New Onset Diabetes Mellitus in Dengue Shock Syndrome**

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Sir,

Dengue fever is a mosquito-borne tropical disease and the most common arboviral illness in humans. Worldwide around 2.5-3 billion people live in 112 countries that experience dengue transmission. Estimates suggest that number of people infected range from 50 to 528 million per year, resulting in approximately 0.5 million hospitalizations.¹ ² Dengue hemorrhagic fever (DHF) is an endemic disease in India.² Four serotypes of dengue virus were documented till now which are DEN-1, DEN-2, DEN-3 and DEN-4.² Various common complications include encephalitis, myocarditis, acute motor weakness, Guillain-Barre like syndrome, acute liver failure, lupus erythematosus, haemophagocytic syndrome, acute kidney injury etc.

Two patients aged 30 years and 39 years were admitted in intensive care unit with history of fever and shortness of breath. No history of alcoholism was found. Patients were diagnosed with dengue fever as the NS1 antigen and dengue IgM antibody was positive. RT-PCR for dengue (reverse transcriptase-polymerase chain reaction) was positive in both patients. Echocardiography was normal. Ultrasound abdomen revealed bulky and hypoechoic pancreas indicative of pancreatitis, fatty liver and ascites.

Computerized tomography of abdomen revealed diffusely enlarged pancreas with scattered non enhancing areas suggestive of necrosis, extensive peripancreatic fat stranding, moderate ascites and bilateral pleural effusion. On admission random blood sugars were high (>200 mg/dl) in both patients without any history of diabetes mellitus. Glycosylated hemoglobin levels were 5.1 and 5 for both patients. Patient were diagnosed as severe dengue hemorrhagic fever with acute pancreatitis, new onset diabetes mellitus, acute kidney injury, and decompensated shock. Patient were discharged after repeat ultrasound abdomen showing reduction of pancreatitis and ascites.

Infection with one dengue serotype results in lifelong homotypic immunity and a very brief period of partial heterotypic immunity, but an individual can be infected by all 4 serotypes separately. Infection of target cells in reticuloendothelial system, such as dendritic cells, hepatocytes, and endothelial cells occur. The four cardinal features of dengue hemorrhagic fever (DHF) are increased vascular permeability, fever, hemorrhage, and marked thrombocytopenia (100,000 cells/mm³ or lower). Dengue shock syndrome (DSS) is usually characterized by a rapid, weak pulse with narrowing of the pulse pressure (<20 mmHg (2.7 kPa), regardless of pressure levels, e.g. 100/90 mmHg (13.3/12.0 kPa)) or hypotension with cold, clammy skin and restlessness.

Acute pancreatitis diagnosis was based on clinical features, history of epigastric pain, fever, abdominal tenderness, enlargement of the pancreas on ultrasound examination and CT abdomen with normal hepatobiliary function, increased serum amylase and lipase 3 times above normal. One series regarding DHF outbreak in Taiwan (2002) reported pancreatitis (defined by a lipase level 3-fold greater) in three patients with acute DHF and few other reports from other asian countries.³ Acute pancreatitis causing diabetes mellitus is a very rare manifestation of dengue.⁴ The exact mechanism of pancreatitis is not clear and was thought to be multifactorial.

Several hypotheses were proposed include direct inflammation, destruction of pancreatic acinar cells; autoimmune response to pancreatic islet cells with viral infection as a trigger, similarity between viral and islet cells antigens inducing autoimmune response, edema of the ampulla of vater causing obstruction to the outflow of pancreatic fluid. Aspartate aminotransferase (AST) levels are usually higher than alanine aminotransferase levels, possibly due to coexisting myositis and release of AST from injured muscle cells.

Serotypes 3 and 4 are associated with greater aminotransferase elevation. Liver biopsies in patients with DHF showed microvesicular steatosis, centrilobular focal necrosis, acidophilic bodies, kupffer cell hyperplasia, and mononuclear portal tract inflammation. Kidney injury might be due to glomerular injury caused by direct invasion of virus and deposition of immune complex in glomeruli. Dengue virus causing deposition of antigen-antibody complex in langerhan’s cells has been found. This complication of pancreatitis and new onset diabetes is under-reported and lack of awareness may prove fatal to a patient in dengue shock syndrome (DSS).

**References**


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