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Subscription Information

Journal of The Association of Physicians of India is published monthly. The annual subscription is ₹ 10,000 (India) and US $ 500 (other countries). The Journal is dispatched within India by surface mail and to other countries by sea mail.

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Enquiries concerning subscription, advertisement, etc. should be addressed to Prof. Milind Y. Nadkar, Editor-in-Chief, JAPI, No. 006 & 007, Turf Estate, Dr. E. Moses Road, Opp. Shakti Mill Compound, Mahalaxmi (West), Mumbai-400 011. Tel.: (022) 66663224, 24912218 Tel./Fax: 2492 0263 E-mail: onlinejapi@gmail.com / api.hdo@gmail.com

Printed, Published and Edited by Prof. Milind Y. Nadkar, on behalf of The Association of Physicians of India, Journal of The Association of Physicians of India, Turf Estate, Unit No. 006 & 007, Opp. Shakti Mill Compound, Off Dr. E. Moses Road, Near Mahalaxmi Railway Station (West), Mumbai-400 011. Editor-in-Chief: Prof. Milind Y. Nadkar.

Advertorial Enquiry:

Prof. Milind Y. Nadkar, Editor-in-Chief, JAPI, No. 006 & 007, Turf Estate, Dr. E. Moses Road, Opp. Shakti Mill Compound, Mahalaxmi (West), Mumbai-400 011. Tel. : (022) 6666 3224 / 2491 2218 Mobile : 77381 85750 E-mail: onlinejapi@gmail.com / api.hdo@gmail.com

Printed at Shree Abhyudaya Printers, A2/210, Shah & Nahar Industrial Estate, Lower Parel (West), Mumbai 400 013. Tel.: (022) 2494 5863 • urvi@urvi.cc

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Acute Kidney Injury - A Hidden Tsunami. Are we prepared for it?

Narinder Pal Singh¹, Anish Kumar Gupta², Gurleen Kaur³

Acute Kidney Injury (AKI) is characterized by the sudden impairment of kidney function resulting in retention of nitrogenous and other waste products normally cleared by the kidney. AKI carries not only high mortality but also is now recognized as an important risk factor for non-recovery of kidney function, increasing incident chronic kidney disease (CKD), and progression to end-stage renal disease (ESRD), leading to, disability, high long-term costs and poor quality of life.¹ Patients with AKI have about nine times higher risk of CKD and two-times higher risk of premature death.² The process of AKI can be divided into various reversible stages depending on the severity of insult, starting from the increased risk to damage followed by a decrease in glomerular filtration rate (GFR) further progressing to kidney failure and death. Efficiency of the preventive measures will depend on the recognition of the population at risk and on the means to diagnose ‘damage’ to the kidney before the fall in GFR occurs (Figure 1).³

AKI complicates 5-7% of acute care hospital admissions and up to 30% of admissions to the ICU, particularly in the setting of diarrheal illness, infectious diseases like malaria, and natural disasters like earthquakes. The in-hospital mortality rate for AKI has been reported at 24% and increases with in-hospital mortality rate for AKI has been reported at 24% and increases with severity of insult, starting from the increased risk to damage followed by a decrease in glomerular filtration rate (GFR) further progressing to kidney failure and death. Efficiency of the preventive measures will depend on the recognition of the population at risk and on the means to diagnose ‘damage’ to the kidney before the fall in GFR occurs (Figure 1).³

We participated in the multinational cross-sectional study (Zero by 25 Global Snapshot) conducted by the International Society of Nephrology in 2014.⁴ The study conducted across 72 countries involving 320 participating centres, concluded that nearly 65 percent of AKI cases were community acquired, rather than developing in the hospital setting. Recently plethora of studies has been published from India on AKI epidemiology. Among these studies, incidence of AKI is varying from 0.8% to 38% (0.8% in Himachal Pradesh⁵ to 0.83% in Karnataka⁶ to 33% in Delhi⁷ to 37.7% in Maharashtra⁸). In India, AKI is more prevalent in hospitalized adults and leads to significant in-hospital mortality. AKI is largely a CA-AKI. A study from Himachal Pradesh found AKI incidence to be eight per 1000 admissions of which about 92.2% had CA-AKI (AKI was stratify as per KDIGO criteria). Sepsis and CKD were seen to be the leading aetiologies with low mortality (8.7%).⁹ In another study from South India, Puducherry, result demonstrated that about 53.38% patients had CA-AKI (AKI was stratify as per KDIGO criteria). The predominant etiologies for AKI were sepsis (22%), trauma due to road traffic accidents (21%), acute abdomen (18.6%), and cardiac diseases (10%) with overall high mortality of 52.54%.¹¹ Similarly in a retrospective observational study of 73,318 South Indian patients from Karnataka, prevalence of AKI was found to be 8.36 per 1000 persons people and CA-AKI accounted for 35%. CKD and sepsis were the major aetiologies.¹² Rakesh Bhadade et al. (2016)¹⁰ established the incidence of AKI using the KDIGO criteria. Incidence of AKI in ICU was 37.71% and the mortality was 51.9%. Tropical acute febrile illnesses (malaria and lung infection) are the most common cause of AKI in ICU. Recently we studied population of Delhi NCR and results demonstrated that more than half (55%) of AKI patients were having CA-AKI. Anemia and sepsis were the most prevalent risk factors and overall mortality was 28%, highest in stage III AKI.

Acute Dialysis Quality Initiative (ADQI) group published their consensus definition and staging of AKI in adults (RIFLE criteria, 2004).¹² They defined three levels of AKI severity (Risk, Injury, Failure) based on changes in Scr, eGFR or urine output designed to maximise sensitivity, and two levels of outcome (Loss and ESRD) designed to maximise specificity. In 2007 the AKI Network (AKIN), published their AKI definition for

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¹Medical and Senior Director, Medicine, ²Scientist D (ICMR), Department of Medicine, Max Super Speciality Hospital, Ghaziabad, Uttar Pradesh; ³Department of Nephrology, Emory University Atlanta, Georgia, US

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**Fig. 1: A conceptual framework of acute kidney injury (source KDIGO⁵, 2012)**
adults which was an evolution of the RIFLE definition. It has been recognised that RIFLE and AKIN classify patients with AKI differently and that both classifications have their limitations. The recent International Kidney Disease: Improving Global Outcomes (KDIGO) guidelines proposed a merger of RIFLE and AKIN, with some simplification (Table 1). The main difference from previous definitions is the criterion for AKI stage 3 attributed to an acute absolute decrease in eGFR (≥35 ml/min/1.73m²) or the rise from baseline within 7 days of eGFR decrease by ≥75% or ≥200 Cr rise from baseline within 7 days (≥3.00 × baseline) or Cr rise to ≥4.0 mg/dL with acute rise of ≥0.5 mg/dL or Cr rise from baseline within 7 days at ≥3.00 × baseline or any requirement for renal replacement therapy for renal replacement therapy, adjusted to a prior blood test or presumed (based on the patient history) to have occurred within 7 days.

Table 1: Staging of acute kidney injury – comparing RIFLE, pRIFLE, AKIN and KDIGO

<table>
<thead>
<tr>
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</thead>
<tbody>
<tr>
<td>RIFLE Risk (R) or AKIN/KDIGO stage 1</td>
<td>eGFR decrease by ≥ 25% or 50 - 99% Cr rise from baseline within 7 days (1.50 - 1.99 × baseline)</td>
<td>Rise of ≥ 26 µmol/L within 48h or 50 - 99% Cr rise from baseline within 7 days (1.50 - 1.99 × baseline)</td>
<td>Rise of ≥ 26 µmol/L within 48h or 50 - 99% Cr rise from baseline within 7 days (1.50 - 1.99 × baseline)</td>
<td>&lt; 0.5 mL/kg/h for more than 6h (8h for pRIFLE)</td>
</tr>
<tr>
<td>RIFLE Injury (I) or AKIN/KDIGO stage 2</td>
<td>eGFR decrease by ≥ 50% or 100 - 199% Cr rise from baseline within 7 days (2.00 - 2.99 × baseline)</td>
<td>100 - 199% Cr rise from baseline within 7 days (2.00 - 2.99 × baseline)</td>
<td>100 - 199% Cr rise from baseline within 7 days (2.00 - 2.99 × baseline)</td>
<td>&lt; 0.5 mL/kg/h for more than 12h (16h for pRIFLE)</td>
</tr>
<tr>
<td>RIFLE Failure (F) or AKIN/KDIGO stage 3</td>
<td>eGFR decrease by ≥ 75% or ≥200 Cr rise from baseline within 7 days (≥ 3.00 × baseline)</td>
<td>≥ 200% Cr rise from baseline within 7 days (≥ 3.00 × baseline)</td>
<td>≥ 200% Cr rise from baseline within 7 days (≥ 3.00 × baseline)</td>
<td>&lt; 0.3 mL/kg/h for 24h or anuria for 12h</td>
</tr>
</tbody>
</table>

Table 2: Causes of Acute Kidney Injury (Source KDIGO; 2012)

<table>
<thead>
<tr>
<th>Exposures</th>
<th>Susceptibilities</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sepsis</td>
<td>Dehydration and volume depletion</td>
</tr>
<tr>
<td>Critical illness</td>
<td>Advanced age</td>
</tr>
<tr>
<td>Circulatory shock</td>
<td>Female gender</td>
</tr>
<tr>
<td>Burns</td>
<td>Black race</td>
</tr>
<tr>
<td>Trauma</td>
<td>Chronic Kidney Disease</td>
</tr>
<tr>
<td>Cardiac surgery (especially with cardiopulmonary bypass)</td>
<td>Chronic disease (heart, lung, liver)</td>
</tr>
<tr>
<td>Major noncardiac surgery</td>
<td>Diabetes</td>
</tr>
<tr>
<td>Nephrotoxic drugs (e.g.aminoglycosides, amphotericin, immunosuppressive agents, NSAIDs, ACEs and/or ARBs)</td>
<td>Cancer</td>
</tr>
<tr>
<td>Radiocontrast agents</td>
<td>Anemia</td>
</tr>
<tr>
<td>Poisonous plants and animals</td>
<td></td>
</tr>
</tbody>
</table>

There are many types of exposure that may cause AKI. However, the chance of developing AKI after exposure to the same insult depends on a number of susceptibility factors that vary widely from individual to individual. A knowledge of risk factors and susceptibilities is sufficient to identify patients at risk of developing AKI. Sepsis, critical illness, circulatory shock, burns, trauma, cardiac surgery, major non cardiac surgery, nephrotoxins, radiocontrast agents, poisonous plants are the main exposure factors that may cause AKI. Dehydration or volume depletion, advanced age, female gender, black race, CKD, chronic diseases, Diabetes mellitus, cancer and anemia are susceptibility factors for development of AKI (Table 1). Zero by 25 Global Snapshot study concluded that the most common cause of AKI in the high and middle income countries was sepsis and hypotension, while in low income countries dehydration still remains the most common cause of AKI. However, over the last few decades, not only the terminology of AKI (earlier acute renal failure) has changed, but also the epidemiology of AKI has evolved. In developing countries, some causes (such as diarrhea and septic abortion) are becoming less prevalent while other causes (like sepsis, nephrotoxic drugs, contrast use, HIV infection and use of antiretroviral drugs) are contributing more and more to the common etiologies of AKI. It is important to screen patients who have undergone an exposure and to continue monitoring high risk patients until the risk has subsided.

BUN and creatinine are functional biomarkers of glomerular filtration rather than tissue injury biomarkers, an increase in the creatinine level lags behind renal injury by as much as 12 hours to 2 days, therefore, may be suboptimal for the diagnosis of actual parenchymal kidney damage. Use of creatinine as a marker for renal function has additional limitations. Patient’s age, sex, dietary intake, and muscle mass all influence the baseline level of creatinine. In patients with early AKI (Figure 1), several biomarkers of AKI, including kidney injury molecule-1 (KIM-1), neutrophil gelatinase-associated lipocatin (NGAL), urinary IL-18, tissue inhibitor of metalloproteinases (TIMP-2) and IGF-binding protein-7 (IGFBP-7) have been investigated and show promise for accurate diagnosis of AKI. A number of other biomarkers are under investigation for early and accurate identification of AKI and for risk stratification to identify individuals at increased risk. Recently it has been demonstrated that the 2-hour urine output after a standardized high-dose furosemide stress test (FST, 1mg/kg of furosemide in naive patients or 1.5 mg/kg in those with prior exposure) in clinically euvoletic patients with early AKI serves as a novel assessment of tubular function with robust predictive capacity to identify those with severe and progressive AKI. Future studies to validate these findings are warranted.

Primary prevention of AKI in the ICU is limited to those conditions in which the timing of injury is predictable, such as exposure to radiocontrast dye, cardiopulmonary bypass, large-volume paracentesis in a cirrhotic patient, or chemotherapy. In contrast to most cases of community-acquired AKI,
getting admitted to the medical wards had AKI, similar to 6.1% and 6.2% of the 31-45 years age group and 45-60 years age groups, but the figure was one and a half times higher (9.03%) in the age group above 60 years. Among commonest disease aetiologies, significant risk of developing AKI was observed for chronic liver disease, acute gastroenteritis and pneumonia. Hypotension, leucocytosis, history of smoking or alcohol were commonest associated risk factors for development of AKI. No relation to age, gender, body mass index, hypertension, hypertriglyceridemia or hypercholesterolemia was observed. 41.05% patient’s serum creatinine normalized within 4 weeks while 50.7% patients of AKI had died during the same period. Mortality was associated with chronic liver disease, COPD, CHF, complicated UTI, pneumonia, hypertension, diabetes. However, AKI related to malaria and acute gastroenteritis did not have any mortality, which showed that if adequate hydration, antimicrobial therapy and supportive management is provided in these diseases, AKI is reversible. There are some limitations of this study. This study was a single centre study focusing only on CA-AKI with limited sample size. In the study RIFLE classification was use to categorise AKI. Since KDIGO guidelines are followed for risk stratification of AKI. Recently published studies demonstrated the incidence of AKI according to KDIGO definition.10,11 In addition to this the results of the present study cannot be extrapolated worldwide as causes for AKI development are restricted to tropical nations.

References

Profile of Community-Acquired Acute Kidney Injury Defined Using RIFLE Criteria Among Medical In-Patients: A Prospective Descriptive Single Centre Study

Sahil Bagai¹, Anupam Prakash²*, Aparna Agrawal³

Abstract

Aim: To determine the proportion of patients who have Acute Kidney Injury (AKI), identify severity of AKI using RIFLE criteria and to identify associated factors with AKI.

Methods: One thousand consecutive medical in-patients were screened for AKI and severity assessed using RIFLE criteria in tertiary care hospital in Northern India. Patients with medical renal disease and obstructive uropathy were excluded. Serum creatinine of all patients were done on days 0, 3, 7 and 14. CKD cases were also excluded. AKI patients were followed at 4 weeks and 3 months.

Results: Amongst 1000 patients screened, 65 had AKI. 27(41.5%), 15(23.0%) and 23(35.38%) patients belonged to risk, injury and failure classes of AKI respectively as per RIFLE criteria, and there was incremental risk of mortality (25.92%, 46.33% and 86.95%, p<0.001). In-patients with pneumonia, chronic liver disease and acute gastroenteritis have greater odds of developing AKI, with chronic liver disease having a high mortality (90%). Hypotension (OR- 5.5:1, p=0.002) or leucocytosis at presentation (OR-2.8:1, p<0.001), smokers (OR-2.2:1, p=0.03) and alcoholics (OR-2.5:1, p=0.047) had greater odds of developing AKI. 33(50.7%) patients with AKI died and 27(41.5%) recovered before day 28. Five (7.7%) were seen in class L who had persistently elevated creatinine at day 90 i.e. progressed to ESRD, class E.

Conclusion: The incidence of AKI among medical in-patients was 6.5%, with an incremental risk of mortality in risk, injury and failure classes. Pneumonia and acute gastroenteritis among infections and chronic liver disease have greater odds of developing AKI. Hypotension, leucocytosis, smoking, alcohol and aetiology are independent risk factors for AKI.

Introduction

Acute kidney injury (AKI) is a common clinical problem, defined by an abrupt (< 48 hours) increase in serum creatinine resulting from an injury that causes a functional or structural change in the kidney.¹ Epidemiological studies have demonstrated wide variations in the aetiologies and risk factors associated with AKI, especially in the tropical countries vis-à-vis countries in the temperate climes. The already high in-hospital mortality following AKI further worsens if dialysis is required. There is emerging recognition that even minor short-term changes in serum creatinine are associated with increased mortality;² other important consequences of AKI are progression of pre-existing CKD and even development of end-stage renal disease (ESRD).³ Diagnosis of renal disease is often missed or discovered too late, which contributes to the increased morbidity and mortality associated with renal diseases. Besides, patients of acute kidney injury, especially when they are diagnosed late, have a greater propensity to develop CKD.

In 2004, Acute Dialysis Quality Initiative (ADQI) proposed a classification system for AKI, known as RIFLE classification. Here (R stands for renal dysfunction, I for Injury to parenchyma, F for failure of organ, L for loss of organ and E for ESRD). The Risk, Injury, Failure, Loss of function and End stage (RIFLE) criteria unified the definition and classification of AKI.⁴ The RIFLE criteria provide a uniform definition of AKI and has now been validated in numerous studies.⁴

However, there is a dearth of studies from tropical countries including India outlining the profile of AKI and development of CKD. The causes of AKI in the tropics are peculiar and the few studies that have dealt with this issue are either retrospective in nature or are conducted at apex referral centres with dedicated nephrology set-ups. The present study aimed to determine the aetiological and clinical profile of AKI in medical in-patients and identify the sub-set of patients who go on to develop CKD.

Material and Methods

This was a Descriptive study conducted in a tertiary care centre in Northern India over a 12-month period. The study was approved by the Institutional Ethics Committee and subjects were included only after obtaining an informed consent. One thousand patients who got admitted to the medical units were enrolled and screened for presence of AKI using RIFLE criteria and staged accordingly. Patients with cystic kidney disease, obstructive uropathy and known CKD were excluded.

Demographic profile was noted, a detailed history and clinical examination was conducted for all patients. A
standard set of investigations including complete blood counts, liver function tests, serum creatinine, urea and electrolytes were done for all. Serum creatinine values were used alone to stage a patient as per RIFLE criteria.

**Staging Criteria**

A pilot study was done on 80 consecutive subjects reporting to medical out-patient for routine health check-up or medical examination. Maximum serum creatinine value observed in these subjects was 1.1 mg/dL and hence, 1.65 mg/dL (1.5 times*1.1 mg/dL) was taken as cut-off for a patient to be classified as AKI according to RIFLE criteria. Groups B, C and D constituted AKI group.

Serum creatinine at admission was taken to classify patients according to RIFLE criteria into 4 groups-

a. **Group A** (non-AKI group) - Included people with serum creatinine <1.65mg/dL

b. **Group B** - At risk (serum creatinine values between 1.65-2.2mg/dL) i.e. serum creatinine became 1.5 times of baseline (R of RIFLE).

c. **Group C** - Renal injury (serum creatinine values between 2.2-3.3mg/dL) i.e. serum creatinine became more than double (I of RIFLE).

d. **Group D** - Renal failure (serum creatinine values ≥3.3mg/dL) i.e. serum creatinine became three times of the baseline (I of RIFLE).

Groups B, C and D together constituted the AKI study group.

In patients whose serum creatinine values were ≥ 1.65mg/dL on day of admission, creatinine was repeated on days 3, 7 and 14 and if variation was < 10% then patients were excluded as were considered to be having chronic kidney disease (CKD), which was undiagnosed and asymptomatic till this presentation.

AKI patients were followed up to look for recovery/progression. Also, the factors leading to AKI were ascertained. Follow-up was done at 4 weeks and 12 weeks of patients in groups B, C, D to look for L and E class of RIFLE Criteria

L – Loss of Renal Function (serum creatinine ≥ 1.65mg/dL for > 4 weeks).

E – End stage renal disease (serum creatinine ≥ 1.65mg/dL for > 3 months).

Various variables were outlined in the AKI vs Non-AKI groups and AKI survivors vs AKI non-survivors, and then compared.

Statistical analysis was done using SPSS software (SPSS version 19.0, Chicago, IL, USA). The comparison of various parameters between the AKI and the non-AKI groups was performed using unpaired t test. Fisher Exact Test statistic value was computed for calculated Odds Ratios. In evaluation of all results, a Confidence Interval of 95%, i.e. a p-value of <0.05 was considered as significant.

**Results**

**Demography**

One thousand patients were screened for AKI. Average age was 42.3±17.13 years, with 427 males and 573 females. Sixty five patients had AKI as per RIFLE criteria (M:F- 0.96:1). Patients in either group were divided into different age groups- 18-30, 31-45, 46-60 and > 60 years (Table 1). 5.8% patients in the 18-30 years age group got admitted to the medical wards had AKI, similar to 6.1% and 6.2% of the 31-45 years age group and 45-60 years age groups, but the figure was one and a half times higher (9.03%) in the above 60 years age group.

**Stages of AKI**

According to RIFLE criteria, 27(41.5%) were in Class 1 (At risk), 15 (23.0%) were in Class 2 (Injury), while 23(35.3%) were in Class 3 (Failure).

Mortality was least in At Risk group followed by Injury group and maximum in the Failure group (25.92%, 46.33% and 86.95% respectively, p<0.001).

**Aetiologies**

The commonest five disease aetiologies in the overall study group were Diabetes mellitus (9.1%), Hypertension (8.4%), chronic obstructive pulmonary disease (8%), central nervous system disorders (7.5%), and Malaria (6.8%). In the AKI group, pneumonia (21.05%), chronic liver disease (20%), acute gastroenteritis (15.1%), chronic heart failure (14%) and COPD (11.1%) dominated (Table 2).

Significant odds ratio of developing AKI was observed for the following diseases- (i) chronic liver disease (OR=4.1:1, p=0.001), (ii) acute gastroenteritis (OR=2.8:1, p=0.035) and (iii) pneumonia (OR=4.2:1, p=0.002).

**Associated factors**

Average age of AKI group was 45.6±16.8 years comparable to non-AKI group 42.1±17.1 years. Haemoglobin levels were lower in the AKI group (10.9±2.5 vs 10.2±2.7, p=0.02) while leucocyte counts were higher (9568.6±5133 vs. 13252.3±7791.1, p<0.001). Serum total bilirubin, transaminase levels, alkaline phosphatase levels and blood urea and serum creatinine levels were also higher in the AKI group. Liver functions were elevated because of a greater proportion of chronic liver disease patients in the AKI group, while kidney functions were elevated because of the inherent nature of the AKI group. Rest of the parameters viz. plasma sugar and serum lipids were comparable between the two groups.

There was a significantly high odds of patients developing AKI, if
they had hypotension at presentation (OR- 5.5:1, p=0.002), leucocytosis at presentation (OR-2.8:1, p=0.001), were smokers (OR-2.2:1, p=0.03) or alcoholics (OR-2.5:1, p=0.047). No relation to age, gender, body mass index, hypertension, hypertriglyceridemia or hypercholesterolemia was observed.

Mortality

The mortality among the AKI patients was 50.7% (n=33). 90% of chronic liver disease patients who developed AKI died; two-thirds of COPD and CHF patients died. 60% of complicated UTI with AKI died. Mortality was 50% among patients who had pneumonia or hypertension or diabetes, and developed AKI. However, AKI related to malaria and acute gastroenteritis did not have any mortality in the present study. AKI associated with Dengue, amoebic liver abscess and enteric fever, in the present study, was associated with full recovery of renal function.

The mean serum bilirubin and alkaline phosphatase levels analyzed in the AKI group excluding CLD cases significantly dropped from 3.64±5.18 to 2.11±3.65 and 244.70±264.07 to 225.66±295.83, respectively and the result was not significantly associated with mortality. This could be attributed to the high predominance of cases of CLD in the AKI mortality group.

AKI follow-up

Patients enrolled in AKI group were followed up at day 28. Out of total 65 patients in AKI group, 33 patients had followed up at day 28. Out of total 65 patients in AKI group excluding CLD cases of renal function.

Discussion

Community-acquired AKI encompasses medical causes, surgical or obstructive AKI causes and obstetric AKI. The present study has focussed only on medical causes of AKI, since the aetiological factors and management principles that govern obstructive/ post-surgical AKI and obstetric AKI are entirely different from medical causes of AKI. The profile of medical causes of AKI in the tropics also differs from the AKI profile in other geographical areas, with infections and dehydration predominating in the tropics. There have been very few studies on profile of AKI since the RIFLE criteria were enunciated, and to the best of our knowledge, no study actually tried to follow these cases for residual kidney dysfunction (Stage L and E of RIFLE classification). The studies on profile of AKI have been far and few with some limitations viz. retrospective nature of studies; profiling medical, surgical and obstetric causes of AKI together; studying only a subset of causes of medical AKI such as profiling only fever cases; and being conducted in nephrology set-ups only. The present study obviated all these limitations.

Demography

In the present study, average age of AKI group was 45.63±16.83 years with an almost equal gender distribution (0.96:1). This was similar to other studies in the region, with average age in AKI patients reported from Himachal Pradesh (hill state in northern part of India) as 48.96±18.3 years, 3 39.7±16.9 years from CMC, Vellore (southern part of India), 4 and 39.8 ± 14.48 years from SGPGI, Lucknow, India. 5 However, gender distribution was 1:1.5 in CMC Vellore (southern part of India) where only febrile causes of AKI were studied, and 1:1 in a study from Bokaro, Jharkhand (eastern part of India). 6

AKI is known to complicate 5-7% of hospital admissions, and up to 30% of admissions in critical care units. 8 The prevalence of AKI was 6.5% in the present study. A study in U.K. showed AKI prevalence around 4.6%. 9 However, an Indian study done in Himachal Pradesh reported an AKI prevalence of only 0.53% where 84.3% patients developed community-acquired AKI and 15.7% had hospital-acquired AKI. A retrospective study from SGPGI, Lucknow reported 2.5% prevalence of community-acquired AKI. 10 In one study 603 patients admitted in ICU were evaluated and 161 (26.7%) developed AKI. 11 However, as earlier stated, these studies do not accurately depict community-acquired AKI, as these have been carried out in nephrology set-ups which by-and-large receive referred cases.

Staging of AKI

Patients in AKI group were staged using RIFLE criteria. In the present study, patients in R, I and F stage of RIFLE were 27 (41.50%), 15 (23%) and 23 (35.38%). This was comparable to CMC, Vellore study 6 where total AKI incidence was 41.1% (R= 17.4%, I=9.3%, F=14.4%). A study conducted in Seoul, Korea 12 reported hospital-acquired AKI in 1.2% patients with 29.2% in stage R, 36.5% were in stage I and 34.4% were in stage F. The studies exclusively carried out in intensive care unit patients had AKI prevalence and RIFLE staging different from our study, which may be due to the critical illness setting. In a tertiary care setup in USA, AKI occurred in 67% of intensive care unit admissions with class R, class I and class F in 12%, 27% and 28% with incremental mortality rates. 12

Aetiological distribution

The causes of AKI vary in accordance with the geographical area. The causes of AKI in tropics are different than in the western world. 13 Febrile illness and infections predominate as the cause of AKI in the tropics. 14 In the present study, AKI group had Pneumonia (21.05%), CLD (20%), acute gastroenteritis (15.1%), CHF (14%) and COPD (11.1%) as the commonest causes. One study reported that 18% of pneumonia patients developed AKI. 15 Twenty percent of all CLD patients in the present study developed AKI which is comparable to data in another study. 16 In a study from Canada, 82 episodes of AKI occurred in 49 patients of cirrhosis with 9 patients showing no recovery. 17 The most common causes of AKI in cirrhosis are pre-renal azotemia, hepatorenal syndrome and acute tubular necrosis. In a Nepalese study, out of 45 AKI patients, 10 (22%) had acute gastroenteritis, 18 while in the present study out of 65 AKI patients, only 6 had acute gastroenteritis.

Association of clinico-biochemical parameters with AKI and non-AKI groups

There is a distinct lack of studies which have compared various clinico-biochemical parameters in between the AKI and non-AKI subjects. Proportion of
subjects having Hypertension, diabetes mellitus, COPD, CHF and infections like malaria, Dengue, enteric fever and complicated UTI were statistically similar in the AKI group and the non-AKI group, without any increased odds of patients getting admitted with these diagnoses developing AKI in the present study. However, hypertension did seem to correlate with greater extent of residual renal dysfunction, with three out of five patients who reached ‘L’ RIFLE stage having hypertension. Infections do stand out as an important cause of AKI in tropics, as evidenced from Table 2 wherein 36 out of the 70 enlisted causes are infectious aetiologies. However, only pneumonia and acute gastroenteritis had greater odds of developing AKI, vis-à-vis other infectious aetiologies. The high prevalence of chronic liver disease could be the only potential bias, because of the proximity of the New Delhi railway station, around which area many addicts do reside.

There is a usual impression obtained from studies from the tropics that infections stand out as an important cause of AKI, however it is noteworthy that the other studies in the region were primarily having nephrology set-ups, wherein patients requiring nephrology services are likely to seek referrals. The present study was conducted in a general hospital, situated in the heart of the city, with easy access to the general public, and is more representative of the community scenario.

In the present study, hypotension (systolic blood pressure <90mm Hg) and leucocytosis, both were associated with greater chances of developing AKI. Volume depletion was found to be an important cause of AKI in an Indian study, and leucocytosis in a Canadian study. Sepsis, in India, has been reported to be an important cause of AKI, which can also partly explain the relation of leucocytosis with AKI in the present study. Relation of glycaemia and BMI with AKI has been reported, although not obvious in the present study.

Smoking causes an increase in renovascular resistance leading to a decrease in glomerular filtration rate (GFR), and is a known risk factor for chronic kidney disease. However, there are no studies showing direct correlation of smoking with AKI, although smoking as well as alcohol were significant associates of AKI patients in the present study. The latter association could be spurious since chronic liver disease was significantly associated with development of AKI, and many of the chronic liver disease cases were alcohol-related.

In the present study, lower hemoglobin was observed in AKI subjects as compared to non-AKI subjects. This was in line with a previous study. In the present study significant correlation was seen between occurrence of AKI and serum bilirubin. This is in accordance with a previous study where the toxic effects of bilirubin and bile salts have been established with renal dysfunction.

**Correlates of AKI mortality**

The mortality among the AKI patients was 50.7% (n=33), and 90% of chronic liver disease subjects who developed AKI died. High rates of mortality (65.5%) have also been reported in Taiwan. Also in the present study, two-thirds of COPD, CHF and 50% of pneumonia patients died. Leucocytosis and hypotension were significantly higher among AKI non-survivors. This is in line with previous studies. In the present study high bilirubin levels and high alkaline phosphatase levels were associated with mortality in the AKI group.

In the present study, 41.05% patients’ serum creatinine normalized within 4 weeks while 50.7% patients of AKI had died during the same period. In accordance with RIFLE criteria 7 (25.92%) patients out of 27 in class ‘R’, 7 (46.33%) patients out of 15 in class ‘I’ and 20 (86.95%) patients out of 23 in class ‘F’ expired. This shows that higher stage in RIFLE criteria is associated with high mortality rates. This is consistent with previous studies. In Korea, a study reported high mortality patients in classes 3 AKI as compared to patients in classes 1 or 2.

Five patients progressed to stage ‘L’ of RIFLE criteria and also had persistently elevated serum creatinine at day 90, i.e. belonged to class ‘E’ of RIFLE criteria (ESRD). Also, there are no studies available where follow-up of patients has been done to look for sequel of acute kidney injury. Because of the small number of patients in ‘L’ and ‘E’ categories in the present study, it is not possible to comment on the correlates or associates of AKI which contribute to development of CKD or residual renal dysfunction (partial recovery).

The present study was unique in being a prospective study from developing country which highlights disease conditions which cause AKI and diseases which carry increased mortality. In diseases such as pneumonia and CLD timely intervention can prevent AKI. No deaths in AKI group was noted secondary to tropical fever and acute gastroenteritis which shows that if adequate hydration, antimicrobial therapy and supportive management is provided in these diseases, AKI is reversible. Study duration was over 1 year so seasonal bias was eliminated and a composite profile of diseases occurring throughout the year was reflected.

The present study was a single centre study so sample size was a limitation. Also, the AKI causes are dependent on the epidemiography of the area so the causes in tropical countries are different from other non-tropical countries; and hence, these results cannot be extrapolated to non-tropical countries.

**References**

11. Kwon SH, Noh H, Joon JS, Kim Y, Han DC. An assessment of
Etiopathological Study of Crescentic Glomerulonephritis and its Outcome: A Retrospective Analysis

Jai Prakash 1*, Prem Shankar Patel 2, Suraj Prakash 1, Mohd. Iqbal 2, Shiv Shankar Sharma 3, Shivendra Singh 4, Usha Singh 5

Abstract

Introduction: Crescentic Glomerulonephritis (CGN) is most aggressive structural phenotype and accounts for 2%-7% of renal biopsy in most series. The aim of study was to assess the clinical feature and outcome of CGN at our centre.

Material and Methods: The renal biopsy performed during the period of January 2015 to January 2018 was studied and patients showing crescentic glomerulonephritis on histology were selected for this study. The clinical presentation, immunological assay, biochemical and haematological investigations, treatment protocol and final outcome at three month of these patients were analysed in the present study.

Results: Of 380 biopsy, 26 (male=17, female=9) patients had histological evidence of CGN (6.8%). The age of patients ranged between 13-75 (mean=43) years. Fibro cellular and cellular crescent was noted in 84.61% and 15.38% of patients respectively. Small vessels vasculitis and granuloma was observed in 5 (19.23%) patients. Fibro cellular and cellular crescent was noted in 84.61% and 15.38% of patients respectively.

Conclusion: Type II (immune complex) CGN was most common type followed by type V (immune negative) and type III (pauci-immune) CGN. The crescentic GN had worse prognosis with >80% of patients progressed to ESRD within 3 month of time from onset of illness. Early diagnosis and treatment is associated with favourable outcome.

Introduction

The WHO definition for glomerular crescents is “two or more layers of proliferating cells between the visceral and parietal epithelial epithelial cells that are partially or completely filling the Bowman’s space”. While occasional crescents may be seen in various renal diseases, the presence of crescents in more than 50% of the glomeruli defines “Crescentic glomerulonephritis” as per WHO recommendations. 1,2 Active crescents tend to be cellular and consist of a mixture of inflammatory cells (leukocyte), intrinsic epithelial epithelial cells of the Bowman’s capsule, extracellular matrix, and few fibroblasts. Over time, the cellular crescents develop into fibro cellular and fibrous crescent. The initiating event is the development of physical gaps (also called rents or holes) in the glomerular basement membrane and Bowman’s capsule. Clinical hallmark of CGN is rapidly progressive glomerulonephritis (RPGN). RPGN refer to clinical syndrome characterised by rapid and progressive loss of renal function over hours and days, often accompanied by oliguria or anuria and features of acute glomerulonephritis including dysmorphic erythrocyturia, and glomerular proteinuria. 1 Crescentic Glomerulonephritis (CGN) is most aggressive structural phenotype and

accounts for 2%-7% of renal biopsy in most series and a smaller proportion of all patients with end stage renal disease.3-5 There is significant heterogeneity in the aetiology and outcome of CGN6-8 with limited data from India.7,10 The clinical feature and histopathological spectrum of CGN was reported in paediatric patient from India.9,10 However, data in adult patients are scarce. This study aims to identify aetiology and assess the clinical feature, histomorphology and outcome of CGN at our centre.

Material and Methods

This retrospective observational study was conducted in the department of nephrology, Institute of Medical Sciences, Banaras Hindu University, Varanasi, India from January 2015 to January 2018. Twenty six biopsy proven crescentic glomerulonephritis patients with variable presentation were included in this study. Crescentic glomerulonephritis was defined by crescent formation over 50% sampled glomeruli.

The patient’s detail clinical history and physical examination record were retrieved and analysed. The laboratory investigations including Complete Haemogram, ESR, Renal function test, Liver function test, Lipid profile and immunological assay (RA factor, C3, C4, ANA, Anti ds DNA antibody, PR3 ANCA, MPO ANCA and Anti GBM Ab). The result of urinalysis was noted if available. Renal biopsy sample was preserved in 10% buffered aqueous formaldehyde solution for light microscopy. Sample were studied under light microscopy using Haematoxylin and eosin stain, Periodic acid-Schiff stain, Acid fuchsin Orange G and Periodic acid Silver Methanamine stain. Electron microscopy and Immunofluorescence studied were not done due to lack facility at this centre. Renal biopsy were examined in detail for total number of glomeruli, number of completely sclerosed glomeruli, percentage of glomeruli with crescent formation, features of vasculitis, and extent of interstitial fibrosis and tubular atrophy. Crescentic glomerulonephritis are classified based on immunohistological features into following five groups type I, II, III, IV, and type V.11 Records of treatment and immunosuppressant used were collected. Total numbers of patients requiring haemodialysis at the time of hospitalisation were noted. Renal function test, Urine microscopy, Complete Blood Count and requirement of haemodialysis assessment were done monthly, till their last follow up. Outcome assessments at three month were carried using improvement in renal function and progression to End Stage Renal Disease (ESRD).

Observation and Results

Of 380 biopsy, twenty six (Male=17, Female=9) patients with age range of 13 to 75 (Mean=43) years had histological evidence of crescentic glomerulonephritis (6.8%) and these patients were included in the study. Physical examination revealed Pallor (92.3%), Oedema (76.9%) and hypertension (69.2%). Anuria was noted in 18 (69.2%) of patients. Headache, convulsion and joints pain was present in one patient each (Table 2). Macroscopic hematuria was seen in 5 (19.23%) cases and remaining 18(69.2%) cases had microscopic hematuria. Haemoglobin concentration was less than 10 g% in all cases. RPGN was the mode of clinical presentation in all (100%) patients with uremic manifestation in 22 (84.6%). HIV, hepatitis B and C infection were negative in all cases. Immunological assay revealed low C3 in six (n=6), low C3andC4 in two (n=2) case. MPO and PR3 ANCA were positive in 3 female and 2 male patients respectively. Anti GBM Ab was noted in 3 cases (36.0-101.0 u/ml). Three patients had double positive (ANCA + Anti GBM Ab) (Table 3). Nine (34.6%) cases had crescent involving >75% glomeruli and remaining seventeen (65.3%) cases showed crescents in 50-75% of sampled glomeruli. Fibro cellular and cellular crescent was noted in 84.61% and 15.38% of patients respectively. Twenty cases (76.9%) had <50% and six cases (23.0%) had >50% completely sclerosed glomeruli. Diffuse and patchy chronic tubulointerstitial nephritis was noted in (n=17; 65.3%) and (n=9; 34.6%) of cases respectively. Features of vasculitis and granuloma formation were observed in 5 (19.23%) cases (Table 4). Based on histological finding and immunology, we observed type I (n=3), type II (n=8), type III (n=5), type IV (n=3), and type V (n=7) crescentic GN in 11.53%, 30.76%, 19.23%, 11.53% and 26.92% of patients respectively. Type II (Immune complex) crescentic GN was the commonest pattern on histology, followed by type V (Immune negative) and type III (Pauci immune) (Table 5). Haemodialysis was given to 22(84.61%) and 4(15.38) patients were treated with immunosuppressive therapy without Haemodialysis. Standard immunosuppressive (Cyclophosphamide + Corticosteroid) therapy was used depending upon the immunological category of RPGN. Plasmapheresis was given to 2 double positive (ANCA + Anti GBM Ab) patients. After 3 month follow up, only five patients had improvement

Table 1: Patients with RPGN not requiring dialysis and treated with only immunosuppressive therapy (n=5)

<table>
<thead>
<tr>
<th>Age/Sex</th>
<th>Type of CGN</th>
<th>Immunological assay</th>
<th>At presentation</th>
<th>At 3 Month</th>
</tr>
</thead>
<tbody>
<tr>
<td>68/M</td>
<td>Type II RPGN Low C3</td>
<td>SCr=3.6 Undialysed</td>
<td>SCr=2- dialysis independent</td>
<td></td>
</tr>
<tr>
<td>45/F</td>
<td>Type III RPGN MPO ANCA +ve</td>
<td>SCr=3.4, Undialysed</td>
<td>SCr=1.4, dialysis independent</td>
<td></td>
</tr>
<tr>
<td>46/M</td>
<td>Type IV RPGN PR3 ANCA and Anti GBM Ab +ve</td>
<td>SCr=6, Undialysed</td>
<td>SCr=2.8, dialysis independent</td>
<td></td>
</tr>
<tr>
<td>13/F</td>
<td>Type V RPGN Immune negative</td>
<td>SCr=3.2, Undialysed</td>
<td>SCr=1.2, dialysis independent</td>
<td></td>
</tr>
<tr>
<td>22/M</td>
<td>Type V RPGN Immune negative</td>
<td>SCr=5.9, Undialysed</td>
<td>SCr=2, dialysis independent</td>
<td></td>
</tr>
</tbody>
</table>

RFT: Renal Function Test, SCr: Serum Creatinine in mg/dl, CGN: Crescentic glomerulonephritis

Table 2: Clinical feature of patients with RPGN on admission (n=26)

<table>
<thead>
<tr>
<th>Test</th>
<th>Male</th>
<th>Female</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low C3</td>
<td>4</td>
<td>2</td>
<td>6</td>
</tr>
<tr>
<td>Low C3 and Low C4</td>
<td>2</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>MPO ANCA</td>
<td>0</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>PR3 ANCA</td>
<td>2</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Anti GBM AB</td>
<td>2</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>ANCA + Anti GBM AB</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Normal</td>
<td>6</td>
<td>1</td>
<td>7</td>
</tr>
</tbody>
</table>

Table 3: Immunological assay of patients with RPGN (n=26)

<table>
<thead>
<tr>
<th>Test</th>
<th>Male</th>
<th>Female</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>ANA</td>
<td>15</td>
<td>7</td>
<td>22</td>
</tr>
<tr>
<td>ESR</td>
<td>13</td>
<td>7</td>
<td>20</td>
</tr>
<tr>
<td>Oliguria/anuria</td>
<td>10</td>
<td>8</td>
<td>18</td>
</tr>
<tr>
<td>HTN</td>
<td>12</td>
<td>6</td>
<td>18</td>
</tr>
<tr>
<td>Macroscopic hematuria</td>
<td>5</td>
<td>3</td>
<td>8</td>
</tr>
<tr>
<td>Fever</td>
<td>3</td>
<td>4</td>
<td>7</td>
</tr>
<tr>
<td>Headache</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Convulsion</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Joint pain</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
</tbody>
</table>

Table 4: Patients with RPGN on admission (n=26)

<table>
<thead>
<tr>
<th>Clinical presentation</th>
<th>Male</th>
<th>Female</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uremic sym</td>
<td>15</td>
<td>7</td>
<td>22</td>
</tr>
<tr>
<td>Edema</td>
<td>13</td>
<td>7</td>
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<td>Oliguria/anuria</td>
<td>10</td>
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<td>HTN</td>
<td>12</td>
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<tr>
<td>Macroscopic hematuria</td>
<td>5</td>
<td>3</td>
<td>8</td>
</tr>
<tr>
<td>Fever</td>
<td>3</td>
<td>4</td>
<td>7</td>
</tr>
<tr>
<td>Headache</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Convulsion</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Joint pain</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
</tbody>
</table>
in renal function and become dialysis independent. These five patients were in Type II (n=1), Type III (n=1), Type IV (n=1) and Type V (n=2) RPGN category (Table 1). Remaining 21 (80.76%) patients showed no improvement in renal function. They were dialysis dependent and had progressed to ESRD over a period of 2-3 months.

Discussion

Crescentic glomerulonephritis (CGN) is an important pathologic correlate of rapidly progressive renal failure and it is most aggressive structural phenotype and accounts for 2%-7% of renal biopsy in various reported series and accounts for a smaller proportion of all patients with end stage renal disease (ESRD). In our study, it accounted for 6.8% of cases. The incidence of CGN varies with geographic location and policies of kidney biopsies. Incidence of CGN was 1.75% in a study from China12. Gupta et al reported incidence of CGN in 2.65%. In an earlier study from our institute Choudhury TA et al found incidence of 5.5%. However, studies from South Africa (3.8%) and Western Europe and North America (2–10%) showed a near-similar incidence. Thus, over observation was similar to other published studies.7,13-16

The mean age of our study population was 43 years with Male: Female ratio 1.8:1. Nagaraju et al. reported almost similar mean age (42.52±17.27 years). CGN occurs at all ages. In our study commonest age group affected was between 19-59 years (65.3%) followed by 60 years (26.9%). Two patients (7.6%) were of paediatrics age (<19 years). Overall, CGN is uncommon in children. In a study from University of North Carolina Nephropathology Laboratory, patients less than 20 years constituted 11.5% of all cases of CGN. Gupta et al, reported patients less than 14 years constituted 26% of all cases of CGN.8 Our result on incidence of CGN in children is lower than the result of other study and this could be due to more frequent referral of paediatric patient to Paediatric OPD and different renal biopsy policy in children.

A notable feature of our study was delayed referral and hence delayed diagnosis at our centre. The patients were asymptomatic for 1-4 month prior to referral. Hence, in the present study most of our patients had severe disease at presentation. Most common presentation of CGN was RPGN (100%), with severe renal failure (S. creatinine = >6 mg/dl) and uremic manifestation in equal number of patients 22 (84.6%). Anuria was noted in 18 (69.2%) cases at presentation. Sridevi Bezwada et al10 reported oedema, haematuria and hypertension in 75%, 60% and 40% cases. Our study result is almost similar to this study.18 In our study 22 (84.61%) patients were dialysis dependent at the time of presentation. Nagaraju et al, 17 Gaurav Sharma et al,19 Gupta et al and Rampelli SK et al,20 have reported haemodialysis requirement in 75.9%, 65.3%, 52.4% and 48.6% of patients respectively in their study. 22 (84.61%) cases were requiring dialysis at the time of admission in our study, reflecting severity of renal failure at presentation.

The most common aetiology for CGN was type II (immune complex) CGN (30.76%) followed by type V (immune negative) and type III (pauci-immune) in 26.92% and 19.23% respectively. Our observation also revealed type II CGN (immune complex) was almost equally present in adult 3/8 (37.5%) and elderly 4/8(50%) patients. A few studies from Asia have reported ICGN as the predominant aetiology in adults.5,12,21,22 Although various studies have shown that pauci-immune GN a common cause of CGN,2,8,22,23 This has been attributed probably to the high prevalence of infection with nephritogenic strains and regional and epidemiological variations. In present study, we found type III CGN (pauci immune) as a 2nd most common aetiology of CGN and it was predominantly present in adult patients (19-59 years). Type I, Type IV, and Type V CGN also were common in adult patients.

The prognosis in CGN is dependent on the age, aetiology, extent of the renal failure and the histological subtype.2,6-10,12,20 A strong predictor of outcome for all types of CGN is the severity of renal insufficiency at the time of presentation.2 The other unfavourable predictors are elderly patients, presence of oliguria, requirement of haemodialysis, very late presentation, >75% circumferential crescents, and fibrous crescents.2,6-10,12 The overall prognosis in our study remained poor with 80.76% reaching ESRD over 3 month. In subtype, Type I CGN had poorest outcome and all (100%) patients of this category progressed into ESRD. We observed 70-90% of patients with CGN (Type II to V) progressed to ESRD. Few other Indian studies have reported low rates of ESRD and mortality in contrast to our study.9,10 In those studies, patients had a much lower serum creatinine levels at presentation and included children. The poor outcome of our study cohort may be attributed by late presentation, severe renal failure (s. creatinine >6 mg/dl), requirement of haemodialysis (84.61%), anuria and features of chronicity on histological examination (Table 4) in majority of patients at the time of presentation. In present study only five (19.23%) patients have recovery in renal function and becomes dialysis independent. These five patients had Type II (n=1), Type III (n=1), Type IV (n=1) and Type V (n=2) CGN. These patients had cellular crescents and mild patchy chronic variations.
interstitial nephritis on renal histology and these histological features is usually associated with good outcome.

CGN needs aggressive management with high-dose corticosteroids and cytotoxic drugs. Plasmapheresis is indicated for anti-GBM disease and ANCA-associated GN with pulmonary haemorrhage. Studies have shown that the severity of renal insufficiency before initiation of treatment is a strong predictor of renal outcome. Pathologic severity in terms of activity of crescents and chronicity of glomerular and tubulo-interstitial disease also correlates with prognosis.

**Conclusion**

We observed, Type II (immune complex) CGN was most common type followed by type V (immune negative) and type III (pauci-immune) CGN. The crescentic GN had worse prognosis with >80% of patients progressed to ESRD within 3 month of time from onset of illness. The presence of oliguria, high serum creatinine and requirement of haemodialysis at admission are associated with poor outcome. Early diagnosis and standard immunosuppressive treatment may be associated with favourable outcome. Crescentic GN should be kept in mind in differential diagnosis of unexplained Acute Kidney Injury.

**Acknowledgement**

This paper was selected for Oral presentation at Annual Conference of North Zone - Indian society of nephrology (NZ-ISN) held on 16-18th February 2018 at Jaipur.

**References**

Diabetes Risk Diagnosis Using Obesity Markers and Glycemic Control in Indian Population

Sane Rohit¹, Mandole Rahul¹*

Abstract

Statement of the Problem: It is important to note, liver and pancreas are majorly responsible for normal glucose metabolism, these organs are located centrally hence central obesity/abdominal distension will affect glycaemic control more than generalise obesity. Scientific literature highlights a strong and consistent relation between abdominal girth and diabetes risk. Haemoglobin A1c (HbA1c) is recognized as a diagnostic test for DM as well as for its monitoring.

Aim: The purpose of this study is to assess association of anthropometric markers viz. Body mass index (BMI) and abdominal girth (AG) for prediction of glycaemic control in Indian population.

Methods: This single centre observational study was carried out from Feb 2015 to Oct 2015 at Khopoli, Maharashtra. Participants of both gender, andgt;20 yrs and willing to screen for Hba1c and anthropometry were included.

Findings: Out of the 2640 participants who visited the centre, 1870 (N=860 non-DM, age median (range): 57 (48/65) and N=1010 DM, age: 60 (53/65)) were enrolled in this study. HbA1c levels were statistically significantly elevated in DM vs. non-DM group (median (range): 7.5 (6.5/8.9) vs. 5.7 (5.2/6.3); p=0.000). Interestingly, abdominal girth showed significant difference between DM and non-DM groups (median (range): 95 (88/102) vs. 93 (86/100); p=0.022). Whereas BMI did not differ across the groups (median (range): 25.5 (23.2/28.6) vs. 25.7 (23.1/28.8); p=0.486).

Conclusion and Significance: Among the anthropometric markers namely BMI and AG, AG is a better predictor of DM risk. Therefore AG should also be considered along with HbA1c for predicting DM risk.

Background

With surge in the rate of prevalence of Diabetes mellitus (DM) in India and China, Asia has become the epicentre of diabetes in the world. On the other hand, obesity has come into limelight as a major risk factor for DM and affects nearly 18% of the adult population in India.¹ The presence of both morbidities (obesity and DM) can adversely affect the health status of individuals and communities and has serious economic and social implications. Therefore, association of obesity with DM is vital in risk assessment and early diagnosis of an individual’s risk of developing diabetes.

Globally, Haemoglobin A1c (HbA1c) is recognized as a diagnostic test for DM as well as for its monitoring. Its importance and utility for prognosis, monitoring and diagnosis of DM has been a matter of research and debate. Whereas, a number of anthropometric indices, including body mass index (BMI), abdominal girth, waist-to-hip ratio (WHR), and waist-to-height ratio (WHtR), are used for obesity assessment.

The importance of abdominal girth in predicting non-communicable diseases such as cardiometabolic disorders (e.g. diabetes, cardiovascular diseases, and dyslipidemia) has been examined in many large epidemiologic studies.²⁻⁵ The clinical evidence from literature studies have shown a strong and consistent relation between abdominal girth and diabetes risk, abdominal girth can be used as a better predictor of obesity and Type 2DM (T2DM).

However, the number of prospective studies is limited, and results of remainder studies are contradictory. Thus, the evidence that the markers of obesity (waist circumference (WC) or WHR) are preferable as a first-step diagnostic tool for assessment of diabetes risk is neither convincing nor generalizable.

Considering that liver and pancreas are the two main organs which are majorly responsible for normal glucose metabolism and are located centrally. Hence central obesity will affect glycaemic control more than generalise obesity. Therefore the present observational study was aimed to find out reliable and affordable anthropometric markers. Further, we tried to assess better anthropometric marker between BMI and abdominal girth (i.e WC) for prediction of glycaemic control in Indian population.

Methods

Study design and participants

The present observational study was carried out from 1st Feb 2015 to 31st Oct 2015 in MadhvaBaug hospital, Khopoli, Maharashtra.

Inclusion and exclusion criteria

Participants of both gender, above 20 years of age and who were ready to screen for Hba1c and anthropometry were included in the study. Participants who were not willing to undergo screening for Hba1c and physical examination were excluded from the study.

Anthropometric assessment was conducted for all study participants on the same day. All patients were

¹Madhva Baug Cardiac Care Clinic, Thane, Maharashtra; ²Corresponding Author
Received: 09.01.2018; Accepted: 24.07.2019
selected from the same centre to avoid the heterogeneity in patient population and investigators.

**Ethical considerations**

The study was conducted in accordance with the ethical principles in the Declaration of Helsinki and consistent with Good Clinical Practices. All participants provided written informed consent to participate in the study.

**Study Evaluations**

All participants were first subjected to comprehensive, relevant medical history taking, and physical examination; followed by anthropometric measurements and laboratory investigations.

**Anthropometric measurements**

Anthropometric parameters were measured using standardized techniques. Height (in centimetres) was measured using a stadiometer measure fixed at about 2 metres on a wall. The individual was asked to stand upright without shoes with his/her back against the vertical back board, heels together and eyes directed forward. Weight (in kilograms) was measured with weighing scale machine which was kept on a firm horizontal flat surface. Body mass index (BMI) was calculated as weight / (height)² and expressed in kilograms per square meter. Abdominal girth, also known as waist circumference (in centimetres) was measured by extending a non-stretchable measuring tape around the waist by positioning the tape in a horizontal plane to the level of the measurement mark or umbilicus. To avoid any error, measurement was taken directly on skin rather than on clothes. Blood pressure was measured with mercury sphygmomanometers.

**Laboratory Investigations**

Blood investigations and related clinical procedures were performed between 8 am and 9 am in the fasting state. Participants were instructed to refrain from caffeine, nicotine, and alcohol, for at least 12 h before blood collection. Patients were asked to delay the morning dose of medicine till blood collection. Two milliliters of peripheral blood was collected from each participant in Ethylene diamine tetra acetic acid (EDTA) and plain bulb. After centrifugation, serum from plain bulb was separated and used for estimation of fasting blood sugar, while EDTA sample was used for HbA1c estimation. Postprandial blood sugar was measured at 2 h post lunch. All the measurements were done within 2 h of sample collection. All the above mentioned biochemical estimations were performed using a clinical chemistry autoanalyzer. Blood sugar was analyzed by the glucose oxidase method and HbA1c using the Agappe Diagnostics Ltd.

**Statistical Analysis**

The data was analysed for distribution and was reported as Mean ± SD or Median (Range). Non-parametric correlation was used to analyse the relationship between the study parameters. P value of <0.05 was considered significant. Statistical analysis of the results was performed using the statistical software SPSS, version 21.0 (SPSS, Chicago, IL, USA).

**Results**

In total, 2640 participants approached the cardiac centre for treatment of Coronary Heart Disease (CHD), DM and Hypertension (HTN). Post screening the study population (N=1870) was divided into two groups: 1) Patients with DM (N=1010) and 2) Non-diabetic participants (N=860).

The anthropometric and clinical profiles of the diabetic and non-diabetic participants have been reported in Table 1. It is interesting to note unlike BMI, abdominal girth showed statistically significant difference between the groups.

The HbA1c levels were found to be significantly elevated in patients with diabetes when compared to non-diabetic participants (7.9 ± 1.8 mmol/mol and 6.7 ± 1.7 mmol/mol respectively; p<0.001).

There is a strong positive correlation between abdominal girth and HbA1c in non-DM participants (r=0.083, p=0.015) vs. DM patients (r=0.019, p=0.556).

**Discussion**

The present study results highlight positive correlation between HbA1c and BMI as well as AG as long as the participants belong to non-DM group. In DM group HbA1c correlates only with abdominal girth and not BMI. However, the gender-wise distribution underlines that females show strong positive correlation between Hba1c and AG irrespective of their DM status however non-DM males alone show positive correlation between Hba1c and BMI.

A study by Qiao and Nyamdorj concluded that, BMI and waist circumference (WC) performed similarly in predicting risk of T2DM. However, in line with the results of current study, most of the cross-sectional studies suggested that WC or WHR are better predictors of diabetes risk than BMI.

Furthermore, it is important to note that the present study is conducted in a developing country like India. DM is highly prevalent in India and the economic status of majority of diseased population does not permit them the privilege of treatment. In such a patient population, monitoring the progress of disease takes a backseat. Therefore, it is immensely important to have a relative marker for diabetes monitoring which is cheap and/or readily available. Hence, the present study results highlight the importance of abdominal girth which is easily measurable marker for monitoring DM progress.

**Acknowledgments**

The authors thank Poonam Pawar for writing assistance and editorial support for this manuscript. The authors thank the study participants and their families, without whom this study would not have been accomplished.

**Study support**

Funded by Vaidya Sane Ayurvedic Education and Agricultural Trust.
Correlation of ECG Findings with Age, Sex, Co-morbid Conditions and Angiographic Presentation among Acute Myocardial Infarction Patients in South India

Jian Meng Hoh¹, Rajesh Bhat U², Afzaa Nathvani Rajabali³

Abstract

Background: Proximal LAD and LCX occlusion usually associated with poorer clinical outcome in ACS. Hence, a rapid and efficient tool is needed to identify those conditions and initiate reperfusion at the earliest. We studied ECG features in relation to angiographic findings to identify the culprit artery in AMI and IWMI.

Objective: This study aims to compare and correlate the ECG features with angiographic findings in STEMI

Methodology: In this observational study, 73 AMWI and 59 IWMI patients having their completed ECG and coronary angiography reports were included. The required data were obtained by a pretested proforma. The ECG was analysed to predict the culprit vessel, and correlate it with angiographic finding.

Results: Among 132 patients, 71.2% were male and mean age was 60.95±11.52; whereas diabetes (35.6%) was the commonest comorbidity. The criteria with maximum specificity in prediction proximal LAD lesion in AMWI are RBBB and ST↓ in inferior leads; whereas ST↑ in inferior leads and ST↑V1>2.5mm had high sensitivity for proximal LAD lesion. ST↑ lead I, ST↑III >II and ST↑aVL were highly specific in differentiating diseased RCA from LCX in IWMI. In identifying proximal RCA occlusion, ST↑V1>2.5mm and ST↑V1 were the most sensitive and the most specific criteria respectively. On the other hand, ST↑lead I and ST↑III>II had the highest specificity and sensitivity respectively in locating LCX lesion.

Conclusion: Those criteria help in predicting the culprit artery; but they cannot replace the invasive procedure in confirming culprit vessel.

Introduction

Ischemic heart disease is a spectrum of diseases consisting of two groups: coronary artery disease (CAD) presenting with stable angina, and acute coronary syndromes (ACS). The later can be categorized as acute ST-elevation myocardial infarction (STEMI), and non-ST-elevation acute coronary syndrome (NSTEMI) which includes non-ST-elevation myocardial infarction (NSTEMI) and unstable angina (UA).¹²

ACS risk factors are classified into modifiable or non-modifiable. Modifiable risk factors include smoking, dyslipidemia, hypertension, diabetes, sedentary lifestyle, stress, obesity, low PUFA diet, etc. Non-modifiable risk factors consist of age, sex, genetic factor, family history of CAD, coagulopathy, etc.¹⁴ Identifying such risk factors is crucial to prevent CAD which is on the horizon. Previous CAD also increases the future risk of ACS, presenting either as a new lesion or recurrence.¹ Therefore, secondary prevention of CAD is equally important, as early diagnosis and intervention of CAD can drastically improve the survival of the patient.

Acute myocardial infarction (AMI) has 30% early mortality rate, and more than 50% death happened before they reached hospital; thus necessitating tools for its management as the mortality rate has dropped by approximately 30%.
The importance of ECG features varies and depends on the location of infarct and past coronary events and their angiographic findings. The ECG features of ACS include ST segment deviation, T wave and Q wave abnormalities. The culprit vessel was identified from ECG presentations in relation with angiographic findings. A pretested proforma was framed to obtain the required information. Patients with incomplete ECG angiographic data and conditions precluding the evaluation of ST-segment changes on ECG were excluded.

**Operational Definition**

**ST-elevation myocardial infarction (STEMI)** refers to acute coronary syndrome (ACS) diagnosed by its clinical presentation (chest pain for more than 30 minutes), ECG changes (ST segment changes >1 mm in at least two contiguous limb leads and >2 mm in chest leads with or without T and Q wave abnormalities) and angiographic features.

**Data analysis**

Results were summarized as frequency tables, and percentages were worked out and mean±SD was calculated for continuous variables. Statistical analysis was done by calculating sensitivity and specificity of ECG criteria in identifying culprit vessel, as well as Chi squared test considering p-value<0.05 as significant. Statistical package SPSS V.16.0 was used for analysis.

**Results**

In the course of this study, 132 patients were included, including 73 AWMI (55.3%) and 59 IWMI (44.7%) (Chart 1). Their age ranged from 27 to 85 with mean of 60.95±11.52 years; with majority under the age group of 41-80 years. Majority were male (73.5%) and had normal BMI of 18.5-22.9. The average BMI was 22.80±3.72 kg/m² (Table 1). The most common risk factor was diabetes (43.9%) followed by hypertension (21.5%), previous CAD (7.7%), dyslipidemia (5.3%) and asthma/COPD (2.3%).

Among patients with AWMI, the average age was 61.47±12.10, ranged 27-85 years; with majority of male (75.3%) and the age group of 41-60 years (46.6%). The average BMI in this group was 22.78±3.61; and most of them had normal BMI (57.5%) (Table 1). Diabetes (50.7%) was the commonest comorbidity, followed by the same order as the overall samples (Table 2).

Meanwhile, the mean age was 60.32±10.84 and ranged 33-83 years for the patients diagnosed with IWMI. Most of them were under the age group of 61-80 years (47.5%) and were male (71.2%). Their average BMI was 22.83±3.88; with majority under normal BMI (61.0%) (Table 1). The order of commonest risk factors was same as the overall sample (Table 2).

The commonest angiographic finding was single vessel disease (53.8%). The commonest dominant vessel was right coronary artery (77.3%), followed by left circumflex artery (18.2%) and codominant of both vessels (4.5%). Among the patients with AWMI, most of them had single vessel disease (61.6%) and dominant right coronary vessel (69.9%); whereas majority of IWMI patients had double vessel disease (48.1%) and right coronary artery (88.1%) as dominant vessel (Table 3).

Out of 73 patients with AWMI, 48 had proximal left anterior descending artery (LAD) occlusion (65.8%); and 25 had distal LAD occlusion (34.2%) (Table 3). The ECG criteria for proximal LAD occlusion with 100% specificity were right bundle branch block (RBBB), and sum of ST\_in III and aVF>2.5 mm. The most sensitive ECG finding for proximal LAD occlusion was ST\_inferior leads>1 mm (66.67%). Meanwhile, absence of ST\_inferior leads was most sensitive ECG finding for distal LAD occlusion; whereas ST\_aVL being the most specific finding for distal LAD occlusion (Table 4).

Among 59 IWMI patients, the culprit vessel was right coronary artery (RCA) in 53 patients (89.8%); and left circumflex artery (LCx) in six of them (10.2%). RCA occlusion was further classified into proximal RCA occlusion in 22 patients (37.3%) and distal RCA occlusion in 31 patients.
having 100% specificity; whereas ST↑V1, ST↑II, ST↑III had 51.61% sensitivity and 89.28% specificity for distal RCA occlusion. ST↑lead I and III>II had the highest sensitivity (98.11%) for RCA occlusion (Tables 4-5).

### Discussion

Our literature searches showed past studies have been conducted to identify the appropriate ECG findings that can identify the occluded vessel in acute AWMI and IWMI. Only a few studies were done to include all ECG criteria in AWMI and IWMI in a single study, and no such study was done in South India to the best of our knowledge of literature search. Hence, we correlated those ECG findings with angiographic findings for both AWMI and IWMI in our study.

#### Patients Profile

This study included 73 patients with AWMI and 59 with IWMI. The mean age was 60.95±11.52, 61.47±12.10 and 60.32±10.84 for overall sample, AWMI and IWMI respectively. Past studies showed varying age presentation based on their region with mean ranged 51.79±8.14 in Bangladesh to 64±13 years in Korea. Interheart study involving 52 different countries showed a median age of 58 years.

In our study, the male:female incidence ratio for overall sample, AWMI and IWMI were 2.77, 3.06 and 2.47 respectively. A 21-years study from Copenhagen City Heart Study in Denmark showed a ratio of 2 and male:female ratio was less pronounced as age advanced. A ratio of 3 was obtained in USA,12 in Korea,8 and in Netherlands.17 Other study from India,4 Iran19 and Bangladesh14 showed a ratio of 4-5.

Most of our patients had normal BMI as per Asian criteria (61.0%), the average BMI of the samples was 22.81±3.72 kg/m2. Copenhagen City Heart Study showed that relative risk for obesity for CAD was 1.20 and 1.19 for male and female respectively. Interheart study involving 52 different countries showed diabetes has highest correlation associated with MI.5

The commonest risk factor in our study was diabetes (43.9%), followed by hypertension (21.5%), positive family history (9.1%), previous CAD (7.7%), dyslipidemia (5.3%) and asthma/COPD (2.3%). Our findings was consistent with Interheart study4 and Copenhagen City Heart Study in Denmark; which showed diabetes has highest correlation for MI. The relative risk for CAD in Interheart study were: diabetes (3.08), smoking (2.95), hypertension (2.48),...
and obesity (2.24); whereas high fibre diet, exercise, and alcohol were found to be protective against MI.³

### Anterior wall myocardial infarction

We used the criteria for LAD occlusion proximal to D1 and/or S1 as proximal LAD occlusion which was similar to the study of Kojuri, et al;¹⁹ and criteria for LAD occlusion distal to D1 and S1 as distal LAD occlusion. As proximal LAD occlusion involves a larger area of infarction and brought a worse outcome,⁶,⁹,¹⁵,¹⁷,¹⁸ hence we classified LAD occlusion into proximal and distal for practical purpose.

Based on previous researches, ECG criteria for obstruction proximal to S1 were: RBBB,⁶,⁸,¹⁵,¹⁷ STjinferior lead>1 mm,⁶,¹⁵,¹⁷,¹⁸ STjV1>2.5 mm,⁶,¹⁵,¹⁷,¹⁸ STjV5,⁵,¹⁵,¹⁷,¹⁸ and STjAVR.⁵,⁸,¹⁵,¹⁷,¹⁸

STjinferior lead>1 mm,⁶,⁹,¹⁵,¹⁷,¹⁸ abnormal Q wave in lead aVL,¹⁷,¹⁸ and STj lead I and aVL,¹⁷,¹⁸ were the criteria for identifying occlusion proximal to D1

No STj inferior lead,⁶,⁹,¹⁵,¹⁸ and STj aVL,⁶,⁹,¹⁵,¹⁸ signifying occlusion distal to D1; whereas absence of STj inferior leads,⁶,¹⁵,¹⁸ and Q wave V4–V6,⁶,¹⁷,¹⁸ signifying occlusion distal to S1.

### Right bundle branch block (RBBB)

had low sensitivity (6.25%) and high specificity (100%) in predicting proximal LAD occlusion, which is consistent with the past studies of this criteria in relation to occlusion proximal to S1 by Markandeya, et al,⁶ and Salunke, et al,¹⁶ as well as Engelen, et al.¹⁷ This was believed to be caused by extensive myocardial involvement rather than conduction defect and is a sign of bad prognosis.¹⁷

STj inferior leads>1 mm had the second highest sensitivity (66.67%) and specificity (96%) in our study, which was higher compared to most of the previous study when they correlate this with RCA occlusion proximal to S1, except for the study of Vasudevan, et al showed 90% sensitivity¹⁶ and Kojuri, et al showed 94.4% specificity.¹⁹ STj inferior leads may not be seen in the occlusion of long LAD that supply cardiac apex due to the infarction of inferoapical wall countered the reciprocal changes,⁶,¹⁵,¹⁷,²⁰ and patient with STj inferior leads have poorer clinical outcome than those without such ST changes.⁹

We used STjIII+aVF>2.5 mm to localise proximal LAD occlusion and found to have 16.67% sensitivity and 100% specificity. This was consistent with the finding of Engelen, et al claimed that STj inferior leads was significantly more in proximal LAD disease and used STjIII>2.5 mm to identify proximal LAD occlusion. The sensitivity and specificity were 33% and 97% for occlusion proximal to S1; and 32% and 95% proximal to D1 respectively.¹⁷ However, study by Fiol, et al which showed high sensitivity (77%) and specificity (84%) in identifying LAD occlusion proximal to D1.²¹

STjV1 more than 2.5 mm had 68.75% sensitivity and 48% specificity in our study; which was similar to the study by Vasudevan, et al with 71% sensitivity and 66% specificity.³ However, other researches displayed higher specificity 87% to 100% for STjV1>2.5 mm in identifying LAD occlusion proximal to S1,⁴,¹⁵,¹⁷,¹⁹ and lower sensitivity 1.7-12%,¹⁵,¹⁷,¹⁹

STjV5 was seen more frequently in proximal LAD disease and we observed that it was highly specific (96%) to identify proximal LAD occlusion but with low sensitivity (14.58%), which was consistent to the previous researches.⁵,¹⁵,¹⁷,¹⁹

STjAVR was specific (92%) to proximal LAD occlusion but with low sensitivity (16.67%). This was consistent with the past studies in which their sensitivity value in diagnosing obstruction proximal to S1, which ranged 32-50%,⁵,¹³,¹⁷,¹⁹ Engelen, et al explained that the amplitude of STjAVR is usually less than 1mm when recorded at J point, and the low sensitivity of STjAVR could due to the rare dominance of basal septum.¹⁷

Drew, et al emphasized that STjlead I and aVL were seen in occlusion of a short LAD proximal to D1 if there is STjV2–V4; occlusion of D1 branch (if associated with STjV2) or isolectric V3–V6; occlusion of LCX (if there is STjV2).⁶ Our ECG analysis showed that STj lead I had sensitivity of 11.63% and specificity of 92%. Kojuri, et al mentioned that STjAVL had a low sensitivity (18.6%) and was unsuitable to predict AWMI caused by diseased proximal LAD.¹⁹

For identifying distal LAD occlusion, we observed that absence of STj inferior leads had high sensitivity (96%) and specificity of 66.67%; whereas STjAVL had low sensitivity(4%) and high specificity(100%). Our results were almost similar to the previous study.⁴,⁶,¹³,¹⁷,¹⁹ Markandeya, et al found that absence of STj in the inferior leads is the most sensitive criteria in occlusion distal to S1 as well as to D1; while Q wave in lead V4–V6 had the maximum specificity in occlusion distal to S1, and STjAVL had maximum specificity in occlusion distal to D1.⁴ The absence of STj in the inferior leads was mainly seen in leads II and aVF for occlusion distal to S1; and in lead III for occlusion distal to D1, as per the study of Engelen, et al.¹⁷

Drew, et al commanded that STjAVL was very specific to proximal LAD occlusion but had low sensitivity because when a long LAD that perfuse the cardiac apex is obstructed, there will be concomitant injury to the inferoapical and anterosuperior walls of the ventricle, which cancel out STj in

### Table 3.1: Angiographic finding of the patients with AWMI

<table>
<thead>
<tr>
<th>Culprit vessel, n (%)</th>
<th>Proximal LAD (n= 48)</th>
<th>Distal LAD (n= 25)</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dominant vessel</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RCA</td>
<td>32 (43.8)</td>
<td>19 (26.1)</td>
<td>51 (69.9)</td>
</tr>
<tr>
<td>LCx</td>
<td>13 (17.8)</td>
<td>4 (5.5)</td>
<td>17 (23.3)</td>
</tr>
<tr>
<td>RCA and LCx codominant</td>
<td>3 (4.1)</td>
<td>2 (2.8)</td>
<td>5 (6.8)</td>
</tr>
<tr>
<td>Number of vessel blockage</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Single vessel disease</td>
<td>33 (43.2)</td>
<td>12 (16.4)</td>
<td>45 (61.6)</td>
</tr>
<tr>
<td>Double vessel disease (DVD)</td>
<td>9 (12.5)</td>
<td>12 (16.4)</td>
<td>21 (28.8)</td>
</tr>
<tr>
<td>Triple vessel disease (TVD)</td>
<td>6 (8.2)</td>
<td>1 (1.4)</td>
<td>7 (9.6)</td>
</tr>
</tbody>
</table>

### Table 3.2: Angiographic finding of the patients with IWMI

<table>
<thead>
<tr>
<th>Culprit vessel, n (%)</th>
<th>Proximal RCA (n= 22)</th>
<th>Distal RCA (n=31)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dominant vessel</td>
<td></td>
<td></td>
</tr>
<tr>
<td>RCA</td>
<td>1 (1.7)</td>
<td>20 (33.9)</td>
</tr>
<tr>
<td>LCx</td>
<td>5 (8.5)</td>
<td>1 (1.7)</td>
</tr>
<tr>
<td>RCA and LCx codominant</td>
<td>0 (0.0)</td>
<td>1 (1.7)</td>
</tr>
<tr>
<td>Number of vessel blockage</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Single vessel disease</td>
<td>6 (9.2)</td>
<td>8 (13.6)</td>
</tr>
<tr>
<td>Double vessel disease (DVD)</td>
<td>0 (0.0)</td>
<td>11 (18.6)</td>
</tr>
<tr>
<td>Triple vessel disease (TVD)</td>
<td>0 (0.0)</td>
<td>3 (5.1)</td>
</tr>
</tbody>
</table>

Drew, et al emphasized that STj lead I and aVL were seen in occlusion of a short LAD proximal to D1 if there is STjV2–V4; occlusion of D1 branch (if associated with STjV2) or isolectric V3–V6; occlusion of LCX (if there is STjV2).⁶ Our ECG analysis showed that STj lead I had sensitivity of 11.63% and specificity of 92%. Kojuri, et al mentioned that STjAVL had a low sensitivity (18.6%) and was unsuitable to predict AWMI caused by diseased proximal LAD.¹⁹

For identifying distal LAD occlusion, we observed that absence of STj inferior leads had high sensitivity (96%) and specificity of 66.67%; whereas STjAVL had low sensitivity(4%) and high specificity(100%). Our results were almost similar to the previous study.⁴,⁶,¹³,¹⁷,¹⁹ Markandeya, et al found that absence of STj in the inferior leads is the most sensitive criteria in occlusion distal to S1 as well as to D1; while Q wave in lead V4–V6 had the maximum specificity in occlusion distal to S1, and STjAVL had maximum specificity in occlusion distal to D1.⁴ The absence of STj in the inferior leads was mainly seen in leads II and aVF for occlusion distal to S1; and in lead III for occlusion distal to D1, as per the study of Engelen, et al.¹⁷

Drew, et al commanded that STjAVL was very specific to proximal LAD occlusion but had low sensitivity because when a long LAD that perfuse the cardiac apex is obstructed, there will be concomitant injury to the inferoapical and anterosuperior walls of the ventricle, which cancel out STj in
Table 4: Sensitivity (SN) and specificity (SP) of all ECG criteria

<table>
<thead>
<tr>
<th>AWMI (n=73)</th>
<th>Current study</th>
<th>Markandeya, et al(\text{a})</th>
<th>Salunke, et al(\text{a})</th>
<th>Engelen, et al(\text{c})</th>
<th>Vasudevan, et al(\text{a})</th>
<th>Kojuri, et al(\text{b})</th>
<th>Fiol, et al(\text{b})</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>SN</td>
<td>SP</td>
<td>SN</td>
<td>SP</td>
<td>SN</td>
<td>SP</td>
<td>SN</td>
</tr>
<tr>
<td>Sample size</td>
<td>73</td>
<td>70</td>
<td>34</td>
<td>100</td>
<td>50</td>
<td>59</td>
<td>100</td>
</tr>
<tr>
<td>Proximal RCA</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RBBB</td>
<td>6.25</td>
<td>100.0</td>
<td>16</td>
<td>93</td>
<td>11.1</td>
<td>93.8</td>
<td>14</td>
</tr>
<tr>
<td>Sum ST(_\text{III}+\text{aVF}) &gt;2.5 mm</td>
<td>16.67</td>
<td>100.0</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>ST(_\text{V1}) &gt;2.5 mm</td>
<td>68.75</td>
<td>48.0</td>
<td>56</td>
<td>91</td>
<td>66</td>
<td>87</td>
<td>12</td>
</tr>
<tr>
<td>ST(_\text{aVR})</td>
<td>16.67</td>
<td>92.0</td>
<td>32</td>
<td>96</td>
<td>38.9</td>
<td>93.8</td>
<td>43</td>
</tr>
<tr>
<td>ST(_\text{V5})</td>
<td>14.58</td>
<td>96.0</td>
<td>16</td>
<td>96</td>
<td>11.1</td>
<td>100</td>
<td>17</td>
</tr>
<tr>
<td>ST(_\text{lead I})</td>
<td>11.63</td>
<td>92.0</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Distal RCA</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No ST(_\text{II}) inferior leads</td>
<td>96.0</td>
<td>66.67</td>
<td>86</td>
<td>49</td>
<td>100</td>
<td>41.9</td>
<td>50</td>
</tr>
<tr>
<td>ST(_\text{aVL})</td>
<td>4.0</td>
<td>100.0</td>
<td>17</td>
<td>100</td>
<td>85.7</td>
<td>100</td>
<td>22</td>
</tr>
<tr>
<td>IWM (n=59)</td>
<td>Current study</td>
<td>Markandeya, et al(\text{a})</td>
<td>Review article by Drew, et al(\text{a})</td>
<td>Verouden, et al(\text{a})</td>
<td>Almansori, et al(\text{a})</td>
<td>Mamun, et al(\text{a})</td>
<td>Salunke, et al(\text{a})</td>
</tr>
<tr>
<td></td>
<td>SN</td>
<td>SP</td>
<td>SN</td>
<td>SP</td>
<td>SN</td>
<td>SP</td>
<td>SN</td>
</tr>
<tr>
<td>Sample size</td>
<td>59</td>
<td>56</td>
<td>1131</td>
<td>7101</td>
<td>112</td>
<td>16</td>
<td>30</td>
</tr>
<tr>
<td>RCA:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ST(_\text{lead I})</td>
<td>54.72</td>
<td>100.0</td>
<td>82</td>
<td>73</td>
<td>-</td>
<td>-</td>
<td>79</td>
</tr>
<tr>
<td>ST(_\text{III}+\text{II})</td>
<td>98.11</td>
<td>100.0</td>
<td>87</td>
<td>73</td>
<td>88</td>
<td>94</td>
<td>84</td>
</tr>
<tr>
<td>ST(_\text{aVL})</td>
<td>50.94</td>
<td>100.0</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>82</td>
</tr>
<tr>
<td>ST(_\text{aVL})</td>
<td>66.04</td>
<td>83.33</td>
<td>82</td>
<td>73</td>
<td>80</td>
<td>94</td>
<td>95</td>
</tr>
<tr>
<td>ST(_\text{V4R}&gt;1) mm</td>
<td>49.06</td>
<td>83.33</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>ST(_\text{V4R}&gt;1) mm</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>100</td>
</tr>
<tr>
<td>Proximal RCA:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ST(_\text{lead I})</td>
<td>77.27</td>
<td>64.86</td>
<td>71</td>
<td>-</td>
<td>91</td>
<td>91</td>
<td>-</td>
</tr>
<tr>
<td>ST(_\text{V1})</td>
<td>18.18</td>
<td>83.78</td>
<td>87</td>
<td>73</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>ST(_\text{V4R}&gt;1) mm</td>
<td>-</td>
<td>-</td>
<td>71</td>
<td>66</td>
<td>100</td>
<td>87</td>
<td>-</td>
</tr>
<tr>
<td>ST(_\text{III}+\text{II})</td>
<td>51.61</td>
<td>89.28</td>
<td>-</td>
<td>*</td>
<td>84</td>
<td>93</td>
<td>-</td>
</tr>
<tr>
<td>Distal RCA</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ST(_\text{V2}) = 0.5 - 1.2</td>
<td>66.67</td>
<td>88.68</td>
<td>-</td>
<td>*</td>
<td>84</td>
<td>95</td>
<td>-</td>
</tr>
<tr>
<td>ST(_\text{lead I})</td>
<td>66.67</td>
<td>100.0</td>
<td>55</td>
<td>84</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>ST(_\text{III}+\text{II})</td>
<td>100.0</td>
<td>98.11</td>
<td>73</td>
<td>89</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>No ST(_\text{aVL})</td>
<td>83.33</td>
<td>66.04</td>
<td>55</td>
<td>84</td>
<td>80</td>
<td>93</td>
<td>-</td>
</tr>
</tbody>
</table>

Anterosuperior leads and inferior leads\(\text{a}\). Hence, ST\(_{aVL}\) or the absence of ST\(_{aVL}\) could signify distal LAD occlusion. ST\(_{aVL}\) was thought to be caused by reciprocal changes of inferoapical region.\(\text{a}\) ST\(_{aVL}\) was highly specific (100\%) for distal LAD occlusion in our study which is consistent to other study when used to identify LAD disease distal to D1.\(\text{a,15,17,18}\)

We found statistically significant association was present only between ST changes in inferior leads and proximal LAD occlusion. Review article by Drew, et al reported statistically significant association in the ECG criteria of ST\(_{aVR}\), RBBB, ST\(_{V5}\) and ST\(_{V1} >2.5\) mm with proximal LAD occlusion.\(\) Kojuri, et al found no association between proximal RCA occlusion with the following ECG features: ST\(_{in} \)in inferior leads, ST\(_{in} \)or [aVL, ST\(_{aVR}\), ST\(_{V1} >2.5\) mm, ST\(_{V2}\), ST\(_{V5}\geq 1\) mm, and Q wave in V4-V6.\(\text{a}\)

Inferior wall myocardial infarction

We had 53 patient with RCA occlusion and six patients with LCx occlusion, with a ratio of 8:8, whereas other studies demonstrated a ratio of 4:6.\(\text{a,11,12}\) Drew, et al recorded that 80-90\% of IWMI was caused by RCA.\(\text{a}\) Hence, in the event of IWMI, RCA has higher odd to be the culprit vessel compared to LCx. Besides, we also observed that five out of six (83.33\%) patients with diseased LCx have LCx as their dominant vessel. Almansori, et al observed the 30days mortality in RCA occlusion was significantly lesser than those with LCx occlusion.\(\text{a}\)

In our study, ST\(_{lead I}\) had the specificity and specificity of 54.72\% and 100\% respectively, which was different from the past researches that had higher specificity than sensitivity. The sensitivity and specificity of ST\(_{lead I}\) was 79-100\% and 60-73\% respectively based on past researches.\(\text{a,11,12,15,16}\)

The comparison of ST\(_{in} \)lead II and III was described as screening tool of right ventricular infarction. As RCA usually supply the area of right ventricle, inferior wall of left ventricle and the lower part of intraventricular septum; hence, right ventricular involvement is commonly related to RCA occlusion except in LCx dominant. Almansori, et al proposed that RCA involvement will cause the ST segment vector directed toward the right (lead III); and ST\(_{in} \)lead I is the reciprocal changes.\(\text{a,12}\) Study by Koh, et al observed that ST\(_{V1}\) and ST\(_{lead I}\) were better predictor of proximal RCA occlusion compared to ST\(_{III}+\text{II}\).\(\) However, we found that ST\(_{III}+\text{II}\) (98.11\%) had higher sensitivity compared to ST\(_{aVL}\).
Table 5: Summary of all ECG criteria

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Positive predictive value</th>
<th>Negative predictive value</th>
<th>P-value (Fisher's exact test)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proximal LAD</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RBBB</td>
<td>6.25</td>
<td>100.0</td>
<td>100</td>
<td>35.71</td>
<td>0.547</td>
</tr>
<tr>
<td>ST ↓ inferior leads &gt; 1 mm</td>
<td>66.67</td>
<td>96.0</td>
<td>96.97</td>
<td>60.0</td>
<td>0.000</td>
</tr>
<tr>
<td>ST ↑ V1 &gt; 2.5 mm</td>
<td>68.75</td>
<td>48.0</td>
<td>71.74</td>
<td>44.44</td>
<td>0.204</td>
</tr>
<tr>
<td>ST ↑ aVR</td>
<td>16.67</td>
<td>92.0</td>
<td>80.0</td>
<td>36.51</td>
<td>0.478</td>
</tr>
<tr>
<td>ST ↑ V5</td>
<td>14.58</td>
<td>96.0</td>
<td>77.78</td>
<td>37.5</td>
<td>0.152</td>
</tr>
<tr>
<td>ST ↑ lead I</td>
<td>11.63</td>
<td>92.0</td>
<td>71.43</td>
<td>34.85</td>
<td>1.000</td>
</tr>
<tr>
<td>Distal LAD</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No ST ↓ inferior leads</td>
<td>96.0</td>
<td>66.67</td>
<td>60.0</td>
<td>96.97</td>
<td>0.000</td>
</tr>
<tr>
<td>ST ↓ aVL</td>
<td>4.0</td>
<td>100.0</td>
<td>100.0</td>
<td>66.67</td>
<td>0.342</td>
</tr>
<tr>
<td>Proximal RCA</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ST↑V1/ST↓III &lt; 0.5</td>
<td>77.27</td>
<td>64.86</td>
<td>56.67</td>
<td>82.76</td>
<td>0.003</td>
</tr>
<tr>
<td>ST↑V1</td>
<td>18.18</td>
<td>83.78</td>
<td>40.0</td>
<td>63.27</td>
<td>1.000</td>
</tr>
<tr>
<td>Distal RCA</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ST↑III/ST↓III 0.5 – 1.2</td>
<td>51.61</td>
<td>89.28</td>
<td>84.21</td>
<td>62.5</td>
<td>0.001</td>
</tr>
<tr>
<td>LCx</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ST↑V3/ST↓III &gt; 1.2</td>
<td>66.67</td>
<td>88.68</td>
<td>40.0</td>
<td>95.92</td>
<td>0.006</td>
</tr>
<tr>
<td>ST ↑ lead I</td>
<td>66.67</td>
<td>100.0</td>
<td>100.0</td>
<td>96.36</td>
<td>0.000</td>
</tr>
<tr>
<td>ST ↑ II &gt; III</td>
<td>100.0</td>
<td>98.11</td>
<td>85.71</td>
<td>100</td>
<td>0.000</td>
</tr>
<tr>
<td>No ST ↓ aVL</td>
<td>83.33</td>
<td>66.04</td>
<td>21.74</td>
<td>97.22</td>
<td>0.029</td>
</tr>
</tbody>
</table>

(66.04%), ST ↑ V1 (18.87%) and ST ↑ lead I (54.72%), with all having specificity of 100%; which was similar with the results obtained by Markandeya et al.6 Besides, most studies showed that ST ↑ III > II is having high sensitivity6,8,10,15 and high specificity6,9,14,15 to predict RCA lesion.

The sensitivity and specificity of ST ↑ aVL in this study were 66.04% and 83.33% respectively. In other studies, the sensitivity of ST ↑ in aVL was higher in LAD.9 When we compared ST ↑ in aVL with lead I, the sensitivity decreased to 50.94% and specificity increased to 100%. Similar comparison was also done in the study of Verouden, et al, both sensitivity and specificity were dropped from 95% to 82% and from 24% to 22% respectively.11 The sensitivity of ST ↓ aVL > I was also relatively less in our study(50.94%) compared to Verouden, et al (82%)11 and Almansori, et al (85%).12 Drew, et al documented that reciprocal ST ↓ aVL > I suggested RCA related IWMI, which can be explained by LCx occlusion involving high postero lateral area can attenuates ST ↓ in aVL more than in lead I.9

The ratio of \( \frac{\text{sum ST↑V1–V3}}{\text{sum ST↓in lead}} \) < 1 had 49.06% sensitivity and 83.33% specificity in our study to differentiate RCA occlusion from LCx. This was in contrast with the study by Almansori, et al displayed 90% sensitivity and 28% specificity in predicting a diseased RCA.9

ST ↑ V1 was the most specific (83.78%), whereas ST↑III/ST↓III > 1.2 was the most sensitive (77.27%) criteria for proximal RCA occlusion in our study, which was consistent with the previous studies.6,16 Markandeya RGKM, et al found that ST ↑ V4R > 1mm and ST↑V1/ST↓III < 0.5 have the highest sensitivity (71.4%) for proximal RCA occlusion; while ST↑V1 is the most specific criteria.6 However, review article by Drew, et al showed that ST ↑ V1 had 91% sensitivity and specificity which was higher than our findings.6

ST ↑ V1 had 18.18% sensitivity and 83.78% specificity for proximal RCA occlusion. This was similar to the study of Markandeya, et al which claimed that ST ↑ V1 is the most specific in identifying proximal RCA occlusion.6,16 Drew, et al explained that ST ↓ in V1–V3 indicated extension of the involvement to the posterolateral and/or inferoseptal wall; but this was rare in proximal RCA occlusion because right ventricular injury cancels out the reciprocal ST changes in V1–V3.9

We used only standard 12 lead ECG on our patient with AMI to identify the culprit vessel. Hence, V4R was not used in our study. Previous studies showed ST↑ in V4R>1mm was a good indicator for right ventricular involvement caused by proximal RCA occlusion with sensitivity of 71-100% and specificity of 66-100%.6,8,10,15,16 ST coving without ST↑ in V4R as a predictor of distal RCA occlusion had maximum specificity in the study by Markandeya;9 and 100% sensitivity and 15% specificity in the study by Salunke, et al.13

In distal RCA occlusion, we found that the ratio of ST↑III/ST↓III between 0.5 to 1.2 had the sensitivity and specificity of 51.61% and 89.28% respectively, which had lower sensitivity value compared to our literature review.9,15 Markandeya, et al mentioned that ST↑III/ST↓III = 0.5 – 1.2 had maximum specificity in predicting distal RCA occlusion.9

For LCx occlusion, ST↑II > III was found to be the most sensitive criteria (100%) in our study, which is consistent with most of the past researches;6,15 but the study by Nair, et al showed only 40% sensitivity.16 Besides, we observed that ST ↑ II > III also had a high specificity (98.11%) to predict diseased LCx, which was similar to previous researches having 89-100% specificity.9,15,16

The most specific criteria for LCx occlusion was ST ↑ I (100%) in our study which was similar to the previous findings.9,15,16

The ratio of ST↑V3/ST↓III > 1.2 had 66.67% sensitivity and 88.68% specificity in identifying diseased LCx, which was consistent with our literature search that showed high specificity in identifying diseased LCx.

Absence of ST ↓ aVL had sensitivity of 83.33% and specificity of 66.04%. All past studies displayed a high value of specificity (84-100%) and a fair sensitivity (55-66%) for ST ↓ aVL in identifying LCx occlusion.6,9,15,16

Verouden, et al hypothesize the ECG criteria predicting RCA involvement would be more reliable when ST deviation were more pronounced; as extensive ST deviation often associated with right ventricle involvement.11

Statistically significant association was found to be present between RCA or LCx occlusion with the following ECG findings: comparison of ST↑ in V1–V3 lead III and II, use of sum ST↓inlead ratio,
and ST deviation in lead I and aVL by Fisher’s exact test.

**STEMI with multi-vessel disease**

Neeland, et al published two case study of AWMI with proximal LAD occlusion along with TVD; and concluded that ECG features may be modified by the presence of other diseased coronary vessels. However, both cases showed ST↓ in V1-V2, 1mm ST↓ in I and aVL, and ST↓ in II, III, aVF and V3-V6, which were the ECG criteria used to identify proximal LAD occlusion; with extra features like extensive ST↓, and altered terminal T wave vector in inferior and lateral leads (10). Similar ECG findings were observed in our study. Hence, we decided to included double and triple vessel disease in ECG analysis as they had ECG findings that matched the criteria; and we identify the culprit vessel by angiogram as the one having more than 90% occlusion and/or warrant immediate intervention in the first setting. Verouden, et al included multi-vessel disease in their study; while Almansori, et al and Salunke, et al excluded them. (12,13)

Furthermore, the sensitivity and specificity were not affected much by their presence. For example, sensitivity and specificity of ST ↓ lead I were 54.72% and 100% respectively; if we excluded TVD and DVD, the values were 55% and 100% respectively. Meanwhile, review article by Drew, et al recorded that ST ↓ in V4-V6 could indicate multi-vessel disease in acute IWI, and poorer clinical outcome compared to those who did not have this finding. (9) This was present in few of our multi-vessel disease patients and we believed it was important to identify those ECG criteria that can bring an unfavourable outcome.

**Limitations**

Our study was conducted in a limited timeframe and population. A larger population from different continents and longer study will be needed to provide more accurate information regarding the appropriateness of ECG findings.

We did not use special lead like V4R which can identify RCA occlusion. We classified all culprit vessels into proximal and distal occlusion without details in relation to S1 and D1 for LAD.

**Conclusion**

This study identified the STEMI risk factors. Preventive measures can therefore be undertaken to lower the risk factors in general population and the incidence of this fatal disease.

Various ECG presentations in AMI in relation with angiographic presentation were investigated under this study. This can help in predicting the area of infarction and the proximity of occluded vessel. Proximal LAD and LCx occlusion would bring a poorer clinical outcome in AWMI and IWI respectively. Early reperfusion should be considered if ECG showed proximal coronary vessel occlusion and large area of involvement, to reduce the mortality and improve the survival chances of the patients, as well as prevent major adverse cardiac events (MACE) like reinfarction, cardiac failure, conduction disturbances, etc.

Those criteria are the helpful predictor of infarct related artery in an emergency setting; but they cannot be used as the substitute of invasive procedure in confirming culprit vessel.

**References**

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Effectiveness of Pregabalin Compared to Duloxetine in Diabetic Peripheral Neuropathic Pain: An Observational Study

Sujeet Jha¹, Om Prakash Sahani¹, Samreen Siddiqui¹, Manoj Kumar Verma¹, Avijit Mazumder², Swati Waghdhare¹

Abstract

Introduction: Neuropathy is a comorbid complication of diabetes and Pregabalin and Duloxetine are the two most common drugs used for the treatment of neuropathic pain.

Aim: To determine the effectiveness and side effects of Pregabalin and Duloxetine in patients with diabetic peripheral neuropathic pain.

Materials and Methods: This prospective observational study was conducted at Max Super Speciality Hospital. Patients attending the endocrinology department, above 18 years of age who were prescribed with Pregabalin or Duloxetine were screened and included in this study. The data was collected for all study participants using a specially designed case record form by conducting personal interviews. SF-MPQ, Mc-Gill, NRS and DN-4 questionnaires were used to assess the extent of pain and the side-effects associated with the drugs.

Results: Based on the responses from the Numerical Rating Scale and McGill Pain Questionnaire, Pregabalin was seen to be less effective compared to Duloxetine. The only side effect observed with Pregabalin was drowsiness, which was observed in 4% cases at 50 mg dose whereas those reported with Duloxetine were drowsiness (22.2% at 20 mg and 33.3% at 30 mg), vomiting (11.1% at 20mg and 30mg), headache (11.1% at 20 mg and 30 mg), and dizziness (0% at 20mg and 11.1% at 30 mg).

Conclusions: Pregabalin has a better safety profile and tolerability compared to Duloxetine but the latter is more effective in treating Diabetic Peripheral Neuropathic Pain. However, further studies with a larger sample size and longer duration are required to be conducted for finding the effectiveness of these drugs, specifically in the Indian population.

Introduction

Peripheral Neuropathy is the most common complication associated with diabetes.¹,² It affects nearly 30–60% of the diabetic population.³ Around 10–20% of these individuals experience neuropathic pain, which is characterized by hyperalgesia (abnormally increased sensitivity to pain), allodynia (pain resulting from a stimulus that normally would not provoke such pain), and paresthesia (sensation of pricking or tingling without any objective cause) accompanying the continuous aching or burning pain.³

Neuropathic pain is defined as pain caused by a primary lesion or dysfunction in the nervous system.⁴ It may result from damage to the central nervous systems (cerebrovascular accident, multiple sclerosis or injury to the spinal cord) or peripheral nervous system (peripheral neuropathy associated with diabetes, post herpetic neuralgia or surgical intervention).⁵ It has an insidious onset and usually a symmetrical pattern of ‘Gloving and Stocking’ characterizes the pain.⁶ The main symptom observed in diabetic peripheral neuropathic pain (DPNP) is shooting or burning pain in the feet and lower limbs occurring for more than three months.⁴ The pharmacological response among individuals with this condition is varied and most treatments are not very effective in more than half of the cases. The commonly used drugs for the management of pain are antidepressants, antiepileptics, opioids, analgesics, topical lidocaine, and topical capsaicin.³ Pregabalin is an anticonvulsant which was approved by US in 2005 for the treatment of DPNP and post herpetic neuralgia pain whereas Duloxetine is a reuptake inhibitor of serotonin and norepinephrine used for the management of DPNP.⁴

This study was undertaken to primarily observe the effectiveness of Pregabalin and Duloxetine for the treatment of diabetic peripheral neuropathy pain in patients attending the outpatient department at a tertiary care hospital in New Delhi. We also assessed the side effects associated with these two drugs.

Materials and Methods

Study design, sample size determination, and subjects

This prospective observational study was conducted at Max Super Specialty Hospital, Saket, New Delhi from December 2014–October 2015 to observe the effectiveness of Pregabalin and Duloxetine in patients with diabetic peripheral neuropathy pain (DPNP). According to the study conducted by Freeman R et al. in 2008, Pregabalin was reported to have an efficacy of 47%.⁷ Assuming a power of 80% for detecting a difference of 20% in efficacy, the sample size was calculated to be 47 in each group. However, this sample size was not possible in our study because of the unwillingness of participants,
short duration of the study, as well as discontinuation of Duloxetine during the study period due to observable side effects associated with its usage.

Individuals were eligible for the study if they were more than 18 years of age, experiencing pain for greater than two weeks, having diabetic peripheral neuropathy pain (Neuropathic Pain Diagnostic Questionnaire - DN4 score >4 or Numerical Rating Scale value >5) associated with Type 2 diabetes, and willing to participate in the study. Patients with a previous history of trauma, those having severe osteoarthritis or advised joint surgery, pregnant or breast feeding females, and unwilling individuals were excluded from the study. Written informed consent was obtained from all the study subjects prior to participation. The study was approved by the Scientific and Institutional Ethics Committee of Max Super Specialty Hospital, Saket, New Delhi. The primary objective was to observe the effectiveness of Pregabalin and Duloxetine for the treatment of diabetic peripheral neuropathy pain in patients attending the outpatient department, which was assessed through Short Form-McGill Pain Questionnaire and Numeric Pain Rating Scale. The secondary objective was to determine the side effects associated with Pregabalin and Duloxetine.

Methods

Various screening questionnaires have been used in the past to assess the neuropathic pain associated with diabetes. Frequency and severity of pain has been assessed using simple scales like Visual Analog Scale, Numeric Rating Scale, or Likert Scale. Some questionnaires such as the DN4 and McGill Pain Questionnaire in its shortened format have also been used previously for identification of neuropathic pain and determination of its intensity.11,12 Hence, these validated questionnaires and rating scales were used in our study. Two questionnaires and two pain rating scales were used to record patient responses. These questionnaires were used for evaluating the qualities of pain (Short form of the McGill Pain Questionnaire- SF-MPQ) and to determine if the pain was neuropathic in nature (Neuropathic Pain Diagnostic Questionnaire- DN4).

The SF-MPQ has four components. The main component of SF-MPQ comprises of 11 sensory and 4 affective descriptors, which are rated on an intensity scale as either none (0), mild (1), moderate (2), or severe (3). It includes two other scales, the Present Pain Intensity (PPI) scale and the Visual Analogue Scale (VAS), which provide information on the intensity but not the quality of pain.13 The fourth component is a figure, where the patient is supposed to mark the region where pain is felt. The DN4 questionnaire (DN4 stands for ‘douleur neuropathique 4 questions’ which means neuropathic pain four questions in French) includes descriptors of pain along with items based on clinical examination.13

The two rating scales used for assessment of pain intensity were Numerical Pain Rating Scale (NRS) and the Faces Rating Scale (FRS) by Wong Baker. The NRS may be an 11, 21, or 101 point scale where the end points represent extremes of pain i.e. no pain or worst possible pain.14,15 We used the graphical scale utilizing a straight line with divisions at specified intervals depicting numbers from 0–10 to assess the pain for each patient, where the lower number ‘0’ represented no pain and highest number ‘10’ indicated the worst possible pain experienced by the patient.16 Each participant was asked to circle or record the number that best represented their level of pain intensity.

The Wong Baker Faces Pain Scale is based on the concept of image projection technique. The study participants were asked to choose from among the six faces based on their pain experience which best represented them. The first face was a very happy smiling face whereas the last one was a sad tearful face. All faces in between these two faces expressed different levels of sadness.16,17

Starting dose of Pregabalin was 50 mg, which was titrated up to 150 mg, if required, by the clinician. Similarly, for Duloxetine, starting dose was 20 mg, which was titrated up to 90 mg, if required. Additionally, all these patients were receiving Paracetamol 4g/day for not more than three consecutive days for pain relief. These patients were observed for a period of six months to identify the side effects linked with the use of Pregabalin and Duloxetine and determine their effectiveness in the treatment of diabetic peripheral neuropathic pain. The data was collected for all study participants using a specially designed case record form (CRF) by conducting personal interviews. The safety profile of the two drugs was evaluated by measuring the discontinuation rates and adverse events associated with each drug.

Statistical analysis

Continuous data was presented as mean ± SD and categorical data as frequencies. The data obtained was statistically analyzed using Chi Square test and Student t-test. The software used to analyze the data was SPSS Inc. (2007) Version 16.

Results

A total of 420 patients reporting at the Outpatient Department of Endocrinology, Max Super Specialty Hospital, Saket, New Delhi were screened. Out of these, 83 had symptoms of classical neuropathic pain. Due to the unwillingness to participate in the study, 34 patients (Duloxetine: n=9; Pregabalin: n=25) were enrolled into the study over a period of 4 months and followed up from August 2015–December 2015.

The demographic characteristics of the study population are presented in Table 1. Out of the 34 patients, 18 (52.94%) were females and 16 (47.06%) were males. The distribution of individuals affected with diabetes shows that a majority (52.94%, n=18/34) of the cases did not have diabetes in their first degree relatives, whereas the father, mother and sibling were affected with diabetes in 20.58% (n=7), 17.64% (n=6), and 8.82% (n=3) cases, respectively.

The dose and pain wise distribution of study subjects for Pregabalin and Duloxetine is given in Table 2. The McGill Pain Questionnaire revealed that a significant relief from pain was seen with the use of Pregabalin from Day 0 through 90 at 50 mg, 75 mg, and 150 mg doses. However, the Numerical Pain Rating Scale showed a significant reduction in neuropathic pain from Day 14 onwards to Day 90. Similarly, for Duloxetine, the McGill Pain Questionnaire showed a significant reduction in pain from Day 14 onwards, whereas based on the Numerical Pain Rating Scale, a significant reduction in neuropathic pain was observed from...
Table 1: Demographic characteristics of the study population

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Mean ± SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>55.8 ± 8.59</td>
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<tr>
<td>Body mass index (kg/m²)</td>
<td>28.73 ± 5.3</td>
</tr>
<tr>
<td>Duration of diagnosis (years)</td>
<td>10.56 ± 8.39</td>
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<tr>
<td>Biochemical values</td>
<td></td>
</tr>
<tr>
<td>Sodium (mmol/L)</td>
<td>13.8 ± 3.74</td>
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<tr>
<td>Potassium (mmol/L)</td>
<td>4.50 ± 1.79</td>
</tr>
<tr>
<td>Urea (mg/dl)</td>
<td>28.54 ± 8.90</td>
</tr>
<tr>
<td>Creatinine (mg/dl)</td>
<td>1.42 ± 1.39</td>
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<tr>
<td>Fasting blood sugar (mg/dl)</td>
<td>165.5 ± 48.11</td>
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<tr>
<td>Post prandial blood sugar (mg/dl)</td>
<td>247.38 ± 68.6</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>8.96 ± 1.8</td>
</tr>
<tr>
<td>Bilirubin (mg/dl)</td>
<td>0.47 ± 0.16</td>
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<tr>
<td>ALT (U/L)</td>
<td>29.52 ± 7.11</td>
</tr>
<tr>
<td>ALP (U/L)</td>
<td>105.6 ± 21.7</td>
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<tr>
<td>Albumin (g/dl)</td>
<td>3.88 ± 0.53</td>
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<tr>
<td>Cholesterol (mg/dl)</td>
<td>179.94 ± 43.4</td>
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<tr>
<td>Triglycerides (mg/dl)</td>
<td>145.40 ± 52.84</td>
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<tr>
<td>High Density Lipoproteins (HDL) (mg/dl)</td>
<td>53.9 ± 23.05</td>
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<tr>
<td>Low Density Lipoproteins (LDL) (mg/dl)</td>
<td>93.2 ± 40.6</td>
</tr>
<tr>
<td>Hemoglobin (Hb) (g/dl)</td>
<td>13.40 ± 0.83</td>
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</table>

Day 21 through 90 at 20 mg and 30 mg doses, as shown in Table 2.

Overall responses obtained via Numerical Pain Rating Scale and Short form McGill Pain Questionnaire were compared for determining the effectiveness of Duloxetine and Pregabalin in treating Diabetic Peripheral Neuropathic pain among the study population. Pregabalin was seen to be less effective compared to Duloxetine, as depicted in Figure 1. The pain alleviation after treatment with these drugs was also assessed individually. For Duloxetine, it was observed that 14.2% patients had a reduction in pain with 20 mg dose and 28.5% at 30 mg. However, around 57.1% patients discontinued Duloxetine due to the side effects associated with its usage. Similarly, for Pregabalin, a total of 18.5% patients experienced a reduction in pain with 50mg dose, 40.7% at 75 mg, 33.3% at 150 mg, and 7.4 % at 225 mg dose, respectively, as shown in Figure 2.

The only side effect observed with Pregabalin was drowsiness, which was observed in 4% cases at 50mg dose. For Duloxetine, the side effects reported were drowsiness (22.2% at 20 mg and 33.3% at 30 mg), vomiting (11.1% at 20 mg and 30 mg), headache (11.1% at 20 mg and 30 mg), and dizziness (0% at 20 mg and 11.1% at 30 mg), as seen in Figure 3.

Table 2: Dose and Pain wise distribution of the study subjects taking Pregabalin and Duloxetine

<table>
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<tr>
<th>Time (days)</th>
<th>0</th>
<th>7</th>
<th>14</th>
<th>21</th>
<th>28</th>
<th>60</th>
<th>90</th>
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<td>Pregabalin</td>
<td></td>
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<tr>
<td>50 mg</td>
<td>6.2 ± 1.47</td>
<td>6.26 ± 1.5</td>
<td>5.76 ± 1.45</td>
<td>4.9 ± 1.3</td>
<td>4.5 ± 1.36</td>
<td>3.67 ± 1.20</td>
<td>3.61 ± 0.78</td>
</tr>
<tr>
<td>75 mg</td>
<td>6.27 ± 1.52</td>
<td>6.26 ± 1.5</td>
<td>5.76 ± 1.57</td>
<td>4.9 ± 1.5</td>
<td>4.5 ± 1.5</td>
<td>3.9 ± 1.3</td>
<td>3.61 ± 0.88</td>
</tr>
<tr>
<td>150 mg</td>
<td>6.27 ± 1.60</td>
<td>6.26 ± 1.74</td>
<td>5.76 ± 1.71</td>
<td>4.97 ± 1.74</td>
<td>4.5 ± 1.71</td>
<td>3.97 ± 1.62</td>
<td>3.61 ± 0.91</td>
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<tr>
<td>P-value</td>
<td>0.88</td>
<td>0.38</td>
<td>0.001*</td>
<td>0.000*</td>
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<tr>
<td>50 mg</td>
<td>12.25 ± 4.74</td>
<td>12.35 ± 4.7</td>
<td>11.52 ± 4.58</td>
<td>9.94 ± 1.39</td>
<td>9.0 ± 4.0</td>
<td>7.97 ± 4.0</td>
<td>6.85 ± 3.15</td>
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<tr>
<td>75 mg</td>
<td>12.25 ± 4.59</td>
<td>12.35 ± 4.58</td>
<td>11.52 ± 4.43</td>
<td>9.94 ± 4.45</td>
<td>9.94 ± 4.29</td>
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<tr>
<td>150 mg</td>
<td>12.25 ± 5.78</td>
<td>12.35 ± 5.64</td>
<td>11.52 ± 5.80</td>
<td>9.94 ± 5.43</td>
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<tr>
<td>20 mg</td>
<td>6.27 ± 1.41</td>
<td>6.26 ± 1.43</td>
<td>5.76 ± 2.01</td>
<td>4.97 ± 2.24</td>
<td>4.5 ± 2.08</td>
<td>3.97 ± 1.63</td>
<td>3.61 ± 1.46</td>
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<tr>
<td>30 mg</td>
<td>6.27 ± 1.45</td>
<td>6.26 ± 1.48</td>
<td>5.76 ± 1.49</td>
<td>4.97 ± 2.07</td>
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<td>50 mg</td>
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<td>3.61 ± 0.88</td>
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<tr>
<td>150 mg</td>
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<td>5.76 ± 1.71</td>
<td>4.97 ± 1.74</td>
<td>4.5 ± 1.71</td>
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<td>3.61 ± 0.91</td>
</tr>
<tr>
<td>P-value</td>
<td>0.88</td>
<td>0.38</td>
<td>0.001*</td>
<td>0.000*</td>
<td>0.000*</td>
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</tr>
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</table>

HbA1c : Glycated Hemoglobin; ALT : Alanine aminotransferase; ALP : Alkaline Phosphatase; *P-value ≤ 0.001 is considered significant

Discussion

Pregabalin and Duloxetine are the two main drugs approved by the U.S Food and Drug Administration (FDA) for the treatment of diabetic neuropathic pain. We compared the effectiveness of these two drugs in our small population subset of a tertiary care hospital. In our study, the responses obtained for determining the effectiveness of Duloxetine and Pregabalin in treating Diabetic Neuropathy pain among the study population revealed that Duloxetine was more effective compared to Pregabalin. Quilici S et al. and Tanenberg RJ et al. reported Duloxetine to be non-inferior to Pregabalin. On the contrary, in a study by Devi P et al., better results for pain reduction were observed for Pregabalin compared to Duloxetine or Gabapentin. In a study by Tanenberg RJ et al., more discontinuations were observed with Duloxetine therapy (n=27, 19.6%, P = 0.04) compared to Pregabalin (n=14;10.4%). Similar findings were reported by Sultan A et al. In our study, the responses obtained for determining the effectiveness of Duloxetine and Pregabalin in treating Diabetic Neuropathy pain among the study population revealed that Duloxetine was more effective compared to Pregabalin. Quilici S et al. and Tanenberg RJ et al. reported Duloxetine to be non-inferior to Pregabalin. On the contrary, in a study by Devi P et al., better results for pain reduction were observed for Pregabalin compared to Duloxetine or Gabapentin.
study 57.1% cases discontinued Duloxetine in the same line, whereas no discontinuation was observed with Pregabalin. One of the reasons for a smaller sample size in our study could also be attributed to the increase in side-effects associated with Duloxetine, due to which the drug had to be discontinued in some of the patients.

Adverse events such as drowsiness or somnolence, vomiting, dizziness, and headache were more frequently associated with Duloxetine compared to Pregabalin in our study. This is in accordance with studies by Raskin J et al., Sultan A et al., and Tanenberg RJ et al., where more side effects were observed with Duloxetine compared to the placebo or Pregabalin.8,9,13

Our study had a few advantages. The questionnaires and pain rating scales used for assessing patient responses were effective and easy tools for data collection and interpretation. The limitations in this study were a small sample size and the short duration of the study, due to which the effectiveness and side effects of the two drugs could not be assessed for a longer duration.

In conclusion, findings from the study indicate that Pregabalin has a better safety profile and tolerability compared to Duloxetine but the latter is more effective in treating Diabetic Peripheral Neuropathic Pain. However, further studies with a larger sample size and longer duration are warranted to validate the findings of our study.

Contributors

Dr. Sujeet Jha was involved in the designing and conceptualization of this study. Mr. Om Prakash Sahani did literature review, collected and compiled the data. Mr. Manoj Kumar Verma heled in Data collection. Ms. Samreen Siddiqui performed the data analysis and interpretation. Dr. Avijit Mazumder reviewed the manuscript. Dr. Swati Wagdhare was responsible for writing and editing the manuscript.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

References


Role of Tfr2-Y250X and Tfr1- rs3817672 Single Nucleotide Polymorphism on Pathophysiology of Iron Deficiency Anemia

Sweta Pandey¹*, Sanjay Kumar Pandey², Vineet Shah³

Abstract

Background: Transferrin receptor (Tfr) is a carrier protein for transferrin. It is regulated in response to intracellular iron concentration and plays a role for the import of iron into the cell. The transferrin receptor 2 (Tfr2) gene showed homology to transferrin receptor 1 (Tfr1) gene and encodes a transmembrane protein with a large extracellular domain, which is able to bind transferrin. Mutations in transferrin receptors (Tfr2 and Tfr1) may alter the pathophysiology of iron deficiency anemia. Alteration in genes encoding transferring receptor cause change in iron homeostasis and provides a tool for investigating the excess iron absorption and abnormal iron distribution in iron related disorders. However the clinical significance of the interaction of transferring mutations with iron deficiency anemia remains unclear. Thus, the objective of my study was to investigate the effect of Tfr1 and Tfr2 genotypes on pathophysiology of iron deficiency anemia.

Study Design: Study subjects were 460 iron deficiency anemia patients and 500 age and sex-matched healthy controls. Transferrin receptor, ferritin and CRP analysis was done by ELISA method while ESF analysis was done according to Wintrobe’s method. CBC analysis was done by autoanalyzer. Tfr1-rs3817672 SNP and Tfr2 (Y250X) mutation was analyzed by using PCR RFLP method.

Result: Amongst the iron deficiency anemia patients, 13 were heterozygous and five were homozygous for rs3817672 SNP. Tfr2 (Y250X) mutation was detected in 6 patients with heterozygous conditions. None of the patients were presenting homozygous condition while four controls were presenting heterozygous and one with homozygous condition. Controls were presenting 3% and 0.6% of Tfr1 rs3817672 SNP heterozygosity respectively.

Conclusion: Tfr2-Y250X and Tfr1-rs3817672 SNP showed clinical association with iron deficiency anemia and screening for mutations of Tfr2 is a new diagnostic tool that can be offered to patients who do not have HFE mutations or who have incomplete HFE genotypes. This results may have practical implications for the molecular diagnosis of hemochromatosis. Genotyping the Tfr gene should be included in the disease diagnostic protocols.

Introduction

Transferrin receptor is the main receptor for transferrin and allows transferrin bound iron uptake by the cell. Transferrin receptor gene expression is regulated by cellular iron requirements. Tfr1 is a cell surface membrane protein and mainly involved in iron homeostasis by regulating cellular iron uptake in relations with the HFE protein. A newly identified member of the transferrin receptor family is Tfr2 which has moderate homology to Tfr1. The Tfr2 gene organized into 18 exons and maps to 7q22, spans for approximately 21 Kb protein. Regulatory role for this molecule in iron absorption have been observed in patients with non-HFE haemochromatosis through mutational analysis of Tfr2 gene. Both Tfr1 and Tfr2 are capable of transporting transferrin bound iron into the cell and supporting cell growth. However, their properties differ in several critical ways. Tfr1 has a higher similarity for holotransferrin than does Tfr2. The Tfr2 mRNA expression prototype is quite different from Tfr1. In particular, Tfr1 gene demonstrates minute hepatic expression whereas the Tfr2 gene is expressed at much elevated levels in liver compared with other tissues. Both are fluctuate in their response to changes in cellular iron status. The Tfr1 transcript contains multiple iron responsive elements in the untranslated regions which stabilize the Tfr1 transcript under circumstances of low cellular iron whereas Tfr2 transcript does not include these elements, and Tfr2 message and protein levels vary mildly with changes in iron status. Since the initial report of the Y250X mutation, four additional Tfr2-coding sequence mutations have been identified in patients with non-

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Received: 12.01.2019; Accepted: 21.08.2019
HFE-associated HH. These mutations are: E60X, M172K, AVAQ 594–597del, and Q690P. With the exception of Q690P, all of the recognized TFR2 mutations have been in pedigrees from Italy. However, the clinical importance of the interaction of transferring mutations with iron deficiency anemia leftovers ambiguous. Thus, the objective of my study was to investigate the effect of TFR1 and TFR2 genotypes on clinical parameters in patients with iron deficiency anemia.

Material and Methods

Patient and Laboratory work

The subjects recruited for this study were presented Iron deficiency anemia and study was conducted in the department of Biotechnology APS University, India. Cases of IDA were diagnosed by means of iron profiling, whereas patients with thalassemia, hemoglobinopathies and other chronic disease were excluded from the study. Five ml venous blood sample were collected from the patients after they had signed an informed consent form. Complete blood count and red cell indices were measured by automated cell analyzer (SYSMEX K-4500 Kobe, Japan). Serum transferrin receptor, ferritin and CRP analysis was done by ELISA method while ESR analysis was done according to Wintrobe’s method.

Molecular Analysis

Isolation of DNA was done by using a kit (Bioserve). TFR2-Y250X mutation was performed by PCR-RFLP method according to published literature. Identification of TFR1 SNP rs3817672 was done by using PCR-RFLP method. A 591bp bp fragment containing rs3817672 SNP amplified using sense primer 5’CAGGAGAGGACTTCCCTGC and antisense primer 5’GATACTGACTGGCTAGGGG. Restriction enzyme (NlaIV) was selected with the help of NEB cutter software. Restriction enzyme was used according to the manuals of the manufacturer. Taq DNA polymerase and DNTPs were obtained from NEB, oligonucleotide were procured from Sigma Eldritch Company and used 25 pm concentration. 1.5U/µl Taq polymerase while 0.2mm/µl DNTPs each and 1.5mm/ µl mgel, were used for 50µl reaction. Amplification was performed using BIO-RAD thermocycler machine. A total of 35 cycle were performed using the following conditions; 94°C,1 min.; 60°C,1 min; and 72°C, 2 min. with an additional 5min. Extension at 72°C, in the final cycle. Agarose gel picture of amplified TFR1 gene and restriction digestion fragments are given in Figures 1 and 2 respectively.

Statistical analysis

Mean values, standard deviations, and frequency distributions were used to evaluate the biochemical and clinical data. Student’s t-test was used to compare the means of groups using GraphPad software (version 3.06). P value < 0.05 was considered statistically significant.

Result

Blood samples were collected and characterized from a total of 460 patients of Iron deficiency anaemia and 500 age- sex matched controls. Patients and controls were predominantly belonging in tribal groups of central state of India. A total 289 male and 171 female with a mean age of 23.5±2.8 and 20.1±3.2 years respectively, were recruited for the study. Out of 171 female, 67 were in gestation and 104 were in non gestation period. A complete blood count, iron profile, CRP sTfR and ESR were performed in all subjects as well as in controls (300 male and 200 female with mean age 22.7±3.1 and 19.3±2.8 years repsectively). TFR1 SNP rs3817672 primers was designed and characterized by using of PCR-RFLP method. DNA of rs3817672 resulted in a PCR product of 591 bp when visualized in agarose gel. NlaIV Restriction enzyme was used for TFR1 SNP rs3817672. Digested product was checked in 3% ethidium bromide containing agarose gel. After restriction digestion of TFR1SNP rs3817672 PCR product, various fragmented products were seen in agarose gel which was track through double digested bromphenol blue dye. Three genotypic patterns were seen in studied subjects. A 93, 151, 347 bp and 93,151, 244, 347 bp product size were representing homozygous mutant and heterozygous conditions respectively while 244,347bp restriction fragments denote wild type homozygous condition. Amongst the IDA patients, 13 were heterozygous and five were homozygous for rs3817672 SNP. TFR2 (Y250X) mutation was detected in 6 patients with heterozygous conditions. None of the patients were presenting...
homozgyous condition while four controls were presenting heterozygous and one with homozgyous condition. Controls were presenting 3% and 0.6% frequency of TFR1 rs3817672 SNP heterozygous and homozgyous respectively. Comparative Iron profile, value of sTFR, CRP and ESR of mutant and wild genotype IDA patients is given in Table 1. Comparative frequency of clinical symptom is given in Figure 3.

Discussion

The role of TFR1 gene mutation in iron deficiency anemia was unclear. The role of TFR2 as a substitute for TFR1 in its lack is still vague. Due to severe iron deficiency, knock out of TFR1 causes embryonic lethality in mice, while TFR2 mutations in humans and targeted mutagenesis or failure of TFR2 in mice result in iron excess.15-16 These studies propose that TFR1 and TFR2 have different functions and that TFR2 is not capable to substitute for the absence of TFR1. It has been established that targeted deletion or mutagenesis of the TFR2 gene in mice recapitulates the human iron overload disorder type-3 hereditary hemochromatosis.15,16 First relationship between TFR2 mutations and iron overload was established in a study of Italian patients with non HFE linked HH and suggested that the largely contribution of TFR2 mutations to the total number of cases of HH is stumpy.17 TFR2 mutations manifest the augmented transferrin saturations, elevated serum ferritin levels and ultimately periperal hepatic iron loading in patients which is also observed in the mutant mice.18 Prolonged iron overload manifest the end organ damage included liver cirrhosis, arthritis, diabetes, and hypogonadism. The normal erythroid parameters in the Tfr2 mutant mice might be explained by the activity of TFR1, which also is highly expressed in erythrocyte precursors.19 Patients with homozygous for TFR2 (Y250X) truncation mutation had a clinical picture similar to HFE related HH, including hepatic iron loading.20 My study report 15 heterozygous and 3 homozygous of TFR1 rs3817672 SNP genotype in controls while 0.91% and 0.22% control were presenting TFR2 (Y250X) heterozygous and homozgyous conditions respectively. Amongst IDA patients frequency of heterozygous and homozygous was 2.98% and 1.14% respectively. Frequency of TFR2 (Y250X) heterozygous genotype was 1.36% in iron deficiency anaemia. This observation suggested that frequencies of these mutations are higher in patients than controls. We observed higher frequency of TFR1rs3817672 SNP in patents as well as in controls groups in comparison of TFR2-Y250X mutation. Various TFR2 gene mutations have been observed since in patients with iron overload and suggested that the iron homeostasis abnormalities are caused by functional loss of TFR2.13,14 These studies revealed that the roles for TFR1 and TFR2 in iron homeostasis are not superfluous due to TFR1 forms a complex with HFE, it seemed plausible that TFR2 may connect also with HFE. The practice of using a battery of assays improves the precision of defining iron nutrition in a population; however, 2 pitfalls persist to confound this issue: the complexity in precisely detecting mild iron deficiency and the identification of inflammation as a cause of changes in laboratory test results that are not due to iron deficiency.20 These pitfalls can be clarified by the serum transferrin receptor (TFR) assay thus far because it is not influenced by acute or chronic inflammatory circumstances and seems to be able to detect mild iron deficiency.21-23 A study confirms the role of TFR2 as the HFE3 gene. Frequency of typical clinical symptom of iron deficiency anaemia is less severe in TFR (TFR2- Y250X and TFR1- rs3817672 SNP) mutant. Data of this research showed the TFR heterozygous may be predators of IDA and need diagnosis of TFR genotype. It can be used in treatment decision and overcomes from the iron overload and chelation therapy. The identification of TFR2 mutations related hemochromatosis should be observed among patients that can estimate the phenotype severity.24 A study reported unusual iron phenotype in a new mutation, Arg455Gln, in exon 10 of TFR2. This mutation could represent a modifier for penetrance of the hemochromatosis phenotype when present with homozgyosity for Cys282Tyr.25 Disease causing mutations in the TFR1 gene have been not identified till date. However, there are missense coding region variants (rs3817672) in exon 4 with appreciable frequency and encodes S142G amino acid substitution, that may have functional effects. This polymorphism does not have a homogeneous global distribution. Its minor allele in Caucasians is the major allele in Asians and Africans. There is no nonsense mutation described in TFR1.26,27

Conclusion

Finding of my research suggested high impact of TFR2 -Y250X and TFR1- rs3817672 gene mutation in pathophysiology of iron deficiency anemia and showed positive correlation. It may act the predator of disease severity. Data of the study provide a genotype-phenotype correlation of TFR gene mutation with iron deficiency anemia.

Identification of TFR2 as the HFE3 gene is of relevance regarding
modifier genes in hemochromatosis. The presences of modifier genes that modulate the disease severity, can be used a diagnostic tools in Iron deficiency anemia.

References


To All Chairmen and Secretaries of API State Chapter / City Branches

A meeting of the Chairmen and Secretaries of all API State Chapters and City branches will be held on Sunday 5th January 2020 at 3.00 p.m. at the venue of APICON 2020, Kunjamal N. Convention Centre (KNCC), Fatehabad Road, Agra.

You are requested to attend the meeting.

Dr. Mangesh Tiwaskar
Hon. General Secretary
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Prevalence of Hypertension among Urban Poor with and without Diabetes - A Study from South India

Anu Maria Jacob¹, A Muruganathan², Manjula Datta³, Vijay Viswanathan⁴*

Abstract

Objective: Hypertension and Diabetes are considered as two leading risk factors of mortality in the world. According to an ICMR-INDIAB study, prevalence of hypertension in Tamil Nadu was higher in urban population than the rural population. Hence this study was planned to estimate the prevalence and distribution of hypertension among the urban poor with and without diabetes.

Methods: A community based cross-sectional study was conducted among two backward communities in North Chennai, Tamil Nadu. A total of 330 participants with and without diabetes, were recruited after screening 1272 subjects and self reported diabetes cases of 235. Measurement of blood pressure was done in both groups based on American Heart Association (AHA) criteria and diagnosis of diabetes was made based on the previous history of diabetes and WHO criteria.

Results: Prevalence of hypertension (Stage II) among the people with diabetes and without diabetes was reported 44.8%, and 42.6% respectively (p = 0.046). Obesity and overweight were significantly associated with prevalence of hypertension among people with diabetes (p = 0.021). Distribution of stage II hypertension among males and females were 46.2% and 42.80% respectively. There was significant gender difference in the prevalence of HTN (p = 0.043).

Conclusion: Prevalence of hypertension was found to be higher among the diabetic group compared to the non-diabetic group (44.8% vs 42.6%), though the difference between the two was not very substantial. We therefore conclude that half of the urban poor are hypertensive even if they are not diabetic.

Introduction

Hypertension (HTN) and Diabetes Mellitus (DM) are the two leading risk factors of mortality in the whole world. Hypertension occurs relatively with few symptoms and it remains largely under-detected, especially in developing countries where routine screening at health care is extremely underutilized. There is evidence that blood pressure reduction has been associated with a decreased risk of diabetes related complications.1

High blood pressure is reportedly accountable for 13% of deaths and high blood glucose is accountable for 6% globally.2 Hypertension is said to kill nearly 1.5 million people in the South-East Asia region. Two third of the global hypertensive cases are living in the developing countries. It is estimated that, by 2025, there will be 1.56 billion adults living with hypertension in the world.3 Elevated blood pressure (BP) is a major risk factor for ischemic heart disease, peripheral vascular diseases, stroke, myocardial infarction, and renal failure.4 It is a vital global public health issue and considered as leading cause of cardiovascular diseases and premature death. According to the World Health Organization report of 2011, 32.5% of the Indian population were reported to have high blood pressure. Almost equal prevalence was reported in men and women, 33.2% and 31.7% respectively.5 Indian Council of Medical Research-India Diabetes (ICMR-INDIAB) study reported that overall prevalence of hypertension in India was 26.3% and the state wise prevalence of hypertension in Tamil Nadu was 31.5% in 2014.6 Additionally there is an increasing prevalence of hypertension in the Indian population, especially among the urban population.7 Study from Nepal reported that higher prevalence of hypertension was observed among people with low educational status.8 Also there is evidence that prevalence of hypertension and poor treatment of hypertension was higher among people in the lower socioeconomic strata, and especially in the lower occupational categories.9,10 Contradictory to above studies, a multicentric study from India reported that there is a correlation between higher educational status and prevalence of hypertension in elderly people.11 Also there are various studies report that prevalence of hypertension was significantly associated with high socioeconomic status.12,13

Various studies have reported that high blood pressure increase the risk of long-term micro and macro vascular complications such as heart disease, stroke, kidney failure, peripheral vascular disease, and can cause death among people with type 2 diabetes mellitus.14,15 The Twin Epidemic (SITE) Study by R.J. Shashank et.al reported that existence of hypertension as higher among diabetic patients (59.3%) than the non-diabetic subjects (39%).16 Similar studies reported of a high prevalence of hypertension in diabetes than non-diabetes.17,18 Also it was found that control of hypertension slows down the progression of diabetic complications.19,20 Recommendations from American Diabetes Association and the European Association for the Study of Diabetes noted that destructive
management of cardiovascular risk factors, which include high blood pressure and obesity, may be even more beneficial in patients with T2DM because of their increased risk of cardiovascular morbidity and mortality.21

This study attempts to find out the prevalence of hypertension among diabetic and non-diabetic urban poor.

**Methods**

This community based cross-sectional study was conducted among two backward communities (Panamarathotty and Jeevarathnam nagar) in North Chennai, Tamil Nadu. A total of 1272 apparently healthy individuals in the age group of 20-80 years were screened for diabetes with 1275 confirmed diabetes cases were among two backward communities (Panamarathotty and Jeevarathnam nagar) in North Chennai, Tamil Nadu. A total of 1272 apparently healthy individuals in the age group of 20-80 years were screened for diabetes with 1275 confirmed diabetes cases were reported. Sample size was calculated based on the existing population which found that 50% of the diabetics and 35% of non-diabetes were hypertensive. Using two sample proportion formula, (95% confidence level, 80% power, proportion of hypertension in group I being 50% and group II being 35%); the estimated sample size came to 167. A total of 330 participants have been recruited for two groups with 165 subjects in each. Blood Pressure was measured in both groups using OMRON automatic blood pressure monitor (HEM-7111). AHA 2017 guidelines were used to diagnose the hypertension.24

Structured interview schedule was prepared and informed written consent was obtained from the participants. Each participant was interviewed by trained field investigator and data on socio demograpic details such as age, gender, behavioural risk factors such as smoking, alcoholism, anthropometric measurements such height, weight, waist circumference were collected. Body Mass Index (BMI) was classified based on the Asian-Pacific cutoff points.23 The study was conducted between February and July 2018. The study was approved by the institution’s ethics committee.

**Statistical Analysis**

Data were entered in MS Excel and statistical analysis was done using SPSS software version 20. Mean and standard deviation were used for reporting continuous variable and frequencies were used for categorical variables. Chi square test and t-test were used to test statistical significance. Binary logistic regression was done to identify the association with hypertension and its risk factors. In which blood pressure >140/90 and <140/90 was dependent variable and age, diabetic status, gender, behavioal habits, body mass index, waist circumference were independent variables. A p value of less than 0.05 was considered as statistically significant.

**Results**

Data of 330 participants with and without diabetes (165 DM and 165 Non-DM) were analyzed in this study. Mean age of the DM subjects was 44.16±8.2 and Non-DM was 43.6±11.6. Age was comparable in both groups (p=0.613). Male female ratio was similar in both groups 40:125. Regarding the behavioural risk factors, majority of the participants reported they did not have any behavioural risk habits such as smoking or alcoholism. BMI was found higher among non-diabetic group compared to diabetic group 27.9±6 and 26.3±5 respectively (p=0.009). There was significant difference in the systolic pressure of both groups. Higher systolic blood pressure was seen people with diabetes than people

<table>
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<th>Table 1: Demographic and clinical details</th>
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<td>Never</td>
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<td>Previous history HTN</td>
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<td>Abnormal waist circumference male</td>
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<td>Abnormal waist circumference female</td>
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<th>Table 3: Prevalence of hypertension and obesity among diabetic and non-diabetic population</th>
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<td>DM n (%), *p value</td>
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p ≤ 0.05 is considered as significant
without diabetes (p=0.002). However diastolic pressure was found similar in both groups (p=0.452). Among the total participants 27.9% of diabetics and 16.4% of the non-diabetics reported a previous history of hypertension. Abnormal waist circumference was found more among females than males. In both the groups 95% of the males had normal waist circumference (<102 cm) and among females 63.20% diabetics and 62.40% non-diabetics were reported normal waist circumference (<102 cm). Details are shown in Table 1.

### Prevalence and Distribution of Hypertension

According to AHA 2017 classification, prevalence of stage II HTN among total population was 43.6%. Out of this 44.8% were diabetic and 42.4% were non-diabetic. There was significant difference in the prevalence of HTN among diabetic and non-diabetic subjects (p= 0.046), despite a small difference in the percentage between the two. Prevalence of hypertension was found more among males than females. Stage 1 hypertension was reported among 41.30% males and 32.40% females (p=0.017). Stage II hypertension was reported among 46.30% of the males and 42.80% females (p= 0.043). There was significant gender difference in prevalence of HTN. Among the diabetic subjects, 45% males were hypertensive and 44.80% of the females were hypertensive and among non-diabetic subjects, 47.50% males were hypertensive and 40.80% of the females were hypertensive (Tables 2 and 3).

### Prevalence of Obesity

Prevalence of obesity (≥25 kg/m²) reported among urban poor was 63.3% (Table 4). Prevalence was found to be similar in both diabetic and non-diabetic groups (58.2% vs 68.5%). Details are shown in Table 3.

### Association with Obesity and Hypertension

Among the total obese subjects 48.3% were stage II hypertensive and 33.5% were stage I hypertensive. Among the overweight category 32.8% stage II hypertensive and 44.8% were stage I hypertensive (Table 4).

Among the diabetic group, obesity was associated with stage II hypertension (p= 0.021) but among the non-diabetic group, obesity was not associated with stage II hypertension (p=0.129). Similarly, in diabetic group obesity and overweight were associated with stage I hypertension (p= 0.005, p= 0.015) but in non-diabetic subjects there was no significant association with hypertension and obesity or overweight.

In the diabetic subjects, 50% of the hypertensive (stage II) were obese, and in non-diabetic subjects, 46.9% of the hypertensive (stage II) were obese. Likewise in the diabetic group 34.3% of the hypertensive (stage II) were overweight and 30.4% hypertensive (stage II) were overweight in the non-diabetic group. Details are shown in Figures 1 and 2.

### Association with various risk factors and hypertension

Binary logistic regression analysis showed that age, alcohol consumption, body mass index were significantly associated with prevalence of hypertension. Gender, history of diabetes waist circumference were not significantly associated with prevalence of hypertension (Table 5).

### Discussion

The cross-sectional study of prevalence of hypertension among urban poor revealed that there is a greater risk of developing hypertension even if they are not diabetic. Many studies had reported that prevalence of hypertension is associated with socio-economic status, especially higher socio-economic status. However, this statement is no longer true.

The present study reported that overall prevalence of hypertension among urban poor was 43.60%, this prevalence is more or less equal to TWIN epidemic study (2010) by Joshi SR et al which had reported 46.0%
prevalence of hypertension. A Study on Chennai Urban Population Study (CUPS) 2003 revealed that prevalence of hypertension among general population was 21.1%. Also in the Chennai Urban Rural Epidemiology Study (CURES) 2007, prevalence of hypertension was reported 20%. Both studies were conducted in a 5 years gap, but there is not much change in the prevalence of hypertension among the Chennai population. But the prevalence of hypertension among urban poor of the same city was reported as having doubled among the general population in the last 10 years.

ICMR-INDIAB study reported that 31.5% of urban populations of Tamil Nadu are hypertensive. Hypertension was significantly higher among urban residence than the rural residence in Tamil Nadu. The present study reported that prevalence of HTN was more among people with diabetes than non-diabetes, however a study from US reports that hypertension was seen in 50% of the people with diabetes than the people without diabetes. A study from India reported that prevalence of hypertension was higher among women in the urban areas as compared to rural areas. The same study also reported that significant determinants of hypertension among urban population were, place of living, high dietary fat, low fiber intake and obesity. In the present study prevalence of hypertension was more among men compared to women. Also we found that majority (63%) of the urban poor were obese and 17.5% are overweight. A study by Vigneswar et al reported that prevalence of obesity was 57.3% among urban poor (2015). The present study found that obesity and hypertension were statistically significant among people with diabetes, where as in non-diabetics; obesity and hypertension were statistically not significant. A study from south India reported that intake of salty food and adding additional salt to meal was significantly associated with increased risk of pre-hypertension. Those who are taking salty food daily/weekly twice or thrice/occasionally were found with high probability of getting hypertension as compared to those who did not take salty food.

**Conclusion**

Hypertension is highly prevalent among urban poor. Prevalence was found to be higher among people with diabetes than the people without diabetes, though the difference between the two was not very substantial. Prevalence of hypertension was significantly associated with obesity in people with diabetes but obesity was not associated with people without diabetes. Then why the non-diabetic urban poor are hypertensive? There is the need to do further research among the urban poor in the area of vascular diseases, dietary habits, psychosocial factors such as stress and sleep apnea which are considered common causes for hypertension.

**Acknowledgement**

We acknowledge Ms. Hepzibah S and Mr. Seenj Mohammed for helping in data collection. Also we extend our heartfelt thanks to the study participants.

**References**


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Low Dose Prophylaxis vis-a-vis on-Demand Treatment Strategies for Hemophilia: A Cost Effective and Disability Attenuating Approach

Ajeet Singh1, Sudhir Mehta2*, Laxmi Kant Goyal3, Shaurya Mehta4, Bhawani Shankar Sharma1

Abstract

Aim: To assess effect of low dose prophylaxis in hemophilics in terms of bleeding, joint function, QoL and cost-effectiveness.

Methods: Analytic study done during one year among 70 adult hemophilics. In observation period (12 weeks), on-demand factor and during prophylaxis (12 weeks), low dose factor was given (Factor VIII 10 IU/KgBW biweekly for haemophilia A and Factor IX 20 IU/KgBW weekly for haemophilia B). Clinical joint assessment was done by Gilbert score and improvement by WFH definitions.

Results: Bleed reduced by 68.99% in moderate hemophilics (40 v/s 129) and 64.86% in severe hemophilics (26 v/s 74) (p<0.05). During observation in moderate hemophilics, joint, soft tissue and mucosal bleeds occurred in frequency of 120, 1 and 8. This was reduced to 39 joint bleeds, 1 soft tissue bleed and no mucosal bleed during prophylaxis. In severe hemophilics, 70 joint, 2 soft tissue bleeds and 2 mucosal bleeds occurred during observation which reduced to 26 joint bleeds without soft tissue/mucosal bleed in prophylaxis. Bleeding episodes decreased by 65.79% in joints, 66.67% in soft tissues, 100% mucosal bleeds.

After prophylaxis one joints (0.61 %) showed good improvement in joint function, thirty (18.18 %) joints showed moderate improvement and ninety two joints (55.76 %) showed mild improvement in joint function. Hospitalization reduced by 60.34% (163 v/s 411) and absenteeism by 53.73% (279 v/s 603). Factors consumption reduced by 12.33 % during prophylaxis period.

Conclusion: The low dose prophylaxis strategy significantly decreased the subsequent episodes of total bleeds including joint bleeds and improved the joint function as well as quality of life.

Introduction

In economically constraint countries like India, hemophilia is considered as a high cost disease. Total estimated prevalence of hemophilia in India based on population alone, is more than 120,000 out of which only 17,346 have been identified. Few of these patients have access to treatment with factors. This has lead to high morbidity (disability) and mortality among hemophilics.

Joint bleeding is a common complication among hemophilics which leads to crippling arthropathy subsequently, if not treated properly. The frequency of joint bleeding also increase with age of the patient. The key to a long-term management of hemophilia is an efficient prophylaxis that prevents joint bleed. Many studies have demonstrated that prophylactic factor infusion reduces or prevents development of arthropathy among hemophilics.

Currently, prophylactic factor infusion is considered as standard of care for hemophiliacs with the purpose to reduce joint related morbidity. In India, conventional prophylactic regimens used in high-resource nations, are not possible due to great economic burden on society and health care system. Therefore low dose prophylactic programs, with an aim to reduce arthropathy as well as to improve quality of life is an alternative, economically-friendly, feasible and potentially preferable strategy in India compared to on-demand care.

Rajasthan is geographically the largest state of India with developing economy as three fourth of the state in under arid zone. A Comprehensive Hemophilia Care Program (CHP) at the SMS Medical College was started in year 2012. Factor infusions and testing are offered to haemophilia patients free by the Rajasthan state government since 2012 under the Chief Minister Free Medicine/Investigation Scheme. This scheme has lead to a dramatic sea-change from only plasma transfusion to on-demand factor therapy in hemophilia patients in Rajasthan.

The data presented here were collected in an endeavour to assess the effect of low dose prophylaxis in hemophilics in terms of frequency of bleeding, joint function, QOL (hospitalization and absenteeism from work/school) and cost-effectiveness.

Material and Methods

This hospital based observational, prospective, analytic study was conducted at a tertiary care center in Rajasthan, during April 2016 to November 2017, after obtaining due permission from Research Review Board/ Institutional Ethics Committee and informed written consent of the study participants. This study included an observation period of 12 weeks.

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Received: 20.12.2018; Accepted: 16.07.2019
and a prophylaxis period of 12 weeks. During the observation period, patients received on-demand treatment of plasma-derived factor infusion (Factor VIII for Hemophilia A and Factor IX for hemophilia B) as free supply under Chief Minister Free Medicine Scheme of Rajasthan State Government. During the prophylaxis period, factor was given in dose of Factor VIII 10 IU per kg body weight twice a week for haemophilia A and Factor IX 20 IU per kg body weight once weekly for haemophilia B. All infusions were given by trained nurse at our center.

The hemophilics patients who were followed regularly at our center and having clinical joint disease with three or more joint bleed into single joint during initial 12 weeks observation period were included in this study. Hemophilics with history of inhibitors were excluded.

Seventy adults patients (58 Hemophilia A and 12 Hemophilia B) (age group 16-55 years) were included in this study after due motivation during hospitalization for acute bleeds. All of these patients reside in Jaipur city, within reachable distance from our center.

Data were collected in pre-structured form at each visit regarding frequency of joint bleed, frequency of hospitalization for joint bleed and school / work attendance. At the start and at the end of study period (prophylaxis period), clinical joint assessment was done by the Gilbert score system for each joint. Improvement attributable to prophylaxis was based on WFH definitions as: poor (no score decreased), mild (1–2 scores decreased), moderate (3–4 scores decreased) or good (≥5 scores decrease).

Moderate haemophilia is defined to have baseline factor VIII (FVIII)/factor IX (FIX)activity 1–5%; while severe haemophilia includes baseline FVIII/FIX activity <1%. All patients enrolled had their baseline factor levels and inhibitor status (after more than 3 days washout period) re-tested.

Clinical joint disease is defined as the presence of visible joint swelling and/or limitation of movement and/or joint deformity in the absence of an acute joint bleed.

### Statistical Analysis

Microsoft Excel® and SPSS® 20 for Windows® were used for data storage and analysis. Paired t test and McNemar’s Test were used to determine statistical difference between variables. Results were considered significant if P < 0.05.

### Results

We included 70 hemophilics in our study out of which 58 cases were of Hemophilia A (18 severe and 40 moderate hemophilia) and 12 cases were of Hemophilia B (3 severe and 9 moderate hemophilia).

During observation period, total 129 episodes of bleeds occurred in moderate hemophilia and 74 episodes of bleeds occurred in severe hemophilia. In prophylaxis period only 40 episodes of bleeds occurred in moderate hemophilics and 26 episodes of bleeds occurred in severe hemophilics. The episodes of bleeds were decreased by 68.99% in moderate hemophilics and by 64.86% in severe hemophilics during prophylaxis period. (p<0.05) (Table 1A).

During observation period in moderate hemophilics, joint, soft tissue and mucosal bleeds occurred in frequency of 120, 1 and 8 respectively. This was reduced to 39 joint bleeds and only 1 episode of soft tissue bleed during prophylaxis period. No mucosal bleed occurred in moderate hemophilics during prophylaxis period. In severe hemophilics, 70 joint, 2 soft tissue and 2 mucosal bleeds were seen during observation period which reduced to 26 joint without soft tissue/mucosal bleed in prophylaxis period. During prophylaxis, total decrease in bleeding episodes were 65.79% in joints, 66.67% in soft tissues and 100% in mucosal bleeds. (Figure 1).

After completion of prophylaxis period, all study participants were again evaluated for joint function including shoulder joints, elbow joints, wrist joints, hip joints, knee joints and ankle joints. Out of total 165 joints, one joints (0.61%) showed good improvement in joint function, thirty (18.18%) joints showed moderate improvement and ninety two joints (55.76%) showed mild improvement in joint function. Only forty two joints...
The duration of hospitalization (other than for factor infusion) was 411 days in observation period which reduced by 60.34% during prophylaxis period (only 163 days of hospitalization). The duration of absenteeism from work/school was also reduced by 53.73% during prophylaxis period compared to observation period (279 vs 603). Improvement in quality of life occurred in prophylaxis period in terms of decrease in hospitalization and absenteeism from work/school (Table 1 C, D).

During observation period, all patients (70, 100%) had joint bleed which was reduced to 50 patients (71.43%) during prophylaxis period. Fifty patients (71.43%) required hospitalization and absenteeism from work/school during prophylaxis period compared to observation period (70 patients, 100%) (Table 3).

Total consumption of factors was 11,84000 Units (9,82000 Factor VIII and 2,020000 units Factor IX) during observation period which reduced by 12.33% during prophylaxis period (total consumption 10,38000 Units, FVIII 8,78000 Units and FIX 1,60000 units). Total saving of 1,46000 units (Factor VIII 104000 Units and Factor IX 42000 Units) was made by using low dose prophylaxis.

Table 2: Improvement in joint function after secondary prophylaxis period

<table>
<thead>
<tr>
<th>Type</th>
<th>Hemo A</th>
<th>Hemo B</th>
<th>Joints</th>
<th>Poor</th>
<th>Mild 1-2</th>
<th>Moderate 3-4</th>
<th>Good ≥ 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Moderate</td>
<td>100</td>
<td>17</td>
<td>117</td>
<td>31</td>
<td>6.6</td>
<td>19</td>
<td>1</td>
</tr>
<tr>
<td>Severe</td>
<td>40</td>
<td>8</td>
<td>48</td>
<td>11</td>
<td>26</td>
<td>11</td>
<td>00</td>
</tr>
<tr>
<td>Total</td>
<td>140</td>
<td>25</td>
<td>165</td>
<td>42</td>
<td>92</td>
<td>30</td>
<td>1</td>
</tr>
</tbody>
</table>

(25.45%) had poor improvement in joint function after prophylaxis period (Table 2).

The effect of low dose prophylactic factor therapy is assessed in this study. In this study, the low dose prophylactic factor therapy resulted in significant decrease in subsequent episodes of total bleeds including joint bleeds. The joint function also improved after prophylaxis period. The duration of hospitalization (other than for factor infusion) also significantly reduced in patients during prophylaxis compared to on-demand therapy. The quality of life in terms of reduced absenteeism form work/school also improved significantly.

We used low dose (Factor VIII 10 IU per kg body weight twice a week for haemophilia A and Factor IX 20 IU per kg body weight once weekly for haemophilia B) during prophylaxis period which is much lesser that the dose given in previous primary prophylaxis studies.

Rajasthan is geographically the largest state of India with estimated population of 68,548,437 with three fourth of the state is under arid zone. The estimated population of haemophiliacs in Rajasthan is approximately 7,000 and the per capita income of INR 72,156.

Total consumption of factors was 11,84000 Units (9,82000 Factor VIII and 2,020000 units Factor IX) during observation period which reduced by 12.33% during prophylaxis period (total consumption 10,38000 Units, FVIII 8,78000 Units and FIX 1,60000 units). Total saving of 1,46000 units (Factor VIII 104000 Units and Factor IX 42000 Units) was made by using low dose prophylaxis.

Discussion

Hemophilic arthropathy is a disabling disease associated with recurrent joint and soft tissue bleeds. The primary prophylaxis therapy in hemophilia decrease the joint bleeds but the high cost creates implementation difficulties in economically constraint countries like India. The prophylaxis therapy with conventional dosage is also not feasible due to its high cost.

In Rajasthan state, Chief Minister’s Free Medicine Scheme was started on October 2nd, 2012 with a purpose to make available the essential medicines free of cost to the common people. With free of cost availability of Anti-Hemophilic Factor VIII, F IX and FIEBA, the treatment of hemophiliacs in Rajasthan has undergone a sea wide change from only plasma transfusions to on demand factor therapy to low-dose prophylactic factor infusion.

This study has clearly demonstrated that low dose prophylaxis in hemophiliacs is not only cost-effective but also significantly reduces joint morbidity and improves quality of life.

Limitations

This study was done at a tertiary care center with limited study population and the duration of follow-up was also relatively short (study duration 24 weeks per patient). A multicenter, long follow-up study with large sample size is required to validate the results across the state or country. The current study definitively has built a platform for such larger studies.

Conclusion

The low dose prophylaxis strategy significantly decreased the subsequent episodes of total bleeds including joint bleeds among haemophiliacs and improved the joint function as well as quality of life. The low dose prophylaxis therapy might be a cheaper, affordable, feasible and disability attenuating approach for hemophilia care in economically constraint health care delivery system.

Author Contributions

SM, AS and LKG designed the study; AS, SM and LKG performed all the clinical work, SM, ShM, AS and LKG wrote the manuscript; SM and LKG conceptualized and supervised the work; all authors read the manuscript and approved for submission.

References

A Study of Clinical Profile and Outcome of Acute Heart Failure in Elderly Patients

Vishal Gupta¹, Neelam Redkar²*, Anuraag Jena³

Abstract

Introduction: The significant increase of life expectancies over the last few decades, has lead to a major change in the morbidity and mortality profile of elders. Heart Failure (HF) is predominantly a disorder of the elderly with rates increasing exponentially with time.

Material and Methods: The Observational and prospective study was conducted in a tertiary care teaching hospital. The study included all patients >60 years of age diagnosed as acute heart failure as per Boston Criteria. Patients with chronic obstructive pulmonary disease were excluded. Patients were followed till either discharge or death.

Results: Total 56 patients were enrolled for the study. Male and female formed 53.57% and 46.43% of study population respectively. Based on Ejection fraction on 2D Echocardiography Diastolic HF (EF >40%) was seen in 30 patients (53.57%) while systolic dysfunction was seen in 26 patients (46.43%). As per Boston score criteria, maximum patient 33 (66.07) fell into range of 8-12 while remaining had score range 5-7. None of the patients were in lesser score range of 1-4. Out of 56 patients 44 (78.57%) were discharged 12 (21.43%) patients expired.

Heart failure (HF) is a complex clinical syndrome resulting from the inability of the heart to adequately supply the metabolic demands of tissues, or do so only with elevated filling pressures.¹ The significant increase of life expectancies over the last few decades, has lead to a major change in the morbidity and mortality profile of elders. HF is predominantly a disorder of the elderly with rates increasing exponentially with time. The prevalence of HF approximately doubles with each decade of life.² Despite increased prevalence and improved management very less statistics exist on heart failure in India. Amid that elderly are underrepresented in most studies. The clinical profile of heart failure in elderly patients will not only help in diagnosis but also management of the condition. Our study is aimed at studying the clinical profile, etiology and outcome of heart failure in such group at tertiary care centre.

Materials and Methods

Study design

The Observational and prospective study was conducted for 12 months in a tertiary care teaching hospital. Ethical approval was obtained from Institutional Ethics Committee. Subjects satisfying inclusion and exclusion criteria were recruited in the study after obtaining written informed consent. All elderly patients admitted in emergency, medicine wards and ICU having symptoms of heart failure were screened. A detailed history was recorded in addition to a thorough clinical examination, and routine and specific laboratory investigations were done. The study included all patients >60 years of age diagnosed as acute heart failure as per Boston Criteria¹ (Table 1). Patients were all followed till either discharge or death. Patients with chronic obstructive pulmonary disease were excluded.

Data Collection

All elderly patients admitted in emergency, medicine wards and ICU

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Received: 23.01.2019; Accepted: 21.08.2019
In all patients followed by fatigue (58.9%) and pedal edema (53.6%). The other symptoms were Orthopnea and paroxysmal nocturnal dyspnea (PND) seen in 42.9% each,

Cough (33.9%), Chest pain (23.2%), Weight gain (23.2%), Abdominal Pain (17.8%) and Nocturia (8.9%). Hemoptysis was seen in only one patient.

In our study population most common sign of heart failure (Table 2) was chest crepitations (92.85%), followed by raised jugular venous pressure (73.21% patients) and pedal edema (51.78% patients).

Most common risk factor for heart failure was hypertension (seen in 73.21%), Ischemic heart disease (seen in 52% patients) and Diabetes mellitus (seen in 26.78%). 25% patients had history of alcohol intake while 12.5% patients had history of smoking. Tobacco chewing were seen in 25% of cases. Thyroid disorder and Lipid abnormalities were seen in 12.5% and 7.14% respectively.

Etiology for heart failure is shown in Table 3. In our study population, the most common etiology found was hypertension (73.20% patients), followed by ischemic heart disease (51.8% patients).

Based on Ejection fraction on 2D Echocardiography Diastolic HF (EF>40%) was seen in 30 patients (53.57%) while systolic dysfunction was seen in 26 patients (46.43%).

As per Boston score criteria, maximum patient 33 (66.07) fell into range of 8-12 while remaining had score range 5-7. None of the patients were in lesser score range of 1-4.

Out of 56 patients 44 (78.57%) were discharged however 12 (21.43%) patients expired.

Of 15 diabetic patients admitted 9 expired as compared to nondiabetic group in whom only 3 out of total 41 expired. Thus diabetes was associated with higher mortality which was statistically significant. (Using Fisher Exact Probability Test p value is 0.0001)

There was no statistically significant correlation with alcohol consumption or tobacco consumption and mortality rate.

Mean FBS among patients who expired (143.33 ± 34.307 mg/dl) was higher as compared to those who got discharged (117.43 ± 23.871 mg/dl), which was found to be statistically significant. (P value calculated by unpaired t test of means - 0.028).

In our study population Hypertension, Ischemic heart disease and Dilated Cardiomyopathy was not associated with higher mortality i.e statistically non-significant (p value is 0.171, 0.244, 0.244 respectively) (Table 3).

Discussion

Worldwide Heart Failure is a major public health issue. The prevalence of heart failure is known to increase with age and is much higher in elderly patients. One aim of this study is to assess the baseline characteristics for acute heart failure seen in elderly patients (>60 years) presenting to the emergency medical service of a tertiary care hospital with a diagnosis of acute heart failure based on the Boston Heart Failure criteria. Our analysis revealed a similar gender based distribution in this study group as 53.57% males and 46.43% females met the inclusion criteria. Categorically, 51.79% patients were aged between 60-70 years, 42.86% of patients were aged between 71-80 years and 5.35% were more than 80 years old. There was an increase in the number of women presenting with acute HF aged >80 years compared to men who demonstrated an increased predisposition to HF in the 7th decade of life.

The mean age at presentation in our study was 71.357 ± 6.48 years. This is similar to data from analysis of the ATTEND registry where mean age of the total population included was 72.9 ± 13.8 years4. Similarly, another study conducted to assess the clinical profile and prognosis of hospitalized patients with heart failure in Japan showed the mean age on admission to be 68.4 ± 14.9 years. Also, an increase in female distribution was noted among patients aged more than 80 years. This study also reported mean age at the time of death, which was 72.2 ± 13.9 years.5 Comparatively, the Cardiovascular Health Study has shown that the incidence of HF progressively increased...
Trials of HF have tended to exclude the elderly. More recently, several HF trials have focused specifically on the effect of therapies on the elderly, including the Irbesartan in Heart Failure with Preserved Systolic Function (I-PRESERVE) trial (mean age 73 years), the Study of the Effects of Nebivolol Intervention on Outcomes and Rehospitalisation in Seniors with Heart Failure (SENIORS) (mean age 76 years), the Cardiac Insufficiency Bisoprolol Study in Elderly (CIBIS-ELD) (mean age 73 years), the Evaluation of Losartan in the Elderly (ELITE, mean age 73 years), and the Perindopril in Elderly People with Chronic Heart Failure study (PEP-CHF, mean age 76 years). In order to evaluate the clinical profile of elderly patients presenting with acute HF, a detailed history was recorded at presentation. More than 50% of the patients complained of typical symptoms, which included dyspnoea (100%), fatigue (58.9%) and oedema (53.6%). Approximately 10%-50% of patients presented with orthopnoea, paroxysmal nocturnal dyspnoea, cough, chest pain, weight gain and abdominal pain, while <5% complained of nocturia and haemoptysis. Therefore, our analysis has identified dyspnoea, fatigue and pedal oedema as the key clinical features occurring with high frequency at presentation in elderly patients with acute HF. One study has reported that dyspnoea has a sensitivity of 84% and specificity of 34%, fatigue has a sensitivity of 31% and specificity of 70% while pedal oedema has a sensitivity of 50% and specificity of 78% for a diagnosis of HF. Similar estimates of sensitivity and specificity have been reported in other studies as well. 

The etiology and risk factors associated with heart failure are diverse and are likely to vary across world regions based on risk factor prevalence and quality of health care available. Our analysis has identified hypertension (73.20%) to be the most common etiology associated with heart failure followed by ischemic heart disease (51.80%) and diabetes mellitus (26.80%). It is also well known that many heart failure cases are associated with multiple risk factors. In our study, the common underlying conditions associated with HF were hypertension (54%), diabetes mellitus (15%) and ischemic heart disease (11%). Similar findings have been reported from previous studies. The Framingham Heart Study also reported the probable causes of HF to be coronary artery disease (52%), hypertension (26%) and valvular heart disease (8%).

Table 2: Biochemical parameters and mortality correlation

<table>
<thead>
<tr>
<th></th>
<th>Discharged (44)</th>
<th>Expired (12)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean cholesterol</td>
<td>169.96 ± 60.928 mg/dl</td>
<td>152.417 ± 42.64 mg/dl</td>
<td>0.354</td>
</tr>
<tr>
<td>Mean triglycerides</td>
<td>119.89 ± 43.860 mg/dl</td>
<td>119.33 ± 43.502 mg/dl</td>
<td>0.969</td>
</tr>
<tr>
<td>Mean HbA1C</td>
<td>5.67 ± 3.0138</td>
<td>7.45 ± 1.1285</td>
<td>0.0001</td>
</tr>
<tr>
<td>FBS</td>
<td>117.43 ± 23.871 mg/dl</td>
<td>143.33 ± 34.307 mg/dl</td>
<td>0.028</td>
</tr>
<tr>
<td>PLBS</td>
<td>159.59 ± 37.525 mg/dl</td>
<td>191.50 ± 55.099 mg/dl</td>
<td>0.023</td>
</tr>
</tbody>
</table>

Table 3: Mortality correlation with Hypertension, Ischemic Heart Disease and Dilated Cardiomyopathy (DCMP)

<table>
<thead>
<tr>
<th></th>
<th>Discharged (44)</th>
<th>Expired (12)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension</td>
<td>34</td>
<td>7</td>
</tr>
<tr>
<td>Ischemic heart disease</td>
<td>21</td>
<td>8</td>
</tr>
<tr>
<td>DCMP</td>
<td>7</td>
<td>4</td>
</tr>
</tbody>
</table>

P: not significant

The etiology and risk factors associated with heart failure are diverse and are likely to vary across world regions based on risk factor prevalence and quality of health care available. Our analysis has identified hypertension (73.20%) to be the most common etiology associated with heart failure followed by ischemic heart disease (51.80%) and diabetes mellitus (26.80%). It is also well known that many heart failure cases are associated with multiple risk factors. In our study, the common underlying conditions associated with HF were hypertension (54%), diabetes mellitus (15%) and ischemic heart disease (11%). Similar findings have been reported from previous studies. The Framingham Heart Study also reported the probable causes of HF to be coronary artery disease (52%), hypertension (26%) and valvular heart disease (8%). Similar findings have been reported from previous studies. The Framingham Heart Study also reported the probable causes of HF to be coronary artery disease (52%), hypertension (26%) and valvular heart disease (8%).
with acute heart failure at presentation. Data analysis has shown increasing age (>70 years) as a significant patient characteristic associated with a higher mortality rate (p=0.001). The comorbidities significantly associated with increased mortality were pre-existing diabetes mellitus (p=0.0001) and hypothyroidism (p=0.032). Physical findings associated with an incremental mortality rate were low systolic blood pressure (p=0.0001) and low diastolic blood pressure (p=0.0001) at the time of presentation. Several laboratory parameters were also assessed in this study group on admission. Analysis of laboratory data has shown that increased WBC count (p=0.007), low serum sodium levels (p=0.008), increased SGPT (p=0.034), raised total bilirubin (p=0.002) and raised direct bilirubin (p=0.019), elevated FBG levels (p=0.028), elevated PLBS levels (p=0.023) and higher HbA1c values (p=0.0001) were associated with an increased mortality rate in elderly patients. These findings are in accordance with previously conducted studies where similar observations have been noted. There are some limitations to this study that should be addressed. Firstly, the sample size for this study was relatively small in comparison to the densely populated region due to which the epidemiology and clinical profile of acute HF in the elderly population could not be assessed across all regions. Secondly, the study group was recruited from a single tertiary care hospital. Hence, it cannot be considered to be entirely representative of elderly patients throughout Mumbai. Thirdly, our dataset did not include past history of hospitalization and due to heart failure and previous treatment, which could be an important variable associated with mortality. Lastly, our laboratory assessment did not include the natriuretic peptides, B-type natriuretic peptide (BNP) and N-terminal pro-B-type natriuretic peptide (NT-proBNP), which are known to be useful biomarkers for HF diagnosis, estimation of severity and prognosis.

References


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Newer Oral Anticoagulant in Chronic Kidney Disease: What we Should Know

Vijoy Kumar Jha¹, A Jairam², D Mahapatra¹

Abstract

Oral anticoagulants are commonly prescribed in patients with kidney diseases having atrial fibrillation and thromboembolic risk. It is very important to understand their clinical pharmacology and changes that may occur as GFR declines. Risks and benefits of newer oral anticoagulants are different in patients with CKD and patients with ESRD. Patients with GFR < 30 ml/min per 1.73 m², including those on dialysis, were systematically excluded from landmark trials. All of the NOACs are dependent on renal clearance to some degree and so the risk of NOAC associated bleeding may be expected to be greater in patients with renal failure. Apixaban may be at least as safe as (or possibly safer than) warfarin in individuals with ESRD. Until more data become available, use of dabigatran, rivaroxaban, and edoxaban in patients with CKD stage 5 and ESRD is not indicated. Available strategies for reversing the anticoagulant effect of NOAC are - specific reversal agents available for dabigatran (idarucizumab) and for the oral direct factor Xa inhibitors - andexanet alfa, antifibrinolytic agents, DDAVP and prothrombin complex concentrates (PCCs). In this review clinical and pharmacological aspects of newer oral anticoagulants in the setting of chronic kidney disease will be discussed.

Table 1: Kidney specific mechanisms leading to atrial fibrillation

| Cardiac structure | i. Concentric LVH with pronounced myocardial fibrosis |
|                  | ii. Larger left atrial and left ventricular size than patients without CKD |
| Endothelial dysfunction | i. Premature atherosclerosis |
|                      | ii. Albuminuria |
|                      | iii. Low-grade inflammation |
|                      | iv. Increased activity of the renin-angiotensin-aldosterone system (RAAS) and the adrenergic system |
| Vascular calcification | i. Abnormalities in mineral metabolism (in particular, levels of phosphorus and fibroblast growth factor 25) |
|                      | ii. Deficiency of active vitamin D in CKD |
|                      | iii. Altered haemodynamics, venous congestion, activation of the RAAS and adrenergic system |
|                      | iv. Renal microinfarcts that result from a postulated systemic prothrombotic state that is associated with AF |

Table 2: Possible mechanism of CKD progression in atrial fibrillation

| i. Pronounced myocardial fibrosis |
| ii. Decline in left ventricular systolic and diastolic function |
| iii. Altered haemodynamics, venous congestion, activation of the RAAS and adrenergic system |
| iv. Renal microinfarcts that result from a postulated systemic prothrombotic state that is associated with AF |

Introduction

The risk for cardiovascular disease complication related morbidity and mortality remains very high in all stages of chronic kidney disease (CKD). Though heart failure, sudden cardiac death and thrombotic cardiovascular events are very common in CKD patients, they are also at a very higher risk of non valvular atrial fibrillation (AF) compared with the general population. Prevalence of AF increases as kidney disease worsens, and it is around 15% by the time they become dialysis dependent, which is more than three times that of age-matched controls.¹ High burden of AF in patients with CKD can be partly attributed to the prevalence of common cardiovascular risk factors and cardiovascular disease among these patients. Newer oral anticoagulants/ non Vit. K antagonist (NOAC) reduce risk of stroke or systemic embolism and bleeding versus warfarin in patients with AF. The use of oral anticoagulant (OACs) in CKD patients is challenging because limited trial data are available. Patients with end-stage renal disease (ESRD) were excluded from most NOAC trials and these patients are also at high risk of thromboembolism and bleeding. Atrial fibrillation and CKD

In the ARIC (Atherosclerosis Risk in Communities) study, reduced GFR and albuminuria were strongly associated with incident AF after extensive adjustment for other cardiovascular risk factors, and the risk of incident AF gradually increased with decreasing cystatin-C based e GFR and increasing albuminuria.² So the burden of AF is increased among patients with CKD and it increases with CKD severity.³ Kidney-specific mechanisms that underlie the high burden of AF among patients with CKD likely operate through their effects on cardiac structure, endothelial function and vascular calcification⁴ (Table 1).

Incident AF is also associated with increased rate of CKD progression to ESRD (Table 2). In the Niigata Preventive Medicine Study (n = 235,818), AF in patients with eGFR >60 ml/min/1.73 m² and no proteinuria at baseline was associated with an 80% higher adjusted rate of decline in eGFR and a 116% higher rate of developing proteinuria during follow-up.⁵ In another study in a large cohort of adults with CKD (n = 206,229), incident AF was associated with a 67% increased risk of ESRD during a mean followup of 5 year.⁶ In CRIC study, incident AF was associated with a threelfold increased risk of CKD progression to ESRD during a mean followup of 5.9 years.⁷ Patients with coexistent AF and CKD have higher risks of stroke, thromboembolism and mortality than those with either CKD or AF alone.³ Both pre-existing AF and incident AF
Table 3: Thrombosis in CKD and AF

<table>
<thead>
<tr>
<th>Vessel wall and/or atrial tissue abnormalities</th>
<th>Atrial fibrosis: Myocyte hypertropy, fibroelastosis, endocardial fibrosis and infiltration, extracellular matrix abnormalities</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ventricular hypertrophy: Extensive myocardial fibrosis</td>
<td></td>
</tr>
<tr>
<td>Vascular factors: Accelerated atherosclerosis, arteriosclerosis (fibrosis and thickening of the media), arterial wall calcification, increased arterial stiffness</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Blood flow abnormalities</th>
<th>Endothelial dysfunction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atrial dilatation</td>
<td></td>
</tr>
<tr>
<td>Loss of atrial systole</td>
<td></td>
</tr>
<tr>
<td>Left atrial appendage characteristics</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Blood constituents</th>
<th>Hypercoagulability: Increased thrombin-antithrombin complex, D-dimer, prothrombin 1 and 2, vWF, tissue factor, PAI1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Platelet dysfunction: Increased aggregability, Increased reactivity</td>
<td></td>
</tr>
<tr>
<td>Microparticles: Increased platelet production, Increased surface tissue factor, increased release of soluble tissue factor</td>
<td></td>
</tr>
</tbody>
</table>

Table 4: Problems with vit. K antagonist (Warfarin) in CKD

i. No data from randomized trials of VKAs exist for patients with ESRD and AF, and observational studies in this population have yielded conflicting results.

ii. Well-controlled anticoagulation with a mean time in the therapeutic range (TTR) of 265-70% is essential for the optimal effects of VKAs but good long-term TTR is difficult to maintain in clinical practice, resulting in global underuse of VKAs mostly due to safety concerns.

iii. The likelihood of optimal TTR decreased with decreasing eGFR despite similar International Normalized Ratio (INR) monitoring intensity suggesting that factors such as reduced nonrenal and renal clearance of warfarin and a smaller therapeutic dosage range have a role in determining TTR in patients with CKD

iv. The risks of stroke and bleeding in warfarin-inexperienced patients with AF and CKD are particularly high in the first 30 days of warfarin treatment

v. Increased vascular calcification (mediated through inactivation of matrix Gla protein)

vi. Warfarin-related nephropathy (WRN)

vii. Impaired drug metabolism and fluctuations in volume status may affect the responsiveness of patients with ESRD to warfarin

after transplantation are significantly associated with poor transplantation outcomes, including mortality.8,9

Thrombosis and CKD (Table 3)

Disorders of coagulation regulatory factors and platelet hyperactivity, occurs in patients with mild renal dysfunction and AF whereas a CKD-specific bleeding tendency occurs in the later stages of CKD as a result of altered platelet function, disorders of the coagulation cascade and activation of the fibrinolytic system.10 Chronic low-grade inflammation, the RAAS, the adrenergic system, atherosclerosis, pronounced vascular calcification, altered mineral metabolism and the accumulation of metabolic compounds due to reduced renal function influence the interaction between these components.11

Vascular stiffness in CKD imposes high pressure loads on vulnerable vascular beds in the brain, kidney and heart and aggravate microvascular damage.12 Increased left ventricular afterload in systole and reduced coronary perfusion in diastole lead to hypertrophy, ischaemia and dilatation of the left atrium and left ventricle. A dysfunctional and/or injured endothelium promotes a procoagulant state resulting from altered endothelial secretion of factors that modulate the coagulation cascade.13 Activation of the RAAS in AF and CKD aggravates the procoagulant state via increased levels of fibrinogen and PAI1. CKD is also associated with increased plasma levels of tissue factor, the key initiator of the coagulation cascade.14,15 It has been found that the benefits of reducing the risk of ischaemic stroke and all-cause mortality outweigh the increased risk of bleedings.15,16

Problems with Vitamin K Antagonist (Table 4)

A subgroup analysis of data from the SPAF (Stroke Prevention in Atrial Fibrillation) III trials showed that the efficacy of warfarin for stroke prevention in patients with stage 3 CKD was similar to that in patients without CKD.17 In a meta-analysis of 13 observational studies that included >48,500 patients with AF in the USA, Europe, Canada and Asia, warfarin use in those with CKD was associated with a 30% lower risk of ischaemic stroke and/or systemic embolism, a 35% lower risk of death and a nonsignificant 15% increase in major bleeding compared with no warfarin use.18

No data from randomized trials of any OAC exist for patients with ESRD and AF, and observational studies in this population have yielded conflicting results. The increased risks

Table 5: Landmark clinical trials of NOAC versus warfarin in patients with AF

<table>
<thead>
<tr>
<th>RE-LY</th>
<th>Rocket-AF</th>
<th>Aristotle</th>
<th>Engage AF TIMI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Agent (mechanism of action)</td>
<td>Dabigatran (direct thrombin inhibitor)</td>
<td>Rivaroxaban (direct inhibitor of activated factor X)</td>
<td>Apixaban (direct inhibitor of activated factor X)</td>
</tr>
<tr>
<td>NOAC dose</td>
<td>150 mg or 110 mg twice daily</td>
<td>20 mg once daily</td>
<td>5 mg twice daily</td>
</tr>
<tr>
<td>Patients (n)</td>
<td>18,113</td>
<td>14,264</td>
<td>18,201</td>
</tr>
<tr>
<td>Renal function exclusion criteria</td>
<td>&lt;30 ml/min/1.73 m2</td>
<td>&lt;30 ml/min/1.73 m2</td>
<td>&lt;25 ml/min/1.73 m2</td>
</tr>
<tr>
<td>Safety and efficacy of NOAC in comparison to warfarin</td>
<td>Similar rates of stroke and major bleeding</td>
<td>Lower risk of major bleeding events with apixaban relative to warfarin in patients with CKD than in those without CKD</td>
<td></td>
</tr>
<tr>
<td>Safety in patients with CKD (risk of major bleeding)</td>
<td>No significant interaction of adverse effects with renal function</td>
<td>No significant interaction of adverse effects with renal function</td>
<td>No significant interaction of adverse effects with renal function</td>
</tr>
<tr>
<td>Efficacy for stroke prevention in patients with CKD</td>
<td>No significant interaction of treatment effects with renal function</td>
<td>No significant interaction of treatment effects with renal function</td>
<td>No significant interaction of treatment effects with renal function</td>
</tr>
</tbody>
</table>

Specifically, the NOACs were associated with a lower risk of ischaemic stroke and systemic thromboembolism compared to warfarin, with similar rates of major bleeding in all trials. The NOACs also demonstrated a lower risk of all-cause mortality compared to warfarin, with the exception of the Engage AF TIMI trial. The results of this trial are consistent with the findings of the RE-LY and Rocket-AF trials, which showed a significant reduction in the risk of all-cause mortality with NOACs compared to warfarin.

In conclusion, the NOACs are superior to warfarin in patients with AF and CKD, with a lower risk of ischaemic stroke and systemic thromboembolism and a similar risk of major bleeding. The NOACs also demonstrated a lower risk of all-cause mortality compared to warfarin, with the exception of the Engage AF TIMI trial. The results of this trial are consistent with the findings of the RE-LY and Rocket-AF trials, which showed a significant reduction in the risk of all-cause mortality with NOACs compared to warfarin.
Table 6: Selection of oral anticoagulants in CKD

<table>
<thead>
<tr>
<th>Drug (renal excretion)</th>
<th>CrCl (ml/min)</th>
<th>30-49</th>
<th>15-29</th>
<th>&lt;15</th>
<th>ESRD on RRT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preferred class</td>
<td>NOAC</td>
<td>NOAC</td>
<td>VKA or NOAC</td>
<td>VKA or NOAC (use with caution)</td>
<td>VKA or NOAC (use with caution)</td>
</tr>
<tr>
<td>VKA (NA)</td>
<td>Maintain TTR ≥70%</td>
<td>Maintain TTR ≥70%</td>
<td>Maintai...</td>
<td>Do not use</td>
<td>Do not use</td>
</tr>
<tr>
<td>Dabigatran (80%)</td>
<td>150 mg twice daily or 110 mg twice daily if patient is aged ≥80 years or is receiving verapamil or is at increased bleeding risk</td>
<td>150 mg twice daily or 110 mg twice daily if patient is aged ≥80 years or is receiving verapamil or is at increased bleeding risk</td>
<td>USA:75 mg</td>
<td>Do not use</td>
<td>Do not use</td>
</tr>
<tr>
<td>Rivaroxaban (35%)</td>
<td>20 mg once daily</td>
<td>15 mg once daily</td>
<td>15 mg once daily</td>
<td>Do not use</td>
<td>Do not use</td>
</tr>
<tr>
<td>Apixaban (27%)</td>
<td>5 mg twice daily or 2.5 mg twice daily if ≤2 of the following criteria are fulfilled:age ≥80 years, body weight ≤60 kg and Scr ≥1.5 mg/dl (133 µmol/l)</td>
<td>5 mg twice daily or 2.5 mg twice daily if ≤2 of the following criteria are fulfilled:age ≥80 years, body weight ≤60 kg and Scr ≥1.5 mg/dl (133 µmol/l)</td>
<td>USA:5 mg twice daily</td>
<td>Other areas do not use</td>
<td>Other areas do not use</td>
</tr>
<tr>
<td>Edoxaban (50%)</td>
<td>80 mg once daily or 30 mg once daily if ≤2 of the following criteria are fulfilled:body weight ≤60 kg, CrCl 30-50 ml/min and concomitant therapy with verapamil, dronedarone or quinidine</td>
<td>30 mg once daily</td>
<td>30 mg once daily</td>
<td>Do not use</td>
<td>Do not use</td>
</tr>
</tbody>
</table>

of thromboembolic and bleeding events in patients with AF and CKD might be in part mediated by increased vascular calcification associated with warfarin use and/or the development of warfarin-related nephropathy (WRN).

Warfarin related nephropathy is characterized by acute kidney injury with or without clinically overt haematuria and tubular obstruction by red blood cell casts on microscopy in patients treated with VKAs with supratherapeutic INR levels. In one study among a cohort of warfarin users, WRN occurred in 33.0% of patients with CKD and 16.5% of those without CKD and associated with increased mortality. Use of VKAs may also result in calcification and occlusion of cutaneous arteries and arterioles, resulting in the development of painful and potentially lethal calciphylaxis among patients with ESRD. It is therefore clear that despite the increased thromboembolic risk of patients with AF and ESRD, the use of VKAs does not result in a risk reduction similar to that seen in patients with normal renal function or mild to moderate CKD. It is also very difficult to maintain good mean time in the therapeutic range (TTR) due to impaired drug metabolism and fluctuations in volume status in CKD setting.

Non Vit. K oral anticoagulants

NOAC drugs have similar or superior efficacy and improved safety and convenience compared with VKA. In randomized clinical trials of these drugs, they were either superior or noninferior to warfarin for stroke prevention and exhibited better safety profiles than warfarin (Table 5).

Due to fixed-dose regimens, no requirement for routine laboratory monitoring of their anticoagulant effects and a low propensity for food and drug interactions, these drugs are better alternative to warfarin for thromboprophylaxis in patients with mild to moderate CKD. In one study, the use of dabigatran was associated with a lower risk of anticoagulant-associated nephropathy than the use of warfarin in patients with and without CKD. Underdosing or overdosing of NOAC was associated with decreased safety and no increase in effectiveness in patients with severe kidney disease. As the Cockcroft-Gault formula was used for renal function assessment, this formula should also be used in clinical assessment to enable appropriate treatment decisions. On the basis of pharmacological modelling, rivaroxaban, apixaban and edoxaban (but not dabigatran) have been approved in Europe for thromboprophylaxis in patients with severe CKD (CrCl 15-29 ml/min) not on dialysis using reduced-dose regimens.

The US Food and Drug Administration (FDA) has also approved the use of reduced-dose dabigatran (75 mg twice daily) in patients with AF and a CrCl of 15-29 ml/min as well as the use of apixaban (5 mg twice daily) in patients with AF and stable ESRD on dialysis based on pharmacokinetic studies. Apixaban dosing for ESRD patient should change because steady-state pharmacokinetic data show that use of apixaban, 5 mg twice daily, resulted in two fold higher plasma levels of apixaban in patients on dialysis than in those with normal renal function, whereas use of apixaban, 2.5 mg twice daily, resulted in similar apixaban plasma levels in the two groups. A steady-state pharmacokinetic study of rivaroxaban, 10 mg once daily, in patients with ESRD showed that this dose resulted in similar drug plasma concentrations to those achieved with a 20 mg dose in healthy individuals. There is evidence of numerical but not statistically significant excess of ischaemic stroke with edoxaban, 60 mg once daily, compared with warfarin in patients with CrCl >95 ml/min. A post hoc analysis of the ENGAGE-AF TIMI 48 trial showed that despite a decreased relative efficacy of edoxaban regimen in the upper range of CrCl, the safety and net clinical benefit compared with warfarin was consistent across the spectrum of renal function. A retrospective analysis of a large database comprising ~30% of all patients on chronic dialysis in the USA showed that among those with AF (n = 29,977), the off-label use of dabigatran (n = 281) or rivaroxaban (n = 244) was associated with a higher risk of hospitalization or death from bleeding than was the use of warfarin (n = 8,064).

Pharmacology of Dabigatran in chronic kidney disease

Dabigatran is available in 75 or 150 mg capsules which contains dabigatran-coated pellets with a tartaric acid core to augment bioavailability at low pH. The core increases dyspepsia risk and gastrointestinal bleeding and patients should not chew, break, or open capsules, because bioavailability increases dramatically. Inter individual drug exposure variability exists.
A single 5-g intravenous dose. Reports anticoagulant effect immediately after dabigatran is higher than dabigatran binding affinity of idarucizumab to patients with major bleeding. A fresh frozen plasma and prothrombin tandem mass spectrometry. Studies correlated with drug concentration and ecarin clotting time are linearly negative predictive value to exclude the presence of dabigatran. Thrombin time and ecarin clotting time are linearly correlated with drug concentration measured by liquid chromatography tandem mass spectrometry.

A recent randomized, controlled trial (RCT) in subjects with normal kidney function questioned the efficacy of prothrombin complex concentrate as an effective reversal agent. In subjects with normal kidney function nonspecific anti-inhibitor coagulant complex (e.g., factor VIII inhibitor bypass activity) but not recombinant factor VIIa reversed dabigatran’s overdosage. One case series of 11 life threatening dabigatran-related major bleeding episodes reported use of hemo dialysis and continuous venovenous hemofiltration. In one study of dabigatran 150 mg twice daily for 3 days in seven patients on hemodialysis reported 49% and 59% drug removal with blood flow rates of 200 and 400 ml/min, respectively, over a 4-hour treatment. FDA has approved idarucizumab to reverse the antithrombotic effects of dabigatran. Binding affinity of idarucizumab to dabigatran is higher than dabigatran to thrombin, neutralizing the anticoagulant effect immediately after a single 5-g intravenous dose.

Reports of major bleeding were reported in frail elderly individuals, patients with CKD, and patients with ESRD after FDA approval. A subgroup analysis reported lower rates of stroke with dabigatran 150 mg twice daily versus warfarin across all creatinine clearance categories (280, 50 to 80, and, 50 ml/min). Dabigatran versus warfarin reduces risk of stroke with an increased risk of gastrointestinal bleeding events. There is only one study in patients on hemodialysis which reported a 1.5-fold higher risk of death or hospitalization from bleeding with dabigatran versus warfarin.

**Pharmacology of Rivaroxaban in chronic kidney disease**

A fixed oral dose with the evening meal: 20 mg/d for patients with a creatinine clearance of ≥50 ml/min and 15 mg/d for patients with a creatinine clearance of 30-50 ml/min is prescribed. With a creatinine clearance of 15 to 50 ml/min, a reduced dose of 15 mg once daily with the evening meal is prescribed in patients with nonvalvular atrial fibrillation. It is not recommended for other indications with a creatinine clearance ≤30 ml/min. It does not interact with foods and interacts minimally with other drugs. It has a shorter t1/2 and more rapid onset of action than warfarin. A subgroup analysis of the Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation (ROCKET AF) with impaired creatinine clearance (≥80 ml/min) reported no effect of kidney disease. Few studies reported a 56% increase in AUC in patients with ESRD after a 15-mg dose administered post dialysis. In another study, single 10-mg dose was conducted in 24 patients with CKD (creatinine clearance < 80 ml/min) and eight healthy controls (creatinine clearance ≥280 ml/min) suggest reduced rivaroxaban clearance with worsening creatinine clearance resulting in increased drug exposure.

**Pharmacology of Apixaban in chronic kidney disease**

Apixaban at 5 mg twice daily is FDA approved for reduction of stroke or systemic embolism in patients with AF. A reduced dose of 2.5 mg twice daily is recommended with serum creatinine ≥1.5 mg/dl, age ≥80 years old, or body weight <60 kg. No significant kinetic changes were observed in peak plasma drug concentration (Cmax) or AUC among patients with CKD. Because of its high degree of protein binding, hemodialysis clearance is low (18 ml/min), resulting in a 14% decrease in drug exposure. In a recent retrospective analysis of patients on hemodialysis, cumulative days of apixaban use in an outpatient setting, higher total daily apixaban doses, and total hemodialysis sessions were independent risk factors for bleeding events (adjusted odds ratio, 13.07; 95% CI, 1.54 to 110.54; adjusted odds ratio, 1.72; 95% CI, 1.20 to 2.48; and adjusted odds ratio, 2.04; 95% CI, 1.06 to 3.92, respectively).

**Pharmacology of Edoxaban in chronic kidney disease**

Edoxaban is recommended at 60 mg once daily for patients with creatinine clearance of 50-95 ml/min and 30 mg once daily for patients with creatinine clearance of 15-50 ml/min. Drug exposure increases by 32%, 74%, and 72% with creatinine clearances of 50-80, 30-50, and < 30 ml/min, respectively. It is only 5% protein bound and is poorly cleared by dialysis (9% with a blood flow rate of 350 ml/min, a dialysate flow rate of 500 ml/min, and an F180NR dialyzer).

**Anticoagulant effect measurement**

PT prolongation occurs to a greater degree than APTT prolongation with factor Xa inhibitors. With the exact same PT value, a prolonged PT on warfarin does not equate to a similar anticoagulant effect as on factor Xa inhibitors. Chromogenic anti-Xa activity assay (e.g., Rotachrom) may be more reliable and accurate. There is strong correlation between anti factor Xa activity and factor Xa inhibitor concentration. Prothrombin concentrate complex, recombinant factor VIIa, and factor VIII inhibitor bypass activity can reverse their anticoagulant effects.

**Advantage of Apixaban**

Apixaban was superior to warfarin in reducing stroke or systemic embolism rates and major bleeding among participants with reduced GFR in the Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation Trial. A meta-analysis of RCTs comparing newer oral anticoagulants with warfarin reported no difference in stroke, systemic embolism risk, or major bleeding in the CKD subgroup (relative risk, 0.64; 95% CI, 0.39 to 1.04 and relative risk, 0.89; 95% CI, 0.68 to 1.16, respectively).
bleeding rates between individuals with creatinine clearance of 50-80 versus 30-50 mL/min on apixaban. A recent Cochrane review reported reduced risk of stroke or systemic embolism and similar risk of major bleeding among patients with AF and CKD treated with apixaban versus warfarin (risk ratio, 0.81; 95% CI, 0.65 to 1.00 and risk ratio, 0.79; 95% CI, 0.59 to 1.04, respectively).

**Anticoagulant reversal**

Bleeding risk with the NOAC always remains in CKD setting because antithrombotic agents or specific reversal agents for some of the NOACs are lacking. Routine coagulation tests cannot be used to determine the degree of anticoagulant making it difficult to determine when the anticoagulant effect has resolved. A 2018 meta-analysis of five observational studies that included 43,850 patients with ESRD found that bleeding rates were lower in individuals treated with apixaban compared with warfarin (odds ratio [OR], 0.42; 95% CI 0.28-0.61). 87% percent of these patients were being treated for atrial fibrillation. Available strategies for reversing the anticoagulant effect of NOAC are specific reversal agents available for dabigatran (idarucizumab) and for the oral direct factor Xa inhibitors - andexanet alfa, pro-hemostatic therapies such as antifibrinolytic agents and DDAVP and nonspecific agents such as prothrombin complex concentrates (PCCs). Idarucizumab should not be administered to patients with a normal thrombin time (TT). The dose is 5 grams (two 2.5 g vials), which can be administered either as two consecutive infusions or as a bolus. Hemodialysis may be used to remove dabigatran from the circulation. Andexanet alfa, a reversal agent for factor Xa inhibitors is a recombinantly produced, catalytically inactive form of factor Xa that acts as a “decoy” to bind and sequester the anticoagulant. This drug was approved by the US FDA in May 2015 for the reversal of anticoagulation by rivaroxaban and apixaban in individuals with life-threatening or uncontrolled bleeding.

**Conclusion**

Options for anticoagulation in setting of CKD have been expanding steadily and providing a greater number of agents for prevention and management of thromboembolic disease. Newer oral anticoagulants that directly target the enzymatic activity of thrombin and factor Xa have been developed. Appropriate use of these drugs requires knowledge of their individual characteristics, risks and benefits. All these agents are renally excreted to variable degrees. For outpatients with moderate renal impairment (creatinine clearance 30-50 mL/minute), the NOACs appear to be at least as safe as warfarin. Of the NOACs, apixaban is the least dependent on renal clearance and so it can be used in advanced CKD. The lack of routine monitoring and short half-lives of these agents make it more difficult to determine if a patient is taking them appropriately or not.

**References**


Generics and Biosimilars; A Step Towards Sustainable and Low Cost Health Care

Puneeta Gupta¹, Mehvish Khan²

Abstract
Millions of people across the globe go without essential medicines resulting in many avoidable deaths each year. It’s no secret that the cost of prescription drugs, including the life-saving ones has been rising far faster than inflation over the last few years. If we take the example of diabetes and as India has the largest number of patients with the condition in the world; it has been shown that patients belonging to the low income group in urban India were spending 27% of their annual income and those in rural India 34% of their annual income on diabetes care; most of which was spent on purchase of medicines. This raises the question of whether current pricing of drugs is based on reasonable expectation of return on investment or whether it is based on what prices the market can bear. The price of pharmaceuticals has become an issue of great concern for people and governments around the world. Thus governments across the globe must make efforts to correct the present distortions around the concept of generic drugs.

Introduction
Access to health care is a human right, and that includes access to safe and affordable prescription drugs. Millions of people across the globe go without essential medicines resulting in many avoidable deaths each year. Any society faces a great moral contradiction when healthcare is so expensive that majority of people cannot afford it.

It’s no secret that the cost of prescription drugs, including the life-saving ones has been rising far faster than inflation over the last few years. Globally, annual spending on anticancer drugs, e.g. is around US$100 billion, and is predicted to rise to $150 billion by 2020. From 1995 to 2014, in fact, there was a sharp increase in the launch price (the cost of a new drug being introduced to the market for the first time) of new cancer drugs. Pralatrexate (Folotyn) for example, a cytotoxic antimetabolite (folate antagonist), is used for patients with aggressive form of non-Hogkins’s lymphoma; cost of which runs from $41,000 to $82,000 annually; Similarly atezolizumab (tecentriq) for the treatment of patients with metastatic urothelial carcinoma, is priced around $12,500 a month.

Now, if we look at the prices of some novel drugs which have been introduced for other common conditions, e.g the injectable compounds for dyslipidemia, approved in 2015, PCSK9 inhibitors, alirocumab (praluent) and evolocumab (Repatha), are costing $14,000 a year. Similarly the new drugs for hepatitis C, sofosbuvir (brand name Sovaldi), was launched at a cost of $1,000 a pill, even drugs, that have long been on the market for long are not immune from this price rise, for example imatinib (gleevac), a drug for chronic myeloid leukemia, tripled in cost from $31,930 in 2005 to $91,930 in 2013, despite no notable changes in the formulation or manufacturing process. The cost of pyrimethamine (daraprim), a 60-year old drug, rose from $13.50 to $750 per pill (a 5455% raise) after pharmaceuticals acquired the distribution licence, sparking a public debate in North America.

The astronomical drug prices and developing world
About 40% of Indians live on income of less than 100 rupees per day and most of them pay out of pocket for healthcare. In fact out-of-pocket (OOP) spending in India is over four times higher than public spending on healthcare. Now if we take the example of diabetes and as India has the largest number of patients with the condition in the world; it has been shown that patients belonging to the low income group in urban India were spending 27% of their annual income and those in rural India 34% of their annual income on diabetes care; most of which was spent on purchase of medicines. The situation becomes even more grim when we take into account the World Health Organization (WHO) report which estimates that around 649 million people in India do not have regular access even to essential medicines.

Drug prices; Isn’t that really just a problem for poor countries?
It is quite understandable that in majority of low- and middle-income countries, drug expenditure can be a critical public health problem with some drugs out of reach for even well-insured patients. But, this high cost is a rising concern in western developed world also; with many people not able to take the medication, their providers prescribe for them. Nearly 1 in 10 American adults don’t take their medications as prescribed by their physicians, because they can’t afford to, (U.S. Centers for Disease Control and Prevention, National Center for Health Statistics).

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Received: 26.11.2018; Revised: 19.07.2019; Accepted: 19.07.2019
This raises the question of whether current pricing of drugs is based on reasonable expectation of return on investment or it is simply based on what prices the market can bear. In fact as complaints grow about exorbitant drug prices, pharmaceutical companies are coming under pressure to disclose the development costs and profits of prescription drugs and the rationale for charging what they do.

Why Does it Cost so much to Develop a New Medicine? The Economics of Drug Discovery and Development (R&D).

For patients, new medicines offer fewer side effects, fewer hospitalizations, improved quality of life and most importantly, the extended lives. But developing medicines is a long, complex process. On average, it takes at least ten to fifteen years for a new medicine to complete the journey from initial discovery to the marketplace. The average cost to research and develop each successful drug was estimated to be $2.6 billion in a study carried out in 2014.7

However, does this significant research and development spending as cited by the pharmaceuticals, should lead to such high pricing so that it is neither affordable at the patient level nor it is sustainable at payer level. Moreover, the enormous amount of money the drug companies spend on marketing and lobbying is undeniable.

Generics and biosimilars; the cheaper alternatives

The prescription drugs can be classified into traditional or chemical pharmaceuticals and biopharmaceutical or ‘biological medicines”. The traditional prescription drugs or pharmaceuticals are molecules with a small, well-defined and stable chemical structure that are typically manufactured through chemical synthesis;

Biologics or biopharmaceutical are medicines which are synthesized or extracted from a biological source often with highly complex structures. The manufacturing processes of biologics involve living systems (eg, mammalian cell lines, microbial agents, plants, fungus) and complex processes (eg, gene isolation, recombinant DNA engineering, protein purification); which require high technological expertise with precision in order to ensure consistency and quality of the final product unlike single molecules which are chemically synthesized with highly predictable structures and functions;

Starting with insulin three decades ago, about 300 biologics are now available for human use. Gene-based and cellular biologicals, for example, often are at the forefront of biomedical research, and may be used to treat a variety of medical conditions for which no other treatments are available; thus bringing hope to those with few other alternatives.

Now apart from above discussed research, development and approval steps which of course require lot of investment, the major factor which gives pharmaceutical companies almost free hand to pricing of drug is the patent on new molecule, giving them exclusive marketing right of their innovation. Thus chemical patent, pharmaceutical patent or drug patent is a patent for an invention in the chemical or pharmaceuticals industry and is usually given for 15 to 20 years An important step towards decreasing the overall cost of the drug and making them available to all including the poorest of poor is the development of generics and biosimilars.

When a pharmaceutical company introduces a costly new drug, they can do so because they have an exclusive patent on it. Once drug patents expire after a stipulated time period, other pharmaceutical companies can copy that branded drug, and sell it for significantly less price as a generic compound

By law, a generic drug product must contain the identical amounts of the same active ingredient(s) as the brand name product, has the same strength, use, indications, form (such as a tablet or an injectable), and route of administration (such as oral or topical). Because of their intrinsic complexity and because no two cell lines, developed independently, can be considered identical, biopharmaceuticals cannot be fully copied. This is recognised by the regulatory authorities and has resulted in the establishment of the term ‘biosimilar’ in recognition of the fact that, whilst biosimilar products are similar to the original product i.e biologics, they are not exactly the same.

With the make-up of the drug already approved, generics and biosimilars do not require the added expenditure of research and development, thus the final cost to the manufacturer and the consumer is much lower because the approval pathway is much shorter than branded drugs.

When multiple generic companies market a single approved product, market competition typically results in prices about 85% less than the brand-name (generic drugs were estimated to have saved the U.S. health care system approximately $1.67 trillion from 2007 to 2016.)

What is the way ahead

The price of pharmaceuticals is an issue of great concern for governments around the world.4 The right to access essential medicines has found its way into international treaties and national constitutions and moral claim for universal access to essential medicines has been put forth not only by faith-based organizations and civil society activists, but also by many drug developers.

Conclusion

The governments across the globe must make efforts to correct the present distortions around the concept of generic medicines by providing quality assurance of medicines and allowing the emergence of a true generics market, where different products can compete on price rather than on brand image.

References

1. Hawkes N. NHS hospital drug costs are set to surpass spending in primary care BMJ 2018; 361 doi: https://doi.org/10.1136/bmj.k1766 (Published 26 April 2018) BMJ 2018;361:k1766)
HIV-2 (Human-Immunodeficiency Virus) : A Myriad of Myths – Presenting as Multiple Large Vessel Arterial Occlusions

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Received: 19.07.2016; Accepted: 26.08.2019

Fig. 1: CT angiogram showing partial occlusion (pointed by arrow) at the level of right subclavian artery

Fig. 2: CT angiogram showing partial occlusion at the origin of superior mesenteric artery from the celiac trunk

Fig. 3: CT angiogram showing near complete occlusion of descending aorta at the level of renal arteries affecting the blood flow to the right kidney

Fig. 4: CT angiogram showing near complete occlusion of transrenal aorta affecting the blood supply to left kidney. Accessory left renal artery is seen arising from descending aorta below the occlusion

A 17 year old unmarried girl presented to us with a 1 month history of bilateral lower limb claudication pain and 1 week history of right upper limb rest pain with oliguria. Examination revealed feeble right radial pulse with radio-radial delay and bilateral cold lower limbs. Blood pressure in right upper limb was systolic 60 mmHg and in left upper limb was 100/60 mmHg. Cardiac and respiratory systems were normal on examination. An urgent CT angiogram was done which revealed occlusion of right subclavian artery (Figure 1), Superior mesenteric artery occlusion (Figure 2) and near total occlusion of descending aorta at the level of renal arteries (Figures 3 and 4). Her anti-phospholipid antibodies and autoimmune serology (ANA, ANCA) for vasculitis was negative. Liver function tests, Hepatitis B and C serology and homocysteine levels were within normal limits. Transesophageal echocardiography excluded any cardionic source of emboli. Surprisingly, her ELISA for HIV antibody was positive. In view of her young age and unmarried status, HIV serology of both parents were done which was negative. Her CD4 count was 36 and Western blot revealed HIV-2 infection. She was started on TDF/FTC/ATV(r) (Tenofovir / Emtricitabine / Boosted Atazanavir) with aspirin and statin. However, her renal dysfunction worsened due to near total renal artery occlusion requiring hemodialysis. She succumbed to her illness after four weeks.

HIV infected patients are at increased risk for venous and arterial thromboembolic events. Multiple markers related to inflammation (IL-6, TNFα, C-reactive protein) and coagulation (tissue factor expression, FVIII, thrombin, fibrinogen and D-dimer levels) are increased in HIV infection, and are predictive of thrombotic risk and mortality. The mechanism may be related to chronic immune activation and inflammatory state in both untreated and treated HIV infection. However, traditional risk factors, including smoking and dyslipidemia must also be considered. One study observed a marked increase in vWF levels as well as a correlation of vWF to first and recurrent venous thrombo-embolic events. Few cases have described the presentation of HIV with arterial thrombosis. Due to the association of HIV infection and autoimmune disorders such as antiphospholipid antibody syndrome, evaluation of serum level of antiphospholipid-antibodies has been introduced as a fundamental step in the management of both symptomatic and asymptomatic HIV patients. Frequency of thrombophilic abnormalities in HIV infection increases with its progression to AIDS and correlates with the severity of immunosuppression, with the presence of concurrent opportunistic infections or neoplastic processes. D-Dimer levels have been strongly linked to both venous and arterial thrombosis in HIV. Targeted interventional studies may help to identify the determinants of coagulation risks in treated HIV infection. Although
aspirin and statins have proven value in reducing cardiovascular risks among HIV-uninfected populations, their clinical utility in treated HIV infection has not yet been demonstrated and merits evaluation.\(^1\) As per a study, HIV infection is an independent risk factor for coagulation abnormalities and this could be a reason to prolong anti-thrombotic treatment in patients with a history of thrombosis.\(^2\)

**References**


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**Frogspaw Tongue**

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A 19 year old male was referred to our clinic from an interventional radiologist for a tongue lesion. The patient presented with a history of vesicular lesions over the tongue since 4 years of age which was asymptomatic initially but later increased in size with on and off bleeding episodes. Patient denied any other comorbidities. His systemic examination was normal. On examination of the tongue, there were clusters of small blue-black vesicles, more over the ventral and left lateral aspect of the anterior two thirds of the tongue and some over the dorsum (Figure 1). They were not tender but bled on touch. He was referred to us after an angiography which was negative for any arteriovenous malformations. A diagnosis of Lymphangioma circumscriptum, most common form of cutaneous lymphangioma, was made. He was advised laser ablation therapy.

Lymphangioma circumscriptum is a congenital lymphatic malformation of the superficial lymphatics that is localised to an area of skin, subcutaneous tissue or a muscle. It is the most common form of cutaneous lymphangioma.\(^1\) It is usually noted at birth or during early childhood but can present at any age.\(^2\) Axillary folds, shoulders, flanks, proximal limbs or perineum are the most common presenting area. Only very few cases are reported on lymphangioma circumscriptum presenting in the tongue.\(^3\) Clinically the condition is painless, noninflammatory and manifests with fluid filled vesicles which may be discrete or grouped into structures resembling frogspawn.\(^2,3\) They may be translucent or may vary in colour from red to blue-black if they contain blood which sometimes bleeds on touch.\(^3\) Whimster\(^4\) described the pathology of lymphangioma circumscriptum as a collection of subcutaneous lymphatic cisterns with a thick muscular coat communicating through dilated channels with the superficial vesicles. The clinical differential diagnoses include hemangioma, vascular malformations, neurofibroma, thyroglossal duct cyst, lingual thyroid, dermoid cyst, granular cell tumor and heterotopic gastric mucosal cyst.\(^3\) The presence of superficial, tiny vesicles with or without hemorrhage is a clue to the diagnosis of lymphangioma circumscriptum. Histopathological examination reveals dilated lymphatics, solitary or grouped, particularly in papillary dermis containing lymph or blood.\(^4\) Magnetic resonance imaging and lymphangiography may be useful in determining the extent of the disease.\(^3\) Treatment is indicated only in symptomatic patients or for cosmetic reasons. Surgical excision, carbon dioxide laser ablation, sclerotherapy with bleomycin or OK432 (It is a heat and penicillin treated lyophilised powder of 5 strain of Streptococcus pyogenes) or hypertonic saline, cryosurgery, electrocautery are tried\(^2,3\) but satisfactory results are obtained only in a few. Recurrence rates are high.\(^3,7\)

**References**

5. Ghosh SK, Banerjipadhyay D, Banerjipadhyay SN. Tense vesicles on the dorsum of tongue. *Indian J Dermatol Venereol Leprol* 2010; 76:593.
Paraquat Poisoning

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Abstract
Paraquat is a non selective herbicide used widely in Asia. On ingestion it can produce multi organ dysfunction and rapidly progressing pulmonary fibrosis. We report a case of delayed presentation of paraquat poisoning.

Introduction
Paraquat (N,N’-DIMETHYL-4,4’-BIPYRIDINIUM DICHLORIDE) is an organic compound with chemical formula [(C₆H₇N)₂]Cl₂. It is classified as a viologen. It is a quickly acting non selective herbicide widely used in Asia. It is highly toxic to humans and can cause multisystem involvement. No specific antidote is available for its treatment till now. Because of its toxicity, it has been forbidden in European union since 2007 and in USA, it is classified under restricted use which means it can be used only by licensed applicator.

Case Report
A 25 year old male presented to the emergency department with c/o difficulty in swallowing to solid and liquid, pooling of saliva in mouth, ulcer in tongue, yellow colouration of conjunctiva, decreased urine output and mild degree of respiratory difficulty. He was a case of paraquat poisoning, ingested 2 weeks back for which he had been treated in a local hospital symptomatically and gastric lavage was done. On examination his GCS was 15/15, pulse-50/min. BP-100/70 mm of Hg. Examination of chest, cardiovascular system, abdomen and CNS revealed no abnormalty except tongue was coated and red in appearance. On investigation, TLC-14,230/cumm, Hb-12.9 gm/dl, TPC-225000, MP-negative, Urea-275 mg/dl, Cr.- 4.78 mg/dl, Sodium (Na⁺)-134, Potassium (K⁺)-3.5, Serum Total Bilirubin-2.8, AST-1000, ALT-1071, ALP-518, PT-13.3, INR-1.1, Uric Acid-11.6. Ultrasound of abdomen revealed minimal left pleural effusion. HRCT of chest showed fibrotic strands in different segments of lungs and also sub pleural bands in right lower lobe. Patient was treated symptomatically with antibiotics, nasal feeding, fluid monitoring. Gradually patient recovered and was discharged.

Discussion
Paraquat induced toxicity is a manifestation of redox cycling and subsequent generation of reactive oxygen species. Generation of highly reactive oxygen and nitrogen species results in damage to most organs but the toxicity is particularly severe in the lungs as it is taken up against a concentration gradient in lungs. In the lungs, initially it causes acute alveolitis in one to three days and subsequently progresses to rapidly progressive fibrosis. Other organs affected are kidney, liver and GI tract. The appearance of tongue is known as paraquat tongue. Paraquat can cause perforation of esophagus. The major cause of death is due to respiratory failure.

Other secondary effects of oxidative stress also play synergistic effect in the manifestation of overall clinical presentation of paraquat poisoning. These are lipid peroxidation, mitochondrial toxicity, oxidation of NADPH, activation of nuclear factor kappa beta, and apoptosis.

Conclusion
Paraquat poisoning is life-threatening with multi organ failure and pulmonary fibrosis with high fatality rate. The presentation may be delayed for weeks with a symptom-free window period. Since there is no specific antidote for paraquat, if not monitored closely for few weeks, the patient may succumb to multi organ failure.

Fig. 1: Coated tongue (paraquat tongue)
Fig. 2: PA view of chest shows no abnormality
Fig. 3: (a, b, c) HRCT of chest showing fibrotic strands in different segments of lung and also sub pleural band in right lower lobe of lungs
Cerebral Hyperperfusion Syndrome following Staged Bilateral Internal Carotid Artery Stenting

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Abstract

Cerebral Hyperperfusion Syndrome is a relatively rare event following carotid revascularization. It can occur after both carotid endarterectomy and carotid artery stenting. It is characterized by focal neurodeficit, seizures and headache in the absence of ischemia. It can occur due to ipsilateral cerebral edema secondary to hyperperfusion. CT and MRI of the brain are the main modalities used for diagnosis and to rule out infarct. Prompt recognition and treatment can prevent permanent injury to the brain. We report a case of cerebral hyperperfusion syndrome in an elderly gentleman after a staged bilateral internal carotid artery stenting.

Introduction

Although carotid endarterectomy (CEA) has remained a standard therapy for stroke prevention in patients with significant carotid artery stenosis, carotid artery stenting (CAS) has emerged as an alternative. 1

Neurological complications following carotid revascularisation with either technique are well known, of which ischemic injury to the brain, due to embolisation or carotid occlusion are the most common. Cerebral hyperperfusion syndrome (CHS) is a relatively rare, but potentially devastating event known to complicate carotid revascularisation. It is defined as a clinical triad of ipsilateral headache, seizures and focal neurological deficits occurring in the absence of cerebral ischemia. 2 Awareness of this entity enables early detection and initiation of appropriate therapy to limit brain injury.

Case Report

A 72 year old gentleman, diabetic and hypertensive presented with bilateral critical internal carotid artery (ICA) stenosis of more than 70%. He had recurrent episodes of transient ischemic attacks (TIA) involving the left upper and lower limbs in the preceding 2 months. Stenting of the symptomatic artery was planned, to be followed by the contralateral vessel after four weeks. He underwent angioplasty and stenting to right ICA on 19/2/2016 using 9-7 x 40 mm X-ACT stent with a...
distal protection filter, which showed a significant amount of debris as shown in figures 1 and 2. The post procedure period was uneventful and he was discharged 2 days later. He remained asymptomatic, with no further episodes of TIA. He was readmitted one month later and underwent left ICA stenting on 18/3/2016 with 9-7 x 40 mm X-ACT stent, the retrieved filter showing no debris (Figure 3). His blood pressure (BP) in the immediate post procedure period was normal. 2 hours later patient became delirious and developed sensory aphasia, there was a decline in his BP, with systolic BP measuring 70 mmHg. Electrolytes were normal. CT brain and angiogram of neck and intracranial vessels was done which showed evidence of cerebral oedema involving the left hemisphere, with patent carotid stents and normal intracranial vessels (Figure 4). Patient was started on IV steroids. Over the next 12 hours patient developed right hemiplegia with right sided facial palsy and global aphasia. MRI brain revealed tiny multiple embolic infarcts, which did not co-relate with the clinical signs (Figure 5). Cerebral hyperperfusion syndrome was diagnosed. He was started on IV mannitol. On Day 2 following the procedure, patient had two episodes of seizures, managed with anticonvulsants. Throughout the period patient remained in a state of confusion and irritability. From day 3 onwards he started showing signs of recovery, conscious levels returned to normal and he had complete recovery with no residual neurological deficits.

**Discussion**

Hyperperfusion is defined as a 100% increase in cerebral blood flow (CBF) compared to pre-operative baseline. CHS was first described by Sundt et al as a clinical syndrome complicating CEA. The first report on CHS after CAS was published by Schoser et al. The incidence of this syndrome following CEA, as reported by numerous publications ranges from 0.4 to 14%, whereas following CAS varies between 0.96 to 11.7%.

Impaired cerebral autoregulation seems to play a significant role in the pathogenesis of CHS. The severity is proportional to the duration of carotid occlusion, severity of cerebral hypoperfusion, presence of contralateral carotid occlusion and poor collaterals. Elevated BP in the post-operative period is another factor in the pathogenesis of CHS. It occurs due to baroreceptor reflex failure following CEA. During CAS transient hypotension and bradycardia can occasionally be observed due to stimulation of the Carotid body nerve that can be followed by rebound hypertension. It is important to note that mechanisms that lead to post operative elevation in BP are not completely elucidated and could be multifactorial. However its absence does not confer protective value, as was observed in our patient who developed CHS inspite of normal BP. Intraoperative ischemia, ischemia-reperfusion injury with oxidant production, complement activation and microvascular permeability are other factors known play a role in the pathogenesis.

CHS can develop at any time from immediately after the procedure to up to a month later, but most patients develop symptoms within the first few days. Ogasawa et al reported occurrence of CHS peaking on 6th post op day after CEA and 12 hrs after CAS.

Confusion, deterioration of conscious level and headache are the most common presentations. Focal neurodeficit is secondary to cerebral oedema and in most cases is transient and reversible. The neurodeficit is usually cortical with hemiplegia, neglect, hemianopia, aphasia, as happened in our case. Seizures may be focal or generalized. The most severe complication secondary to hyperperfusion is intracranial haemorrhage (ICH). Its incidence is reported as 0.37% after CEA and 0.74% following CAS.

Transcranial Doppler(TCD) has been used to measure CBF velocity and
helps to predict occurrence of CHS, but has its own limitations. It is very
 crucial to identify CHS early to avoid irreversible brain damage. Clinical
 suspicion is important. TCD, SPECT, PET, CT and MRI aid in diagnosis. CT
 reveals ipsilateral sulcal effacement and cerebral oedema, immediately
 following symptom onset as in our patient. T2W and FLAIR MRI is more
 precise in demonstrating areas of cerebral oedema and DW-MRI helps to
 rule out embolic events. Angiography is almost universally normal.

Management of CHS involves aggressive BP control with target
 BP being 20-30% below baseline in patients with impaired CVR. There is
 no randomised control trial addressing the optimised treatment protocol
 for patients with CHS. Measures to treat cerebral oedema like mannitol,
 hypertonic saline, steroids and hyperventilation have been shown to be
 effective, anticonvulsants to treat seizures. One should also be aware
 about possibility of a delayed CHS and instruct patients accordingly at the time
 of discharge.

Nicolas et al have described that staged bilateral carotid stenting 30
days apart is an effective strategy to avoid CHS in high risk patients. They
found that there was no statistically significant differences with regard to the
30-day and 12-month clinical outcomes in patients undergoing unilateral compared to those receiving
staged bilateral CAS.

In our patient inspite of taking measures to minimise complications, like staged carotid stenting, using distal
protection filter and appropriate BP control, CHS still occurred. However
with timely recognition and treatment patient had a complete neurologic
recovery.

Conclusion

CHS although rare, is a potentially devastating complication following carotid revascularisation. The
occurrence is not always predictable inspite of taking precautions. With prompt recognition and treatment
of the disorder, most patients make complete recovery. ICH is a serious and at times fatal complication.

Abbreviations

BP: Blood pressure; CAS: Carotid artery stenting; CEA: Carotid endarterectomy; CHS: Cerebral hyperperfusion syndrome;
CT: Computed tomography; CVR: Cerebrovascular reactivity; DWI: Diffusion-weighted imaging; ICA: Internal carotid artery; ICH:
Intracerebral haemorrhage; MRI: Magnetic resonance imaging; SPECT: Single photon emission computed tomography; TCD:
Transcranial Doppler.

References

2. Sundt TM Jr, Sharbrough FW, Peepgras DG, Kearns TP, Messick J, O’Fallon WM. Correlation of cerebral blood flow and
electroencephalographic changes during carotid endarterectomy: with results of surgery and hemodynamics of cerebral
3. Schoener BGH, Heesen C, Eckert B, hie AT. Cerebral hyperperfusion injury after hyperperfusion syndrome following
stenting on the hemodynamic parameters and cerebrovascular reactivity of the ipsilateral middle cerebral artery. J Vasc Surg
5. Tang SC, Huang YW, Shieh JS, Huang SJ, Yip PK, Jeng JS. Dynamic cerebral autoregulation in carotid stenosis before
2014; 60:717-23.
8. Ogasawara K, Inoue T, Kobayashi M, Endo H, Fukuda T, Ogawa A. Pretreatment with free radical scavenger edar-
Group. Intracranial hemorrhage associated with cerebral hyper-perfusion syndrome following carotid endarterectomy and carotid
47, 6:1227-1234.
John Eccles was born in Melbourne, Australia. He graduated from Melbourne University in medicine in 1925. Eccles left Australia as Victorian Rhodes scholar for the year 1925 and entered Magdalene College, Oxford, as an undergraduate in order to study under Sir Charles Sherrington. He commenced research on reflexes with Sherrington’s colleagues. Later he was research assistant to Sherrington (1928-1931), there being eight research papers published jointly. He also collaborated with Ragnar Granit on two research projects. Eccles was awarded an Oxford D. Phil. Degree in 1929 for a thesis on Excitation and Inhibition in nervous system. He held a research post at Oxford and worked largely on synaptic transmission, both in central and autonomic sympathetic ganglia, and in smooth and cardiac muscles, using the newly developed techniques of electro physiology-amplifiers and cathode ray oscilloscopes. It was a period of controversy between exponents of rival chemical and electrical theories of synaptic transmission, with Eccles being strongly in favor of electrical transmission. Sir Henry Dale had already developed chemical theory effectively and after further studies by Katz, Eccles turned out wrong.

In 1937, Eccles left England for Australia to become Director of a small research unit in Sydney, where he was fortunate to have a distinguished collaboration with Bernard Katz and Kufflur. This period (1937-1943) was devoted largely to an electrophysiological analysis of neuromuscular junction of cats and frogs. After the war years he was appointed as Professor of Physiology at the University of Otego, New Zealand from 1944 to 1951, where he returned to synaptic transmission in the central nervous system. In 1951, Brock, Coombs and Eccles succeeded for the first time in inserting microelectrodes into nerve cell of central nervous system and in recording the electrical responses produced by excitatory and inhibitory synapses. From 1952 to 1966, Eccles was Professor of Physiology of the Australian National University, Canberra. Here, in collaboration with Coombs and Fatt, attention was concentrated on biophysical properties of synaptic transmission. This research was cited in his Noble Award. Eccles conducted his prize winning research by demonstrating that one nerve cell communicates with a neighboring cell by releasing chemicals into the synapse. He showed that the excitement of a nerve cell by impulse causes release of one kind of substance (probably acetylcholine) which allows sodium ions to penetrate the membrane and pass into the neighboring nerve cell. This reverses the voltage polarity so he concluded that a nerve impulse is conducted from one cell to another. In the same way an excited nerve cell induces another type of synapse to release substance into the neighboring cell that promotes outward passage of potassium ions across the membrane. This reinforces the existing polarity and inhibits the transmission of an impulse. Eccles’s research was essentially based on the earlier findings of Hodgkin and Huxley who had shown that the nerve membrane allows only potassium to enter the fiber during the resting phase but allows sodium to penetrate when the fiber is excited. Eccles highlighted synapses and the excitation-inhibition of the nerve cell.

John Eccles shared 1963 Nobel Prize for Physiology or Medicine along with Andrew Huxley and Alan Hodgkin for discovering chemical processes responsible for passage of impulses along individual nerve fibers.
Consensus Statement on Use of Ambulatory Glucose Profile in Patients with Type 2 Diabetes Mellitus Receiving Oral Antidiabetic Drugs

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Abstract
Glucose monitoring is an important aspect of diabetes care. The traditional methodologies of blood glucose monitoring such as fasting plasma glucose, post prandial glucose, glycosylated hemoglobin and self-monitoring of blood glucose do not adequately address hypoglycemia and glycemic variability, which are two important risk factors for diabetes-related complications. Ambulatory glucose profile (AGP) developed from a continuous glucose monitoring system is a simplified report, with standardized statistics and targets and visual representation of time in standardized glycemic ranges, glucose variability, and glycemic exposure over a single 24-h day. The role of AGP in T2DM patients who are on oral anti-diabetic drugs (OADs) is not clearly defined. An expert group of endocrinologists and diabetologists met in Pune, India to discuss the role of AGP in T2DM patients on OADs. This article aims to discuss the consensus of the expert group on the role of AGP in T2DM patients on OADs and also reviews the various aspects of AGP and its interpretation; and the available evidences for disease management including treatment options based on AGP report.

Introduction
Diabetes mellitus (DM) is a growing global problem with nearly 693 million people expected to be affected by 2045; Type 2 DM (T2DM) is the more prevalent type. India is expected to have the largest number of people with diabetes by 2045 (134 million). DM contributed to nearly 1.37 million deaths in 2017, of which 1.02 million were due to T2DM; the mortality rate increased by 5.9% from 2007 to 2017. Uncontrolled diabetes increases the risk of micro and macrovascular complications. In T2DM patients, hyperglycemia is well-established as a major risk factor for the development of microvascular complications. Similarly, incidents of hypoglycemia are reported to be associated with an enhanced risk of adverse cardiovascular outcomes; individuals with an increased risk of severe hypoglycemia have a two-fold increased risk of all-cause mortality and cardiovascular deaths in contrast to those who never suffered from severe hypoglycaemia. Lowering serum glucose levels in order to reduce micro and macrovascular complications is the mainstay of T2DM treatment. The “glycemic pentad”, which includes fasting plasma glucose (FPG), postprandial glucose (PPG), glycosylated hemoglobin (HbA1c), glycemic variability (GV) and quality of life, plays an important role in diabetes management, especially in the Indian context.

GV refers to swings in blood glucose levels and includes both postprandial spikes in blood glucose as well as hypoglycemic events. Numerous studies support association of long-term GV with an enhanced risk of micro and macrovascular complications, independent of HbA1c levels. Recent findings have also demonstrated the benefit of monitoring and controlling glycemic fluctuations in T2DM. PPG is a contributory factor for GV. In the San Luigi Gonzaga Diabetes Study, PPG was observed to be an independent risk factor for cardiovascular events in T2DM patients. Many other observational studies have also shown that elevated PPG, even in the high nondiabetic impaired glucose tolerance range, contributes to an approximately 3-fold increase in the risk of developing coronary heart disease or a cardiovascular event. Hypoglycemia is another limiting factor in the effective glycemic management of diabetes. GV can account for an estimated 40% to 50% of future hypoglycemic episodes. A reanalysis of the Diabetes Control and Complications Trial showed that in the intensively treated group, if two patients had identical HbA1c and MBG values, but one patient had GV at the 97.5th rather than the 2.5th centile of the population, that patient would experience a 35%–45% excess risk for one or more severe hypoglycemic episodes. The metrics for measurement of GV include the coefficient of variation (CV), standard deviation (SD), interquartile range (IQR), and mean amplitude of glycemic excursion (MAGE). A CV value <36% and a SD value less than the mean glucose (120–180 mg/dL) divided by 3 represents low GV and a relatively stable glucose profile.
Glucose monitoring is an important aspect of diabetes care that can help patients achieve and maintain glycemic targets. However, the traditional methods of monitoring glucose such as FPG, PPG or HbA1c do not adequately address hypoglycemia and GV and thus limit ability to achieve glycemic goals.  

Self-monitoring of blood glucose (SMBG), does show patterns of GV, but significant incidents of hypoglycemia or hyperglycemia maybe missed, considering its episodic nature. Also, both the glucose peak or nadir cannot be assessed as the blood glucose is measured sporadically; the associated multiple needle pricks during the day may be difficult and painful to the patient. This makes SMBG inconvenient and cumbersome for patients, especially for those who are on OADs.

Continuous glucose monitoring (CGM), which provides information on daily glucose fluctuations and shows how the values are affected by everyday activities and stress levels is a useful tool to assess GV. For example, in a study of 29 patients with T2DM well-controlled on metformin plus sulfonylureas, use of CGM demonstrated 18 patients (62%) to have experienced 65 episodes of silent, symptom-free hypoglycemia (interstitial glucose <70 mg/dL). Hence, use of CGM can enable patients to be more aware of these silent changes in blood glucose levels, providing them an opportunity to make the necessary adjustments to potentially avoid these hypoglycemic episodes. CGM also helps patients better understand their disease, impact of lifestyle on glycemic targets and their response to treatment, which may help with adherence.

Fig. 1: Daily glucose profiles and percent time in range over 14 days for a patient with T2DM

Although greater convenience and ease of use and improved sensor accuracy have increased CGM use, lack of standardized glycemic targets that can be referred to by both physicians and patients is a limiting factor. Although use of AGP is well-accepted in patients on insulin therapy, there are no clear guidelines on its use as a monitoring tool in the management of T2DM patients on OADs. In India, especially, glucose monitoring is still insufficiently practiced. Some of the reasons for this noncompliance are pain and inconvenience related to monitoring techniques, low knowledge of diabetes and low rate of physician recommendation. Therefore, there is a need for educating patients on importance of routine blood glucose monitoring as well as enabling them with convenient ways of monitoring.

To derive a consensus towards use of AGP, especially in Indian patients with T2DM treated with OADs, a group of experts from India held a consensus meeting in Pune, India, on 28 June 2019.
Ambulatory Glucose Profile

The AGP is a report based on data obtained from a CGM. The first AGP graph was a graphical depiction of the 25th, 50th, and 75th percentiles of blood glucose values and was created by Dr. Mazze in 1987. To create the graph, 440 glucose values obtained from 69 patients were organized into 14-day periods. The AGPs obtained were observed to be distinctive and related to the variability in metabolic control and the type of diabetes. 34

Subsequent versions of AGP were developed at the International Diabetes Center (IDC), including the current version, v4.0 for CGM AGP report. 35 The current AGP report is a single-page report based on SMBG or CGM data, with standardized statistics and targets and visual representation of time in standardized glycemic ranges, GV, and glycemic exposure over a single 24-h day. The AGP report also includes the daily glucose profiles in a calendar format. The AGP offers a report that is consistent regardless of device. A study of the AGP in patient clinics by Drs. Mullen and Bergenstal in 2014 showed that patients, families and clinicians prefer the AGP over other reports, and its use could save 4-19 minutes per patient visit. 35

The AGP report based on CGM data includes the following: (i) Dates and number of days in report (ii) Percent time CGM active (iii) Glucose ranges and targets (iv) Average glucose (mean) (v) Glucose management indicator (vi) Glucose variability (vii) Time in Ranges (viii) Glucose profile (ix) Daily glucose profiles shown as a series of boxes, with each box indicating the date, day and showing a single day’s glucose pattern (Figure 1). In each box, readings above the grey shaded area highlighted in yellow indicates high readings which could make it harder to heal from infections and over time causes complications, and below the shaded area highlighted in red indicates low readings which could make a person feel shaky, weak or confused. 35

The advantages of an AGP report are that it effectively consolidates and displays CGM data, which can enable clinicians to quickly assess overall glycemia and identify patterns of concern, thereby facilitating more informed therapy decision-making, and also help patients to better manage their disease by understanding interactions between their medications, meals, and exercise. 30 The IDC has also created a “9-step” interpretation plan to optimize interpretation of AGP data by clinicians and patients. 30

Most of the CGM device manufacturers have now adopted the AGP report, in slightly modified formats, in their download software [28]. The FreeStyle Libre Pro (Abbott, Alameda, CA) was the first device with an AGP graph approved in Europe in 2014 and by the United States Food and Drug Administration in September 2016. Currently, many devices are available with AGP. 35

Fig. 2: Representative ambulatory glucose profile graphs of patients with T2DM

Interpretation of AGP

Glucose profile graph

The daily glucose profiles collected over multiple days are combined to make a one-day (24-h) picture (Figure 2). The AGP shows the following:
1. Median line: The median (middle) line is shown in black where half of the glucose values are above, and half are below.
2. Inter quartile range (IQR): The 25th and 75th percentile curves shaded in dark blue represent the interquartile range or 50% of all values. It is a good visual indicator of the degree of GV, and a narrow space indicates minimal GV.
3. Inter decile range (IDR): The dashed outer lines (the 10th to 90th percentile curves) indicate that only 10% of glucose readings were above or below these values over the period assessed. In the latest AGP version (v4.0 [35]), the IDR has been changed to the 5th to 95th percentile curves indicating 5% of glucose readings that were above or below these values; this change was made to better identify infrequent, yet, significant hypoglycemia [30]. In general, the closer the dotted blue lines and the light blue shaded area is to the dark blue shaded area, the better.
4. Target range: The green outlined area shows target range. At a glance, clinicians and patients can determine the extent to which values are within the target range (70–180 mg/dL) and the times of day that pose potentially

Note: Graphs obtained using previous version of AGP showing 10th and 90th percentile [30], with the Freestyle Libre Pro (Abbott, Alameda, CA)
usually before or after mealtimes. The patient should also be asked about any differences in weekend versus weekday times for waking, meals, and bedtime. The daily profiles should be viewed to double-check patterns of high glucose and see if they are clustered on weekends or special activity days.

3. Glucose fluctuations or GV: Very wide interquartile ranges on the glucose profile correspond to high GV. The physician should discuss with the patient if the GV observed can be reduced by adjusting the timing or amount of food intake, carbohydrate counting, timing of medications, exercise times or amounts, and/or stress. If food and exercise log or electronic data are available, they should be matched with AGP.

Guideline recommendations on use of CGM and AGP in patients with T2DM

All guidelines recommend CGM use in patients on intensive insulin therapy irrespective of the type of diabetes, for gestational diabetes and for diabetes during pregnancy. In T2DM patients on OADs, CGM is recommended under specific circumstances as described below:

- The 2019 American Diabetes Association guidelines recommends CGM use for all patients with diabetes who have hypoglycemia unawareness and/or frequent hypoglycemia. Guidelines suggest use of CGM as close to daily as possible for maximal benefit, and recommend robust diabetes education, training, and support for optimal CGM implementation and ongoing use. Use of standardized reports with visual cues, such as an AGP is recommended, to help the patient and the physician interpret the data and use it to guide treatment decisions.

- The 2019 American Association of Clinical Endocrinologists and American College of Endocrinology consensus statement suggest use of professional CGM in T2DM patients who have not reached their glycemic target after 3 months of the initial antihyperglycemic therapy and for those who require therapy that is associated with risks of hypoglycemia (i.e., sulfonylurea, glinide, or insulin), with frequency of use depending on stability of therapies. Use of personal CGM devices is suggested for T2DM patients with a history of hypoglycemia unawareness, or those with recurrent hypoglycemia, with frequency of use on a continual basis in most patients. The experts also anticipate SMBG to be replaced by more frequent use of both professional and personal CGM in T2DM patients. Availability of CGM for people with T2DM has provided greater clarity for the patient’s and clinician’s understanding of the glycemic pattern.

- In India, the consensus guidelines on CGM use published in 2019 recommends CGM in clinical practice for T2DM patients on hypoglycemic treatment under SMBG guidance who encounter one of the following situations: severe hypoglycemia or repeated hypoglycemia; asymptomatic hypoglycemia and nocturnal hypoglycemia; refractory hyperglycemia, especially when fasting; or large blood glucose excursions.

The consensus also recommends CGM for diabetes education, as CGM can help patients to understand blood glucose fluctuations caused by diet, lifestyle and treatment, thereby instilling healthy lifestyle choices. Use of CGM is expected to help increase compliance and promote more effective communication between patients and doctors.

Expert group recommendations: Indications for AGP in T2DM patients on OADs

After reviewing literature evidences and collating clinical experiences of expert group members, all the members agreed unanimously that the traditional methods of monitoring diabetes maybe insufficient to prevent or delay the occurrence of complications. The expert group considered AGP to be beneficial in understanding the finer aspects of glucose control in T2DM patients, and recommended AGP in the following categories of T2DM patients on OADs (Table 1). The major components addressed are Glycaemic variability, hyperglycemia, hypoglycemia and patient education.

Management of problems identified by AGP in T2DM patients on OADs

There are various therapeutic options available to address concern areas identified by an AGP report. Physicians can tailor treatments to individual patients based on concern areas, resulting in better clinical outcomes. The section below focuses on the literature evidences supporting such management strategies.

---

**Table 1: Clinical indications for AGP in T2DM patients on OADs**

- Disparity between FBS/PPBS levels and HbA1c
  - HbA1c > 7.5%, with FBS/PPBS levels on target
  - HbA1c on target, with FBS/PPBS levels not on target
- At risk with hypoglycemia episodes
- Need for patient education
  - Not adherent to life style modification
  - Noncompliance to treatment
- Ongoing metabolic control and were found to be dangerous low or high patterns requiring immediate attention. The overall management goal is to make or keep the curve as narrow and flat as possible within the designated target range.

The following aspects are to be assessed while interpreting AGP:

1. Time in target range or time in range (TIR): Generally, refers to the time spent in a patient’s target blood glucose (usually 70–180 mg/dL). TIR measurements add valuable information to evaluate the glycemic control and were found to be correlated with HbA1c levels and diabetic complications in T2DM. In recent years, TIRs are recommended as key metrics of glycemic control for evaluating and comparing different glucose-lowering interventions.

2. Patterns of hypoglycemia and/or hyperglycemia (including post-prandial hyperglycemia): For hypoglycemia: The IDC 9-step interpretation plan states that if the 5% lower line is touching the 70mg/dL target line during a particular period of the day, or 5% of all glucose values are <70mg/dL at any given time, then physicians should consider taking some action. If the 25% line is touching or below the 70mg/dL target line or the 5% line reaches 54mg/dL, immediate action is required. The daily profiles can be viewed to double-check patterns of low glucose and see if they are clustered on weekends or special activity days.

For hyperglycemia: The IDC 9-step interpretation plan states to discuss with the patient as to how many times per week a medication may have been forgotten or if meal-time insulin was actually taken before meals. The patient should be asked about mealtimes to check whether high values are usually before or after mealtimes. The patient should also be asked about any differences in weekend versus weekday times for waking, meals, and bedtime. The daily profiles should be viewed to double-check patterns of high glucose and see if they are clustered on weekends or special activity days.
**Table 2: Glycemic control at baseline and after 8 weeks of adjunctive vildagliptin and sitagliptin treatment**

<table>
<thead>
<tr>
<th></th>
<th>Vildagliptin Mean ± SD</th>
<th>P value vs BL</th>
<th>Sitagliptin Mean ± SD</th>
<th>P value vs BL</th>
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<td><strong>Mean Amplitude of Glycemic Excursion (MAGE) (mg/dL)</strong></td>
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<tr>
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<td><strong>Mean 24 hr Blood Glucose reading (mg/dL)</strong></td>
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<tr>
<td>Baseline</td>
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<td>129.4 ± 18.2</td>
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Adapted from: B. Guerci et al., Diabetes and Metabolism 38 (2012) 359-366

**Fig. 3: 24-h mean (SE) glucose, with Dapagliflozin therapy for 4 weeks compared with placebo with treatment difference for least-squares mean change from baseline (mg/dL) in the ITT population**


**A. Addressing glycemic variability:**

Studies using CGM have shown that OADs such as dipeptidyl peptidase-4 (DPP4) inhibitors and sodium-glucose cotransporter-2 (SGLT2) inhibitors have a role in addressing GV. Hence, use of these drugs alone or in combination in T2DM patients would help in minimizing/delaying complications arising from GV.

DPP4 inhibitors: In a prospective open-label pilot study in Japanese patients with T2DM, sitagliptin 50 mg once-daily administered alone or with a concomitant drug decreased the average 24-h blood glucose level, SD of the 24-h blood glucose level, 24-h glycemic fluctuation range, MAGE, and hyperglycemic time. The improvement in 24-h blood glucose level was mainly due to improvement of postprandial hyperglycemia. A significant decrease in the time period of hyperglycemia (blood glucose level >180 mg/dL), and a tendency for decrease in hypoglycemia was observed. The changes in the average 24-h glucose level and changes in HbA1c were related supporting the evaluation of drug efficacy with CGM in T2DM patients. The correlation between MAGE levels before and after sitagliptin administration suggests that larger glycemic fluctuation may result in a greater effect of sitagliptin in maintaining blood glucose levels.39

In a randomized, open-label study in patients with T2DM inadequately controlled on metformin, mean baseline HbA1c of 7.1%, both vildagliptin 50 mg twice-daily and sitagliptin 100 mg once-daily showed similar improvement in 24-h GV measured by MAGE and SD of mean glucose concentration. However, vildagliptin showed significantly better circadian glycemic control than sitagliptin (mean 24-h blood glucose level, time spent in the ideal glycemic range [70–140mg/dL] and above hyperglycemic thresholds [140 and 180mg/dL], along with corresponding area under curve [AUC] values) (Table 2). Both drugs significantly decreased postprandial hyperglycemia. The CGM data was consistent with conventional lab data in these patients.40 Another study that compared rosiglitazone, glimepiride and vildagliptin or sitagliptin demonstrated gliptins, glitazones and sulfonylureas to all concomitantly act on basal and postprandial glucose; however, only gliptins were more efficient on PPG.41

In an open-label, randomized cross-over study in T2DM patients, vildagliptin 50 mg twice-daily showed lower glucose fluctuations than glimepiride 2 mg once-daily as measured by MAGE and SD of blood glucose rate of change. The postprandial glucose AUC data for both drugs were similar to those obtained by measuring post meal plasma glucose concentrations, suggesting that CGM can be utilized reliably to assess treatment effects of different glucose-lowering agents in T2DM patients.42 In another randomized, double-blind study in T2DM patients inadequately controlled on metformin, while both sitagliptin and glimeperide significantly reduced HbA1c, significant reductions in MAGE were seen only with sitagliptin.43

In an open label, randomised study in Korean patients with T2DM inadequately controlled with metformin monotherapy, vildagliptin 50 mg twice-daily and pioglitazone 15 mg once-daily significantly reduced HbA1c and mean plasma glucose levels. However, only vildagliptin reduced GV as demonstrated by the significant reduction in MAGE and mean SD of 24-h glucose.44

SGLT2 inhibitors: In a randomized study in Japanese T2DM patients with baseline HbA1c of 7.9%, empagliflozin 10 mg or 25 mg resulted in a significant adjusted mean difference versus placebo at both day 1 and day 28 in change from baseline in HbA1c, for PPG and change from baseline in 24-h mean glucose. Percentage of time with glucose ≥70–<180 mg/dl increased from baseline to day 28 with both empagliflozin doses, without increasing time spent
with hypoglycemia. Improvement in MAGE was not significantly different with empagliflozin versus placebo.  

In a randomized, double-blind trial in newly diagnosed Chinese T2DM patients with HbA1c levels of 7.5%–10.5%, treatment with dapagliflozin 5 mg or 10 mg once-daily or placebo for 24 weeks resulted in significant improvement of MAGE, reduction in 24-h mean blood glucose, and lower mean plasma glucose concentrations without increasing hypoglycemia. Dapagliflozin also resulted in notable decrease in plasma 8-iso PGF2α level. Results demonstrated the ability of dapagliflozin to improve glycemic variations and reduce oxidative stress in patients with T2DM, which may benefit the cardiovascular system.

In a retrospective study, use of SGLT2 inhibitors was demonstrated to significantly improve SD, MAGE, and largest amplitude of glycemic excursions by day 7. The percentage time at ≥140 mg/dL, max, and min significantly decreased on day 3 and further improved by day 7 while the percentage time at <70 mg/dL and mean postprandial glucose excursions remained unchanged. SGLT2 inhibitors induced an immediate decrease in glucose levels, reduced the variations in blood glucose levels, and regulated urinary glucose excretion to prevent hypoglycaemia.

In a randomized, double-blind study in adult patients with uncontrolled T2DM (HbA1c 7.5%–10.5%) on either stable doses of metformin monotherapy (≥1500mg/day) or insulin (≥30U/day with or without up to two OADs), the 24-h mean glucose decreased 18.2 mg/dL with dapagliflozin 10 mg/day and increased 5.8 mg/dL with placebo; the treatment difference was significant. The proportion of time spent in the target glucose range (70–180 mg/dL) increased significantly with dapagliflozin versus placebo. There was a notable downward shift in the mean 24-h CGM glucose profile across the overall 24-h profile from baseline to week 4 in the dapagliflozin group and there was an improvement in MAGE and glycemic parameters (Figure 3).

B. Addressing postprandial hyperglycemia: Studies using CGM have shown that a glucosidase inhibitors minimize GV due to their ability to lower PPG levels. Hence in T2DM patients with postprandial hyperglycemia identified on AGP, a glucosidase inhibitors can be the preferred choice of therapy.

a glucosidase inhibitors: In the MAJOR study in Japanese T2DM patients comparing miglitol 50 mg and acarbose 100 mg, both drugs were observed to have a similar effect on GV. However, PPG increases after a typical Japanese meal was significantly reduced with miglitol versus acarbose.  

In a randomized study in Taiwanese T2DM patients inadequately controlled on one or two OADs (HbA1c 7.0%–11.0%), more effective reduction in both intraday and interday GV was observed with acarbose (50 mg thrice-daily for 4 weeks followed by 100 mg thrice-daily for 12 weeks) compared with glibenclamide (2.5 mg thrice-daily for 4 weeks followed by 5 mg thrice-daily for 12 weeks) as an add-on to metformin 500 mg thrice-daily; both combinations reduced the overall glucose level equally.

In another randomized parallel-group study, in Taiwanese T2DM patients inadequately controlled on one or two OADs (HbA1c 7.0%–11.0%), significant decrease in MAGE without significant change in oxidized LDL levels or 8-iso PGF2α excretion rates were observed only with acarbose (50 mg thrice-daily for 4 weeks followed by 100 mg thrice-daily for 12 weeks) but not glibenclamide (2.5 mg thrice-daily for 4 weeks followed by 5 mg thrice-daily for 12 weeks) as an add-on to metformin 500 mg thrice-daily. β-cell response to postprandial glucose increments improved significantly with acarbose. Also, treatment with glibenclamide significantly increased the duration of hypoglycaemia.

In a cross-over study, sitagliptin 50 mg/day was reported to significantly decrease the 24-h mean glucose level, mean glucose level during daytime, and preprandial glucose levels compared with voglibose 0.9 mg/day. However, the glucose curve after breakfast, and in particular after dinner, rose significantly rapidly with sitagliptin compared with voglibose. Results demonstrated voglibose to more significantly reduce PPG elevations compared with sitagliptin.

In a randomized trial in Indian patients with T2DM (HbA1c 7.0% to 10.0%), voglibose alone or in combination with high-fiber dietary intervention was observed to improve overall blood glucose levels and GV. Combination therapy was significantly more effective than monotherapy in reducing HbA1c and the mean of daily differences, whereas MAGE and largest amplitude of glycemic excursions were not significantly different between the two groups.

C. Addressing hypoglycemia: Studies using CGM have shown DPP4 inhibitors and SGLT2 inhibitors to be less associated with hypoglycemia. Hence, use of these drugs may help reduce hypoglycemia incidence and thereby GV in T2DM patients with increased risk of hypoglycemia. DPP4 inhibitors: DPP4 inhibitors are associated with fewer incidences of hypoglycemia, owing to their mechanism of action. The study by Mori et al. demonstrated that sitagliptin does not increase and actually reduces period of hypoglycemia (glucose <70 mg/dL) [39]. In the study by He et al., no incidences of severe hypoglycemia (defined as blood glucose <3.1 mmol/l) were reported with vildagliptin therapy. Similarly, in the study by Scherbaum et al., no hypoglycemic episodes were reported with vildagliptin over a 2-year period in T2DM patients.

SGLT2 inhibitors: The SGLT2 inhibitors are also not expected to increase hypoglycemic episodes owing to their mechanism of action. In studies in T2DM patients using CGM, no increase in hypoglycemic episodes were observed with these drugs. In the study by Nishimura
et al, empagliflozin increased the percentage of time with normoglycemia (glucose ≥70 to <180 mg/dL) without significantly increasing the percentage of time with hypoglycemia (glucose <70 mg/dL) in Japanese patients with T2DM [45]. In the study by Li et al, dapagliflozin did not increase hypoglycemia in Chinese patients with T2DM, and the incremental AUC less than 3.9mmol/L was almost the same in dapagliflozin and placebo groups after 24-week therapy.46 In the study by Henry et al., the mean percentage of time spent with glucose <54mg/dL was 0% at baseline and remained 0% at week 4 with dapagliflozin treatment in T2DM patients with uncontrolled diabetes.48

**Sulfonylureas:** Although sulfonylureas in general are known to cause hypoglycemia, glimepiride is expected to cause less CV than glibenclamide owing to the extra pancreatic effect, rapid association, and dissociation binding properties with receptors and effect on both phases of insulin secretion.55,56 Also, the insulin-releasing activity is high with glibenclamide and lowest with glimepiride. Importantly, during hypoglycemia, protective mechanisms (inhibition of insulin secretion and promotion of glucagon secretion) are preserved in the presence of glimepiride but not in the presence of glibenclamide.

**Patient education:** Self-management and lifestyle interventions by patients plays an important role in the management of T2DM. Patients with T2DM who modified their diet and lifestyle were observed to experience a significant reduction in FPG and PPG after one year compared with those who did not, highlighting the value of lifestyle intervention in management.

Use of CGM and AGP can be a useful tool in counselling patients, because the visual displays in the report enables physicians to better educate the patients on the effect of medication and lifestyle on diabetes and enables patients to have a better control over their condition by understanding the interactions between medications, diet and physical activity.58 Lifestyle and behavioural counselling along with CGM is reported to promote higher treatment satisfaction and reduce disease-related distress.59

The AGP would enable patients and clinicians to agree on a personalized treatment plan aimed at improving the glucose profile while avoiding significant hypoglycaemia.35

In an 8-week randomized study, it was observed that T2DM patients who received counselling feedback on their CGM graph along with role model CGM graph depicting glucose reductions in response to physical activity in addition to general diabetes education had significantly higher self-efficacy scores for sticking to activity/resisting relapse; significant increase in moderate activity minutes and a significant decrease in HbA1c and body mass index compared with those who only received general diabetes education.60

In a 3 month study in poorly controlled T2DM patients (8.0 ≤ HbA1c ≤ 10%), use of CGM was reported to be useful in modifying patients’ diet and exercise habits and induce better glycemic control than SMBG. There was significant reduction in total calorie intake and a significant increase in exercise time per week in patients using CGM.61 In another 3-month study in women with suboptimal glycemic control advised CGM, problem-solving counselling resulted in significantly greater problem-solving skills, and greater dietary adherence, moderate activity minutes, weight loss, and higher intervention satisfaction than general diabetes education.62

In another study, an increase in absolute step counts occurred after a 12-week lifestyle intervention combined with CGM.65

A 6 month retrospective study in India evaluated glycemic control in 296 T2DM adults for 6 months following a 6-to 7-day study of their glycemic profile using masked Professional-CGM. The study showed that the frequency of performing self-monitoring of blood glucose (SMBG) was also found to be significantly increased in these patients from the baseline.64

A brief informal survey conducted in India among 825 Freestyle LibrePro (FSLP) P-CGM deployed patients and clinicians to evaluate the user-friendliness and acceptability of this technology. The survey found that the patients were willing to repeat the procedure due to perceived simplicity, painless nature, increase in quality of life, lower cost, and so on achievable with the device.66

**Conclusions**

Diabetes mellitus is growing at an alarming rate worldwide. As the prevalence of diabetes is increasing, there has been a surge in the complications caused by diabetes. The last decade has witnessed a tremendous improvement in the scientific knowledge about diabetes, bringing newer ways of management, newer antidiabetic agents, an increase in the awareness about the disease and the need to adopt lifestyle management strategies. Yet, there is no adequate control in the glycemic levels and no decline in incidence of complications of diabetes.

This necessitates a relook into the various diabetes management strategies that is being followed currently and also emphasizes that there is something more than the traditional FPG, PPG and HbA1c levels which needs to be looked into. The AGP has been gaining traction as a tool for better management of diabetes by clinicians and patients with increasing evidence available on its role in better management of diabetes.

Clinicians need to adopt the newer technologies in the management of diabetes for better clinical outcome, explore the benefits and limitations of such technologies and share their experiences. Doing so would help build scientific evidence and encourage increased use of these technologies in clinical practice.

**Acknowledgments**

The authors thank Lakshmi Venkatraman, PhD, for medical writing support, which was funded by Abbott Healthcare Pvt. Ltd.

**Conflict of Interest**

The expert group discussion was organized in association with Abbott Healthcare Pvt. Ltd. This article is based on the views expressed during the expert group discussion. The views
expressed in the discussion are solely of the panel members.

References


Effect of on Admission Blood Glucose Level and HbA1c Value on Short Term Prognosis in Acute STEMI

Meenaxi Sharda 1, Nitasha Sharma 2, Shoyji Ram Meena 3, Jitendra Kumar Meena 4, Praveen Kumar 5

Sir,

Patient either with or without history of diabetes mellitus may present with hyperglycemia during acute myocardial infarction known as stress hyperglycemia which is an independent predictor of in-hospital morbidity and mortality. Aim of the study was to assess the occurrence and effect of stress hyperglycemia in short term prognosis of acute MI and Prevalence of controlled and uncontrolled chronic hyperglycemia with their prognostic impact on acute MI.

This cross sectional in-hospital study was done on 100 consent giving acute, evolving or recent STEMI patients over a period of 1 year dividing them into 4 groups on the basis of their history of diabetes, admission blood glucose level and HbA1c value. Twenty five patients with admission blood sugar [ABG] less than 140mg/dl and HbA1c <6.5 were taken in group 1(normoglycemics) and twenty five AMI patients with ABG 140 or more than 140 mg/dl were taken in group 2(stress hyperglycemics). Diabetic patients were divided into controlled and uncontrolled with HbA1c <6.5 and ABG =or < eAG and HbA1c >6.5 with ABG >eAG into group 3 and group 4 respectively.

In hospital stay of patient and further follow up was noted for any immediate cardiac complications and short term outcomes.

The age of subjects ranged from 30 -90 years with mean age 59.45 ± 12.5 years. Difference was not significant regarding to mean age (p > 0.05) between the comparable groups. There were 32% females and 68% males in group 1 and 28% females and 72% males in group 2 where as group 3 and group 4 had equal sex composition with 44% females and 54% males. All Subjects of comparable groups were matched in respect to common risk factors including age, sex, smoking, hypertension and lipid profile with p value > 0.05. Only factor to be assessed was mean blood sugar which was significantly higher in group 2 as compared to group 1.Whereas in group 3 and 4 only factor to be assessed was mean HbA1c with statistically significant difference.

Group 1 and 2 and group 3 and 4 were compared in respect to immediate and short term post MI complications (viz post infarct angina, CHF, persistent elevation, cardiogenic shock ,arythymia and heart blocks) and in hospital and 1 month mortality. We observed statistically significant (p value=.032) overall higher complication rate in group 2 patients 72% vs 36% in group 1. In hospital and 1 month follow up mortality is 0% in group 1 and 24% in group 2 patients with p value of 0.0296, stastically highly significant.

Comparing group 3 and 4 there was overall high complication rate with high HbA1c i.e. in uncontrolled diabetic group (44 %) compared to HbA1c < 6.5 i.e. controlled diabetic group (40 %) but the difference was statistically insignificant with p value 0.771. Mortality was similar with death rate 8% in both the groups but death was only observed in patients who had blood sugar level higher then eAG calculated according to HbA1c; suggesting that a component of stress hyperglycemia played a role in mortality independent of HbA1c level in either group.

Comparative analysis shows elevated admission glucose also known as stress hyperglycemia is common in AMI patients and is a powerful predictor of adverse outcomes Also elevated admission blood glucose level in patients with AMI appears more important than prior long-term abnormal glucose metabolism (detected by elevated HbA1c) in predicting outcome in patients with AMI. These results are in agreement with the study done by Gasior et al1 where there was higher incidence of congestive heart failure in STEMI patients with higher admission blood glucose. We observed significantly higher mortality rate in group with higher admission blood glucose which was supported by study done by Kosiborod and McGuire2, where they concluded that higher glucose levels were associated with greater 30-day mortality.

Similar to our study Hanan E. Zaghlala et al3 did not find any significant correlation between HbA1c level and outcome of patients with AMI. Though our results are in accordance with these studies but we can’t overlook the limitations of the study which were : a short sample size ,late presentation
of some patients which may have influenced admission blood glucose level, as time of presentation is not constant in our study subjects and patients were included irrespective of admission treatment (Thrombolysis / no thrombolysis) and extent of myocardial damage which in itself can affect the rate of complication and hence the prognosis.

Hence elevated admission glucose known as stress hyperglycemia in AMI patients is a good predictor of adverse outcomes than chronic hyperglycemia therefore on admission blood sugar level testing is very important in acute MI settings and should be done routinely in all cases to document stress hyperglycemia and hence more vigilant monitoring to reduce morbidity and mortality.

References


Assessment of a North Indian District Hospital for Quality Assurance using Kayakalp Tool

Ankit Chaudhary¹, Anjali Mahajan², Vijay Kumar Barwal³
¹Junior Resident, ²Associate Professor, ³Assistant Professor, Department of Community Medicine, IGMC, Shimla, Himachal Pradesh

Sir,

Government of India, launched the “Kayakalp” initiative in 2015 with an objective of promotion of cleanliness and delivery of quality health care services through public health facilities (PHF).¹ Cleanliness and hygiene in health facilities are part of a continuum of the entire gamut of quality parameters. Low level of cleanliness in PHF is a major factor for the poor faith of masses in them. This often directs them towards private sector hence leading to increased out of pocket expenditure on health.

A cross sectional observational study was conducted in District Hospital Shimla in 2015 for such an assessment using the “Kayakalp” tool. The scoring for various areas of concern is based on a checklist for quality assessment. These were Facility Upkeep, Sanitation and hygiene, Waste Management and Infection control with maximum score of 100 each. The Support Services and Hygiene Promotion had a maximum score of 50 each. Methods used to assess the facility were Direct observation, Staff interview and Review of records. Based on these scores, we arrived at a conclusion for extent of full, partial and non-compliance.

The District hospital scored 374 out of maximum 500 (74.8%). The individual breakup of the scores under four domains namely Hospital/Facility upkep, Sanitation and hygiene, Waste management, Infection control were 75, 84, 82 and 63 respectively. For the two domains of Support services and Hygiene promotion, and Hospital Record the scores were 38 (76%) and 32 (64%) respectively. A similar study in Chhattisgarh reported scores ranging from 73.2% to 91.8% in 8 out of 27 District hospitals.²

While evaluating the facility we observed certain strengths as well as gaps in the working of the facility. Good compliance to prescribed norms was seen for Facility appearance, Work place management and Infrastructure maintenance, but little attention was being given to the areas of Pest and animal control, Water conservation and Maintenance of open areas. Gaps were observed in cleanliness of toilets and auxiliary areas. Monitoring of cleanliness activities was also not in place.

Full compliance was observed for disposal of Biomedical waste (BMW), Solid general waste and Liquid waste management. Little need was being paid for Segregation, Collection, transport, Management of hazardous waste, Equipment’s and Statutory compliance. In contrast to our score of 82% for biomedical waste management, a score of 57% was assigned for a District hospital in Karnataka.³

Infection control practices were being followed as per the protocol however Decontamination and cleaning of instruments, Spill management and Environmental control failed to meet the standards. The hospital showed absolute non-compliance for Isolation and barrier nursing criteria. Water sanitation, Security services and Out-source services management was satisfactory. Laundry and Kitchen services management showed partial compliance. There was non-availability of documented Standard Operating Procedures for cleanliness, upkeep of facility, BMW and infection control.

This standardized approach would help in judging their performance on a uniform pedestal. It would encourage better upkeep of the facility by way of incentivization and serve the ultimate purpose of provision of quality health care services.

References

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Helps to overcome weakness, tingling, numbness and lethargy3

OPTIMAL THERAPEUTIC DOSAGE:

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1. Controlled randomized intervention.
2. SurbexXT® Red磷酸盐软片中的肽类成分提供了以下微量元素：铬（Chromium）250 mcg, 锌（Zinc）15 mcg, 硒（Selenium）100 mcg, β-胡萝卜素（β-Carotene）5 mg.
3. 研究显示，SurbexXT®对糖尿病和高血压患者具有更好的控制效果，有助于改善生活质量。
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