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### Physicians Research Foundation

**BOARD OF DIRECTORS (2020-2021)**

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²The CV benefit of TRESIBA® was demonstrated in the HOMES trial, a trial of patients with type 2 diabetes at high CV risk on basal insulin.

References:
2. Novo Nordisk.
COVID-19 Pandemic - Call for National Preparedness

Falguni Parikh

An outbreak of unusual respiratory disease recognized in December 2019 from Wuhan, China, was caused by infection by a novel coronavirus, initially named 2019-nCoV by World Health Organization (WHO).\(^1\)\(^,\)\(^2\) On 30th January 2020, this outbreak was declared a Public Health Emergency of International Concern as geographic footprint of this virus expanded to involve many other countries. On February 11, 2020, WHO renamed the disease as coronavirus disease 2019 (COVID-19).\(^3\) On the basis of a phylogenetic analysis of related coronaviruses, 2019-nCoV was designated as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) by the Coronavirus Study Group (CSG) of the International Committee on Virus Taxonomy.\(^4\) On 11th March 2020, Director General of WHO has declared COVID-19 to be a global pandemic.\(^5\) It is the first pandemic to be caused by a coronavirus. COVID-19 affects people of all ages but older people (more than 60 years) and those with underlying medical illness like cardiovascular disease, chronic respiratory disease or cancer are at higher risk of getting severe infection.\(^6\) The death rate is 3.4\(^\%\).\(^7\)

As of 17th March 2020, 136 countries and territories have reported cases of COVID-19.\(^8\) There are 179,112 confirmed cases and 7,426 deaths reported globally.\(^9\) Major countries outside China which have recorded high number of cases are South Korea, Italy, Iran, Japan, France, Germany and Spain. The total number of cases and deaths outside China has overtaken the total number of cases in China.\(^10\)

First confirmed case of COVID-19 from India was diagnosed on 30th January 2020 in Kerala in a medical student who had returned from Wuhan. Subsequently 2 other cases were reported from Kerala. All the 3 cases were successfully managed and discharged. As of March 17th 2020, a total of 142 cases of COVID-19 and 3 deaths have been reported in India.\(^11\)

The leading international scientific journals like the New England Journal of Medicine, British Medical Journal, Lancet, JAMA, Annals of Internal Medicine, etc. have published fast tracked original articles published by the institutes and scientists handling these patients to dissipate this experience amongst the medical community.\(^11\)\(^,\)\(^12\) Sharing of information has been a key factor during this outbreak and it has surely had effect on health systems, social services and economic activity.

Although most viral infections may present with similar symptoms, the virus responsible for COVID-19 is different with respect to community spread and severity.\(^13\)\(^,\)\(^14\) It is a highly contagious virus that spreads 2-4 times as rapidly as the flu, has a long incubation period of up to 14 days and can be transmitted by people with mild or perhaps no symptoms. It can survive on contaminated surfaces as well. All of which make it very, very tough to contain. Considerable efforts to reduce transmission will be required to control outbreaks.

WHO has defined four transmission scenarios for COVID-19:

1. Countries with no cases (No cases);
2. Countries with 1 or more cases, imported or locally detected (Sporadic cases);
3. Countries experiencing cases clusters in time, geographic location and/or common exposure (Clusters of cases);
4. Countries experiencing larger outbreaks of local transmission (Community transmission).

India is at stage 2 of transmission. We need to increase the level of preparedness, alertness and response to identify, manage and care for cases of COVID-19.\(^15\) Government of India has invoked powers under the Epidemic Diseases Act, 1897 to enhance preparedness and containment of the virus and declared COVID-19 a ‘notified disaster’ under the Disaster Management Act 2005.\(^16\)

Strategic preparedness and response plan for COVID-19 by WHO aims to slow and stop transmission, prevent outbreaks and delay spread while providing optimized care for all patients especially the seriously ill.\(^17\)\(^,\)\(^18\)

Simple measures like hand hygiene, respiratory etiquette, social distancing, and masks for symptomatic individuals help to prevent spread of the virus. Banning of mass gatherings, school and university closure, workplace closure and public health quarantine has been undertaken. People traveling to countries abroad might come in contact with people affected with COVID-19 during their stay or even while in transit at the airports. Within these countries, few countries have reported very large number of cases and deaths putting passengers from these countries particularly at higher risk of infection.\(^19\) All incoming travelers, including Indian nationals, arriving from or having visited China, Italy, Iran, Republic of Korea, France, Spain, Germany, UAE, Qatar, Oman and Kuwait are quarantined for a minimum period of 14 days. Starting from 13 March 2020, all existing visas, except diplomatic, official, UN/International Organizations, employment, project visas, stand suspended until 15 April 2020. All international Passengers entering India are required to furnish duly filled self-declaration form and undergo Universal Health Screening at the designated health counters at all points of entry (international airports, seaports and ground crossings). Persons with symptoms are made to undergo further medical checks and isolation for strict infection control. Collection and transportation of samples for laboratory testing and appropriate medical care is rendered to them. Contact tracing is

Consultant Internal Medicine and Infectious Diseases, Kokilaben Dhirubhai Ambani Hospital, Mumbai, Maharashtra
done to identify, assess and manage people who have been exposed to a patient with COVID-19 to prevent onward transmission. Contact tracing includes identification of extended social networks and travel history of cases during the 28 days after onset of illness.17

As we move ahead, we need to increase our level of preparedness to identify, manage and care for new cases of COVID-19.20,21 The healthcare facilities have to train the outpatient and emergency department staff in screening and isolating potentially infectious patients and identify and transfer cases safely, without disease transmission. Standard precautions should be adhered to in high volume emergency departments to prevent transmission from ill patients to health care workers and other patients by having a separate triage area.22,23 While home care is advocated for mild cases to avoid overwhelming healthcare facilities, there should be close monitoring for high risk cases and referral system in case of deterioration. Hospitals should be ready for surge of cases and have a plan ready for surge facilities. Adequate stock of medicine, materials and protective gears is desirable. Training drills for staff on personal protective equipment use, cleaning and disinfection are required for infection control and prevention. As of 14th March, there are 52 laboratories identified by the Indian Council of Medical Research for testing of COVID-19. A total of 57 laboratories have been identified to support sample collection and referral. Local health authorities with involvement of private and public hospitals have isolation beds ready and quarantine areas identified. Awareness raising, risk communication and active engagement of the community is being undertaken to decrease misconceptions and counter misinformation. Positive campaign helps to empower the public and avoid panic situation especially when there is information overload on various social media platforms.

Successful handling requires collaborative efforts between society, Municipal Corporation, Government, Public health experts and Healthcare professionals.

As we are a very large country, we can anticipate various limitations as regards containment of infection. Social distancing, isolation and home quarantine are difficult due to small homes and many family members staying together. Working from home is not an option for most people who earn daily wages. The tests for COVID-19 presently are available at few authorized laboratories. However, once private laboratories are permitted to carry out tests, the number of positive patients may see an upward trend. As more sick patients get admitted there can be an increased demand for Intensive care facilities and ventilators.

The Research and Development roadmap for COVID-19 outlines research priorities in 9 key areas. These include the natural history of the virus, epidemiology, diagnostics, clinical management, ethical considerations and social sciences, as well as long-term goals for therapeutics and vaccines.

There is still much to discover about the disease and its impact in different contexts. As healthcare professionals, we need to understand the facts and strategize our response to handle this crisis effectively. We need to protect ourselves and paramedical staff with required personal protection to avoid getting infected. We need to focus our efforts should be directed to flatten the pandemic by taking actions to slow the spread. This will help us to minimize the overwhelming of medical services.

As COVID-19 is a new disease that is distinct from previously encountered viral pandemics, preparedness, readiness and response actions will continue to be driven by rapidly accumulating scientific and public health knowledge.

References

16. MOHFW guidelines for coronavirus [Internet]. Available from: https://mohfw.gov.in/
In T2DM patients,

\[ \text{Vylda} \]
Vildagliptin 50 mg Tablets

*Pure Bliss for Smooth Life*

In Hypertension & Angina,

\[ \text{S-Numlo} \]
S(-)-Amlodipine Tablets IP 2.5/5 mg

*PURITY THROUGH CHEMISTRY*

In Type 2 Diabetes uncontrolled on monotherapy,

\[ \text{XiLia-M} \]
Glimepiride IP 1 mg / 2 mg + Metformin HCl IP 500 mg ER Tablets

*Adding sweetness to life*
A Study of Correlation between High Normal Glycosylated Hemoglobin as Risk Factor for Coronary Heart Disease with Framingham 10 Year Risk Factor in Non-Diabetic Patients

Krishnakant Bhatt1*, Dharmesh Nama2, Gauravkumar Divani3

1Professor (Addl.), 2Senior Resident, 33rd Year Resident, General Medicine, GMC, Surat, Gujarat; *Corresponding Author

Received: 24.07.2017; Revised: 08.11.2019; Accepted: 10.11.2019

ORIGINAL ARTICLE

Abstract

Background and Purpose: Framingham 10 year risk score traditionally used to diagnose future risk. There is need to find simple and powerful marker for future risks of coronary artery disease. Framingham 10 year risk score take many variables together. Recently, abnormal glucose metabolism is a major determinant of CHD. Although the relationship between cardiovascular disease (CHD) and glycaemia is believed to represent a continuum without a threshold effect, as it is a more stable, accurate parameter of glucose homeostasis. Therefore, the aim of the current study was to establish association between high normal HbA1c and Framingham 10 year risk score for coronary artery diseases in non-diabetics.

Methods: A total 100 patients of coronary artery disease, aged 18-80 years were enrolled. Complete physical and systemic examination including vitals was performed. Framingham’s 10 year risk score, Height, Weight, Hip Circumference, Waist Circumference, and Waist-Hip Ratio and BMI are calculated. Investigated for HbA1c, HsCRP and other routine investigations needed to diagnose coronary artery disease. Chi square test was applied to detect association between HsCRP and High HbA1c and Correlation Coefficient(r) was calculated to study linear relationship.

Results: The Chi square Test significant meaning that higher value of HsCRP associated with high level of HbA1c (p=0.04). The Correlation Coefficient(r) is -0.02 so there were no linear relationship between HbA1c and Framingham risk score. In our study average Framingham risk score was 9.72 while average age of patient was 53.7 years. There were linear relationship between patient’s age and Framingham 10 year risk score (r = 0.60).

Conclusions: Coronary artery disease patients had high prevalence of High HsCRP. there was significant association between glycosylated haemoglobin and High HsCRP (P=0.04). We find association between high normal HbA1c and Framingham risk score in non-diabetic patient. But, There is no any linear correlation between high normal HbA1c and Framingham 10 year risk score (r=0.02). We find out that Framingham 10 year risk score has linear relationship with patient’s age and sex. It implies that coronary artery disease calculated by using Framingham 10 year risk score increases with increase in age. But Glycosylated Haemoglobin predicts coronary artery disease risk independence of patient’s age. It predicts low risk in young female patients compare to young male patient in our study. Glycosylated haemoglobin is independent of age and sex of patient. So Glycosylated haemoglobin is good marker for coronary artery disease.

Aim and Objectives

1. To Study Relation between High Normal HbA1c Level and Coronary Heart Disease.
2. To Determine Early Clinical Markers of CHD and its role in Preventive Measures.
3. Calculation of Framingham 10 Year Risk for Developing CHD And Its Correlation with HbA1c

Review of literature

Coronary Heart Diseases is a condition in which there is an inadequate supply of blood and oxygen to a
Atherogenic diet
Physical inactivity
Obesity (BMI ≥30 kg/m²)
Lifestyle risk factors
Age (men ≥45 years; women ≥55 years)
Family history of premature CHD
Diabetes mellitus
Hypertension (BP ≥140/90 mmHg or on antihypertensive medication)
Low HDL cholesterol (<1.0 mmol/L [<40 mg/dl])
Diabetes mellitus
High LDL cholesterol
Pro-thrombotic factors
Pro-inflammatory factors
Impaired fasting glucose
Subclinical atherosclerosis
HDL cholesterol ≥1.6 mmol/L (≥60 mg/dl)

Framingham Risk Score
The Framingham Risk Score is a gender-specific algorithm used to estimate the 10-year cardiovascular risk of an individual. The Framingham Risk Score was first developed based on data obtained from the Framingham Heart Study, to estimate the 10-year risk of developing coronary heart disease. In order to assess the 10-year cardiovascular disease risk, cerebrovascular events, peripheral artery disease and heart failure were subsequently added as disease outcomes for the 2008 Framingham Risk Score, on top of coronary heart disease.

HbA1c and Coronary Heart Disease
Currently, owing to advantages of HbA1c over fasting blood glucose such as low intra-individual variability and being capable of evaluating the long-term blood glucose control, a glycated hemoglobin (HbA1c), a parameter of average blood glucose levels over 12 weeks, has also been suggested using in clinical practice currently. Evidence from epidemiological studies also showed that as compared to fasting blood glucose, HbA1c was more strongly associated with the risks of CHD and mortality from any causes, which further supported the notion that HbA1c was superior to fasting blood glucose in predicting CHD outcomes.

One large-scale study had been done investigating the relationships among HbA1c, C-IMT, and the prevalence of CHD in non-diabetic patients. They found that HbA1c, but not fasting glycemia, was independently associated with CHD and C-IMT.

Recently, HbA1c has become a major parameter of interest that might offer more advantages in terms of prognostic impact, as it is a more stable and accurate parameter of glucose homeostasis. In addition, HbA1c is a good marker of glycosylated proteins, which play a contributory role in atherosclerosis in both diabetic and non-diabetic individuals. However, there is uncertainty as to the nature of this relationship, as some studies report no significant association between HbA1c and CHD in non-diabetic males whereas others do McNeely et al analyzed patients enrolled in the Multi-Ethnic Study of Atherosclerosis (MESA).

However, the association between HbA1c and prevalence of detectable CHD varied by gender; in fact, higher HbA1c was associated with higher prevalence of CHD in women but not in men.

In light of previous findings, our current study was designed to evaluate whether HbA1c level was associated with the severity of coronary heart diseases (CHD) in populations without diagnostic diabetes, and we believed that the clinical implication of our study would add, if any, valuable information to address whether HbA1c level could be used to predict the CHD risk in non-diabetic population.

Material and Methods

A cross-sectional study is done in medicine department, new civil hospital and government medical College, Surat from April 2015 to November 2015. All diagnosed cases of coronary artery disease are selected for this study. Informed valid consent from all participants have been taken in appropriate “participant information
Table 1: Total cholesterol

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<td>&gt;200</td>
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<td>Total</td>
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Table 2: Waist-hip ratio

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<td>36</td>
<td>86</td>
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<td>&gt;1 (male) &amp; &gt;0.85 (female)</td>
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<td>Normal</td>
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<tr>
<td>&lt;1 (male) &amp; &lt;0.85 (female)</td>
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<tr>
<td>Total</td>
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Table 3: Relationship between Framingham risk score and age

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<td>Average</td>
<td>9.72</td>
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<td>53.7 ± 13.5 yrs.</td>
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Table 4: Framingham 10 year risk score and HbA1c

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<td>Low</td>
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<tr>
<td>Total</td>
<td>78</td>
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Result

- A total 100 patients of coronary artery disease, aged 18-80 years were enrolled in the present study. The study group comprised of 63 male and 37 female patients.
- Out of 100 patients in this study, 78 had high normal HbA1c while 22 patients had normal HbA1c. So Prevalence of HbA1c is 78% in coronary artery disease.
- In our study mean age was 53.7 ± 13.5 years. 73% patient with age more than 45 years had Coronary artery disease.
- There is 82 out of 100 patients had high BMI (>23.5 kg/m²). While 18 patient had normal BMI (≤23.5). There is 51 out of 63 male patient had high BMI (81%). There is 31 out of 37 female patients had high BMI (83.8%).
- As shown in Table 2, there were 86 patients had central obesity using waist hip ratio as marker of central obesity. 50 male patients out of 63 male patients had central obesity while 36 out 37 female had central obesity. Waist-hip ratio is excellent marker of central obesity.
- Out of 100 patients 82 had history of hypertension or on medication for hypertension. 51 patients out of 63 had hypertension (81%). Out of 37 female patients 31 had hypertension (84%).
- As shown in Table 1, there is 78 out of 100 patients had high total cholesterol levels. 48 out of 63 male patients had high total cholesterol (76%), while 30 female patients had high total cholesterol (81%).
- In our study, 66 out of 100 patients had high LDL cholesterol. 39 out of 63 male had high HDL cholesterol (62%) while 27 out of 37 female had high HDL cholesterol (73%).
- Out of 100 patients 44 had smoking history. 41 out of 63 male patients had history of smoking (65%). While 3 out of 37 female patients had history of smoking. (P=0.0004)

In our study, 63 out of 73 patients had high HsCRP. 54 out of 63 had high HbA1c (>5.5) while 9 out of 63 patients had Normal HbA1c (<5) in patients with high HsCRP. In previous study Atsushi et al and Daniel et al, most patients had high HsCRP. Chi square test was applied to detect association between HsCRP and High HbA1c. The Test significant meaning that higher value of HsCRP associated with high level of HbA1c (0.04).

In our study we have tried to find out association between Framingham 10 year risk score with high normal HbA1c. As given in Table 4 we find out that 42 out 52 patients had high normal HbA1c in low risk score group. 10 out of 11 patients had high normal HbA1c in intermediate risk score group. While 26 out of 37 patients had high normal HbA1c in high risk score group.

- There were no linear relationship between HbA1c and Framingham risk score. The Correlation Coefficient(r) is -0.02.
- In our study average Framingham risk score was 9.72 while average age of patient was 53.7 years. There were linear relationship between patient’s age and Framingham 10 year risk score. (r=0.60)
- In our study as shown in Table 3 average Framingham risk score was 9.72 while average age of patient was 53.7 years. When we plotted Framingham risk score against patient’s age, there were linear relationship between patient’s age and Framingham 10 year risk score. (r=0.60). So in our study Framingham risk score had linear relationship with patient’s age.
- It is known that Framingham risk score is dependent on many factors like age of the patient, sex of patient, smoking habits, lipid profile and presence of hypertension. When only one factor age was plotted using scatter diagram a reasonable correlation was observed between age of patient and Framingham risk score.
score. It also means that if other variables are kept constant, with advancement of age, Framingham risk score also increases.

Conclusion
In our study, we find association between high normal HbA1c and Framingham risk score in non-diabetic patient. But, There is no any linear correlation between high normal HbA1c and Framingham 10 risk score (r=0.02).

We also find out that Framingham 10 year risk score has linear relationship with patient’s age. It implies that coronary artery disease calculated by using Framingham 10 year risk score increases with increase in age. But Glycosylated Hemoglobin predicts coronary artery disease risk independence of patient’s age.

References
2. Park K. Epidemiology of Coronary Artery Disease, Park’s textbook of Preventive and Social Medicine, Page No.366-367
4. Coronary artery atherosclerosis image, Mayo Foundation for Medical Education Research
myocardial energy demand, (2) protects the myocardium from cardiotoxic effect of FFA by scavenging them, (3) protects heart from hypothermia, (4) provides mechanical protection to the coronary circulation and (5) secretes adiponectin and other adipokines, which have been found to be anti-atherogenic and anti-inflammatory.2 EAT has also been found to play a pivotal role in the pathogenesis of atherosclerosis by secreting adipokines, which triggers systemic inflammation and oxidative stress, are thought to influence the underlying atherosclerotic plaque development via paracrine and vasocrine actions.2

Role of epicardial fat has been found in atrial fibrillation, hypertension3, increased left ventricular mass (LVM)4, left ventricular mass index (LVMI)4 and decreased ejection fraction.5 It has also been found to be associated with metabolic syndrome and insulin resistance.6 Various imaging methods like 2D echocardiography, cardiac magnetic resonance imaging (cMRI) and CT scan can be used to measure EAT.2

Albuminuria has been found to be related to increased all-cause mortality.11 Hypertensive individuals with microalbuminuria have greater incidence of cardiovascular events than patients with normal urinary albumin excretion.12 A recent concept is that microalbuminuria is a marker of extensive endothelial dysfunction or generalised vasculopathy, which may accelerate atherogenesis.14

**Aims and Objectives**

1. To study Epicardial Adipose Tissue (EAT) Thickness in patients with essential hypertension by echocardiography.
2. To compare EAT between essential hypertensive patients with normal urinary albumin excretion (UACR<30) and albuminuria (UACR>30).
3. To observe the relationship between EAT and age, serum creatinine, LVM, LVMI in patients with essential hypertension.

**Materials and Methods**

The study protocol was approved by the Ethics Committee of S.M.S. Medical College and Attached hospital, Jaipur, India. This was a hospital based observational study carried out in the Upgraded Department of Medicine, Jaipur, India from April 2017 to March 2018. Consecutive patients of essential hypertension with or without medication were selected excluding patients with chronic kidney disease, Diabetes Mellitus, previous stroke, valvular heart disease and secondary hypertension. As such 100 eligible consecutive patients were included after explaining about the purpose and nature of the study and written informed consent were obtained from all of the subjects. After a complete medical history and laboratory examination including blood and spot urine samples, all patients underwent transthoracic 2D and doppler echocardiography. Patients’ height, weight and blood pressure were recorded on the day of echocardiogram.

**Blood Pressure Measurement**

The blood pressure (BP) of each patient was twice measured from the left arm after approximately 5 minutes of seated rest. Participants were advised to avoid alcohol, cigarettes, coffee / tea and exercise for at least 30 minutes before BP measurement. Standardized mercury sphygmomanometers were used, and one of two cuff sizes was chosen on the basis of the circumference of the participant’s arm. The Korotkoff phase I (appearance) and phase V (disappearance) were recorded for the SBP and DBP, respectively.

**Laboratory Investigations**

All the participants were advised to come after eight to ten hours of overnight fasting. Taking universal precaution, blood samples were withdrawn and placed into appropriate vials and sent to laboratory for investigations like complete blood count, differential count, blood sugar, liver function tests, renal function tests, total lipid profile, total protein, albumin, etc.

**Blood sugar**

Plasma glucose was measured by using glucose oxidase-peroxidase method on fully automatic analyser by using spectrophotometric method at wave length between 490 to 520 nm. The amount of colour complex formed is directly proportional of the glucose concentration in the serum. Plasma glucose was expressed in terms of mg/dl.

**Urine albumin creatinine ratio (UACR)**

The urine samples for UACR were analysed within 2 hours by using Clinitek Status Analyzer by Bayer HealthCare. The Clinitek Microalbumin Reagent test strips are firm plastic strips that contain two reagent areas that test for albumin and creatinine in urine. The test for albumin was based on dye binding using a high affinity sulfonphthalein dye. Creatinine test was based on the peroxidase like activity of a copper creatinine complex. This device provides a semiquantitative estimate of the albumin content in four categories (10, 30, 80, 150 mg/L) and of creatinine in five categories (10, 50, 100, 200, 300 mg/dl). The UACR is also given in three categories:

- <30mg/g: - Normal
- 30-300 mg/g: - Abnormal
- >300 mg/g: - High abnormal

**Epicardial fat measurement**

All the echocardiographic examinations were performed by using Philips EipQ7 cardiac ultrasound scanner and 2.5-3.5 MHz transducers by the same cardiologist. Patients were examined in the left lateral position by precordial M-mode, two-dimensional and Doppler echocardiography. Left ventricular internal dimensions, interventricular septum thickness and posterior wall thickness were measured at end-diastole. EAT thickness was measured on the free wall of the right ventricle from the parasternal long-axis views. Epicardial fat was identified as an echo-free space in the pericardial layers on the two-dimensional echocardiography and its thickness was measured perpendicularly on the free wall of the right ventricle at end-diastole for three cardiac cycles.7 The left ventricular mass (LVM) was calculated according to the Devereux Formula.8

**Statistical Analysis**

The collected data were transformed into variables, coded and entered in Microsoft Excel sheet. Data were analysed and statistically evaluated using Statistical Package for Social Sciences (SPSS)-PC-17 software (version 17, SPSS, Inc, Chicago, IL, USA). Data are presented as mean and standard deviation (SD) for normally distributed continuous variables, median (minimum-maximum) for skew distributed continuous variables, and
Results

The clinical characteristics of the study subjects are depicted in table 1. The study subjects were divided into two groups on the basis of UACR: Group A with UACR < 30 mg/g and Group B with UACR > 30 mg/g. There were 41 patients in group A and 59 patients in group B. There were significant differences in the age, BMI, blood pressure, duration of hypertension, lipid profile and cardiac indices between the two groups.

In our study, the epicardial adipose tissue (EAT) thickness ranged from a minimum of 2 mm to a maximum of 10.4 mm in patients with essential hypertension. The mean epicardial adipose tissue thickness was 5.42 ± 2.22 mm with a median of 5.3 mm. The mean EAT was found to be significantly higher in patients with significant albumin excretion (UACR > 30 mg/g) as compared to group A (6.65 ± 1.944 mm vs. 3.64 ± 1.13 mm, respectively, p < 0.001) (Figure 1A). Upon correlation analysis, EAT was found to be positively correlated with age (r = 0.749, p < 0.001) (Figure 1B), serum creatinine (r = 0.244, p = 0.014), LVM (r = 0.691, p = 0.001) (Figure 1C) and LVMI (r = 0.677, p = 0.001) (Figure 1D) and negatively correlated with EF (r = -0.599, p = 0.001) (Table 2).

Discussion

We studied the association between epicardial adipose tissue thickness and albuminuria in patients with essential hypertension. We observed a statistically significant association between albuminuria and EAT thickness, that is higher the UACR, higher the EAT thickness. Similarly, in the Framingham Heart Study (2011) both visceral adipose tissue and subcutaneous adipose tissue were found to be associated with microalbuminuria. Also, in our study, EAT was positively correlated with age, serum creatinine, LVM, LVMI and negatively correlated with EF. In concordance to our study, Silaghi A et al (2008) also showed that EAT significantly and independently correlated with age. Nakanishi K et al (2016) found that epicardial fat volume was significantly associated with eGFR. Although, we have excluded patients with renal failure, we found that subjects with increased epicardial fat had creatinine level on the higher side as compared to patients with less epicardial fat. This may be due to the presence of some degree of renal dysfunction indicated by the presence of albuminuria. Jacobellis G et al (2004) showed that LVM and LVMI/height² correlated with the amount of epicardial fat and the correlation appeared to be independent of BMI and age. Similarly, Mookadam et al (2010) also observed that epicardial fat more than 5 mm was associated with increased left ventricular mass. In a study conducted by Mookadam et al (2010)², it was found that epicardial fat more than 5 mm was associated with reduced ejection fraction. Our

Table 1: Baseline characteristics of subjects

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>UACR &lt;30 mg/g (n = 41)</th>
<th>UACR &gt;30 mg/g (n = 59)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMI (kg/m²)</td>
<td>21.72 ± 2.24</td>
<td>25.14 ± 3.20</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>SBP (mmHg)</td>
<td>147.5 ± 8.56</td>
<td>165.8 ± 16.75</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>DBP (mmHg)</td>
<td>82.1 ± 7.27</td>
<td>91.73 ± 10.94</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mid BP (mmHg)</td>
<td>114.8 ± 6.54</td>
<td>128.8 ± 13.01</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Duration of HTN (yrs)</td>
<td>8.14 ± 3.85</td>
<td>10.11 ± 4.88</td>
<td>0.03</td>
</tr>
<tr>
<td>Hemoglobin (g/dl)</td>
<td>11.78 ± 2.41</td>
<td>11.06 ± 2.43</td>
<td>0.149</td>
</tr>
<tr>
<td>RBS (mg/dl)</td>
<td>106.7 ± 25.11</td>
<td>111.8 ± 39.47</td>
<td>0.463</td>
</tr>
<tr>
<td>Blood Urea (mg/dl)</td>
<td>32.06 ± 15.99</td>
<td>39.32 ± 19.77</td>
<td>0.054</td>
</tr>
<tr>
<td>Sr. Creatinine (mg/dl)</td>
<td>0.91 ± 0.28</td>
<td>1.025 ± 0.28</td>
<td>0.042</td>
</tr>
<tr>
<td>Sr.Total Protein (g/dl)</td>
<td>7.29 ± 0.75</td>
<td>6.57 ± 1.23</td>
<td>0.001</td>
</tr>
<tr>
<td>Sr. Albumin (g/dl)</td>
<td>3.72 ± 0.49</td>
<td>3.25 ± 0.68</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>HDL (mg/dl)</td>
<td>31.71 ± 5.70</td>
<td>23.47 ± 6.78</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LDL (mg/dl)</td>
<td>107.9 ± 20.82</td>
<td>161.9 ± 38.9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>T. Cholesterol (mg/dl)</td>
<td>139.4 ± 35.98</td>
<td>187.5 ± 40.53</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Triglyceride (mg/dl)</td>
<td>136.5 ± 59.54</td>
<td>163.2 ± 41.84</td>
<td>0.010</td>
</tr>
<tr>
<td>LVM (g)</td>
<td>107.9 ± 20.82</td>
<td>161.9 ± 38.9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LVM (g/m²)</td>
<td>27.69 ± 6.78</td>
<td>41.37 ± 10.38</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>EF (%)</td>
<td>54.8 ± 6.89</td>
<td>44.44 ± 10.76</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>EAT (mm)</td>
<td>3.64 ± 1.13</td>
<td>6.65 ± 1.944</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

UACR, Urine albumin creatinine ratio; BMI, Body Mass Index; SBP, systolic blood pressure; DBP, diastolic blood pressure; Mid BP, Mid blood pressure; HTN, hypertension; RBS, random blood sugar; HDL, high density lipoprotein; LDL, low density lipoprotein; LVMI, left ventricular mass; LVM, left ventricular mass index; EAT, epicardial adipose tissue thickness.

Table 2: Spearman’s correlation analysis among EATT and other variables

<table>
<thead>
<tr>
<th>Epi Cardial Adipose Tissue Thickness (EATT)</th>
<th>p</th>
<th>R</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>&lt;0.001</td>
<td>0.749</td>
</tr>
<tr>
<td>S. Creatinine (mg/dl)</td>
<td>0.014</td>
<td>0.244</td>
</tr>
<tr>
<td>LVM (g)</td>
<td>0.001</td>
<td>0.691</td>
</tr>
<tr>
<td>LVM (g/m²)</td>
<td>0.001</td>
<td>0.677</td>
</tr>
<tr>
<td>EF (%)</td>
<td>0.001</td>
<td>-0.599</td>
</tr>
</tbody>
</table>

Fig. 1: (A) EAT is significantly higher in patients with significant albumin excretion (UACR > 30 mg/g) as compared to patients with normal albumin excretion (UACR <30mg/g); (B) Positive correlation between EATT (epicardial adipose tissue thickness) and age; (C) Positive correlation between EATT and LVM (left ventricular mass); (D) Positive correlation between EATT and LVMI (left ventricular mass index)
findings are also in concordance with these previous workers.

In our study, systolic blood pressure, diastolic blood pressure and mid blood pressure was significantly higher in patients with higher albuminuria. Murai S et al (2014) found that urinary albumin was closely correlated with blood pressure.\(^{14}\) This was in concordance with our study. Higher albumin excretion was also associated with age, BMI, serum creatinine, lipid profile, LVM. LVMI and left ventricular systolic function. Esther de Beus et al (2015) found that in hypertensive patients with high vascular risk, albuminuria was related to increased LVM.\(^{15}\) Plavnik F.L. et al (2002) observed significant correlations between urinary albumin excretion rate and LVM (r=0.57, p<0.01).\(^{16}\) Jennifer E Liu et al (2003) observed that left ventricular systolic function was lower in patients with albuminuria with step-wise decrease in ejection fraction and stress-corrected mid-wall shortening (MWS) as albuminuria increases in severity.\(^{17}\)

EAT and its role in coronary artery disease (CAD) has been extensively evaluated.\(^{18}\) Similarly, a number of studies suggest the role of albuminuria as a risk factor in cardiovascular disease.\(^{19,20}\) Hence, both epicardial adipose tissue and microalbuminuria are associated with an increased cardiovascular risk. Both of them are related to essential hypertension in one way or the other. Also, in our study we found a significant association between albuminuria and epicardial adipose tissue thickness. So, measurement of one of them will be sufficient to categorise hypertensive patients at high risk.

**Conclusion**

*Albuminuria has long been recognised as a marker of generalised endothelial dysfunction indirectly serving as an indicator of cardiovascular risk. Epicardial adipose tissue, a relatively new entity, has been found to be associated with albuminuria in this study. It is implicated to serve as a cardiometabolic risk factor. Association of epicardial adipose tissue with albuminuria provides a strong evidence that it is also a marker of high cardiovascular risk. This study helps us to stratify hypertensive patients as high risk on the basis of epicardial fat thickness. Echocardiography which is a very non-invasive, easy to do, reproducible, and cost-effective method can be used to estimate it. However, for a better generalisation of this concept, a larger study is required to be done.*

**References**

The Effect of Aerosolized Chlorpheniramine Maleate on Exercise Induced Bronchospasm and Gas Exchange in Asthmatics

Jagdeep Chugh¹, Yad Ram Yadav²*, Harish Srikanth Kulkarni³, Sanjiv Maheshwari⁴

Abstract

Introduction: Exercise induced asthma (EIA) is an acute, reversible, usually self-limiting airways obstruction which sets in after exercise in patients with asthma. One popular mechanism of EIA is the increase in histamine and its metabolites in circulation after exercise, which leads to bronchoconstriction via histamine receptors in bronchi. Chlorpheniramine Maleate is potent, less sedative anti-histaminic drug, which acts by inhibiting histamine release from mast cells. It is also said to have anticholinergic properties. The aerosol route of administration of a drug has the advantages of a faster onset of action, fewer side effects, and greater protection against EIB with respect to small airways function. This study was conducted to evaluate the effect of Chlorpheniramine Maleate aerosol inhalation on flow volumes and gas exchange.

Materials and Methods: 25 established patients of stabilized bronchial asthma (18 to 44 years) with history of EIA attending Allergy OPD, Medical OPD or Chest clinic were included in the present study. Patients were studied for 3 days in a week at the same time of day. Baseline spirometry was done to know test parameters, i.e. FEV₁, PEF and FEF₅₀. Gas exchange study during rest including minute ventilation (VE), oxygen consumption (VO₂), Carbon dioxide produced per minute (VCO₂), Respiratory quotient (R) was carried out. Patient was asked to perform exercise on bicycle ergometer. During exercise VE, VO₂, VCO₂ and R were recorded every 30 seconds. FEV₁, PEF and FEF₅₀ were recorded immediately after and 5 min after completion of exercise. On day 2, same procedure was repeated with saline nebulisation before the exercise. On day 3, aerosolized Chlorpheniramine Maleate was used instead of saline for nebulisation. Values obtained were tabulated and analysed.

Observations and Results: After exercise FEV₁, PEF, FEF₅₀ decreased on all three days, but the fall in these parameters was less on Day III (prior nebulisation with Chlorpheniramine maleate) compared to previous days. There was significant increase in FEV₁, PEF and FEF₅₀ (P<0.01, 0.05 and 0.05 respectively) which was seen 30 mins after inhalation of Chlorpheniramine maleate aerosol compared to placebo. Resting and exercise values of Minute Ventilation (VE), oxygen uptake (VO₂) carbon dioxide expired, on all the three days were comparable and statistically not significant by the end of exercise. On day 2 and 3, ‘R’ as compared to that of day1 was slightly significant during rest and initial minutes of exercise but became insignificant after that till the end of exercise.

Conclusion: This study shows that Chlorpheniramine causes bronchodilation during resting period by acting on the circulating or tissue histamine in asthmatics which contributes to an increase in resting bronchomotor tone. As there is incomplete inhibition of EIA by Chlorpheniramine, there may be some other associated mediator release for pathogenesis of EIA.

Introduction

Exercise induced asthma (EIA) is an acute, reversible, usually self-limiting airways obstruction which develops after strenuous exercise in patients with asthma. EIA is present in 80 per cent of the asthma patients. A joint Task force of European Academy of Allergy and Clinical Immunology and European Respiratory Society defined EIA as symptoms of asthma occurring after heavy exercise, whereas EIB (Exercise Induced Bronchoconstriction) denoted the reduction in lung function occurring after exercise, as seen in a standardized exercise test.

EIA involves decreased specific airway conductance, airway resistance and decrease in airway flow as measured by forced expiratory flow at one second (FEV₁, Peak expiratory flow rate (PEFR): Forced expiratory percent of Vital capacity (FEF25-75%) flow at 25 to 75 %).

Classical mechanisms behind EIA and EIB include the so-called osmolar (or airway drying) and vascular (or ‘thermal’) hypothesis. Increased water loss increases the osmolarity of the extracellular fluid lining the bronchial mucosa, causing water to move extracellularly possibly through the water channels, aquaporins, causing bronchial epithelial cells to ‘shrink’, with an increased intracellular ion concentration leading to release of inflammatory mediators, including newly formed eicosanoids from mast cells, eosinophils, neutrophils, and other cells. Also, increased circulating levels of histamine and its metabolites are found in blood after exercise in cases of EIA.

Effectiveness of medications can be deferred over time because of the variability of asthma, environmental conditions, intensity of exercise, and tolerance to b₂-agonists, as well as patient compliance. Inhaled b₂-agonist monotherapy should be used only for

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short-term prophylaxis against EIA. Providers should only use a single dose of short-acting b2-agonist (SABA) and/or LABA on an intermittent basis because this might protect against or attenuate EIA. SABAs are effective for 2 to 4 hours and LABAS for up to 12 hours. Caution is recommended in daily use of b2-agonists alone or in combination with inhaled corticosteroids (ICSs) because this can lead to tolerance. Tolerance can manifest as a reduction in duration and magnitude of protection against EIA and a prolongation of recovery in response to SABAs after exercise. Leukotriene modifiers can be used daily or intermittently to prevent EIA and do not lead to tolerance. However, they can provide incomplete protection and cannot reverse existing airway obstruction. Mast cell stabilizers, such as cromolyn and nedocromil, can be given shortly before exercise to attenuate EIA but have a short duration of action either alone or as added therapy with other drugs for EIA. ICSs taken alone or in combination with other therapies can decrease the frequency and severity of EIB. However, ICSs do not eliminate EIA in all subjects, and ICS therapy might not prevent occurrence of tolerance from daily LABA therapy. Anticholinergic agents provide inconsistent results in attenuating EIA.

In the bronchi, H2 receptors are predominant and cause bronchoconstriction and they are blocked by classical antihistamines or H2 receptor antagonists like Chlorpheniramine Maleate (CPM). H2 receptors are few in bronchi and cause bronchodilation. They are blocked by H2 receptor antagonists like Cimetidine etc.

Classical antihistaminics like CPM act by blocking histamine release from mast cells and thus, may prevent bronchospasm. These also have anticholinergic properties and bronchodilation produced could be mediated by blockage of vagal reflex bronchoconstrictor mechanism. Chlorpheniramine Maleate is potent, less sedative and when given in aerosolized form, provides higher concentration in lungs with little systemic absorption and thus causing maximum effect on mast cells which line the bronchi and thus blunting the bronchoconstriction due to exercise.

We planned this study to evaluate effect of Chlorpheniramine Maleate aerosol inhalation on flow volumes and gas exchange.

Materials and Methods

The sample size was calculated using a Cochran formula.

Thus 25 established patients of stabilized bronchial asthma (18 to 44 years) with history of EIA attending Allergy OPD, Medical OPD or Chest clinic were included in the present study. The protocol was explained to the subjects and informed written consent was taken. All patients underwent detailed clinical history, thorough physical examination and routine haematological, biochemical and radiological investigations. All patients were advised to refrain from exercise for at least twelve hours before test. They were instructed to stop all
Pulse rate and blood pressure in sitting position was recorded with a standard cuff. Respiratory system examination for detection of rhonchi was carried out in all patients.

Baseline spirometry was done to know test parameters, i.e. FEV₁, PEFR and FEF₅₀, with the help of Body star FG-90. The test was performed three times and highest values were recorded. Patient was then connected to Oxycon-4 and lung gas exchange study during rest including minute ventilation (VE), oxygen consumption (VO₂), Carbon dioxide produced per minute (VCO₂), Respiratory quotient (R) was carried out. Patient was asked to perform exercise on Mijnhardt KEM, Bicycle ergometer. Duration of exercise was 5 to 6 minutes after obtaining high work plateau i.e. 2 watts/Kg of body weight or a maximum of 100 watts, within 3 to 4 minutes in 3 to 4 steps and attaining 75-85% of the predicted heart rate or VO₂ maximum. Exercise was terminated before attaining target heart rate, in event of a drop in systolic blood pressure, pain in chest, exhaustion and fatigue or symptomatic bronchospasm. During exercise VE, VO₂, VCO₂, and R were recorded every 30 seconds. Heart rate was recorded by pulse meter and confirmed by auscultation. After exercise blood pressure was recorded. FEV₁, PEFR and FEF₅₀ were recorded immediately after and 5 min after completion of exercise.

**Day-I**

Height and weight of the subjects, room temperature (°C) and barometric pressure (millibar) were recorded. Body surface area (BSA) was calculated from Nomogram based upon Dubois formula using height and weight. Normal Oxygen consumption under basal condition was calculated (VO₂) from BSA as suggested by ECSR.

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R) from BSA as suggested by ECSR

basal condition was calculated (VO₂)

Nomogram based upon Dubois

Body surface area (BSA) was calculated

within 3 to 4 minutes in 3 to 4 steps and

PEFR 28.10± 29.40 26.61 ± 28.62 1.521 ± 10.36 >0.05

PEFR 6. 16 ± 12.38 11.45 ± 19. 41 4.95 ± 10.59 <0.05

PEFR 3.77 ± 7.01 7.51 ± 8.67 3.72 ± 5.60 <0.01

PEFR 19.87 ± 21.74 10. 12 ± 19.02 1.71 ± 6.89 >0.05

PEFR 1.12 ± 19.02 10.12 ± 19.02 1.71 ± 6.89 >0.05

PEFR 28.10 ± 29.40 26.61 ± 28.62 1.521 ± 10.36 >0.05

PEFR 0.82 ± 0.14 0.82 ± 0.18 0.85 ± 0.15

PEFR 1.11 ± 0.29 1.01 ± 0.28 1.09 ± 0.31

PEFR 1.14 ± 0.30 1.09 ± 0.34 1.12 ± 0.36

*p<0.05

**Table 1: Percentage increase in spirometric indices (30 minutes after inhalation) in comparison to baseline**

<table>
<thead>
<tr>
<th>Spirometric indices</th>
<th>Mean ± SD of % increase after inhalation</th>
<th>Mean diff. and SD</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>CPM</td>
<td></td>
<td></td>
</tr>
<tr>
<td>FEV₁</td>
<td>3.77 ± 0.71</td>
<td>7.51 ± 6.87</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>PEFR</td>
<td>6.16 ± 12.38</td>
<td>11.45 ± 19.41</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>FEF₅₀</td>
<td>2.32 ± 7.19</td>
<td>11.12 ± 18.80</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>

**Table 2: Percentage fall in spirometric indices (5 minutes after exercise) in comparison to pre exercise levels**

<table>
<thead>
<tr>
<th>Spirometric indices</th>
<th>Mean ± SD of % fall after exercise</th>
<th>Mean diff. and SD</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo + exercise</td>
<td>CPM + exercise</td>
<td></td>
<td></td>
</tr>
<tr>
<td>FEV₁</td>
<td>19.87 ± 21.74</td>
<td>10.12 ± 19.02</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>PEFR</td>
<td>28.10 ± 29.40</td>
<td>26.61 ± 28.62</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>FEF₅₀</td>
<td>30.99 ± 33.71</td>
<td>29.92 ± 32.31</td>
<td>&gt;0.05</td>
</tr>
</tbody>
</table>

**Table 3: Mean and SD values of minute ventilation “VE” (lit/min)**

<table>
<thead>
<tr>
<th>Time of recording</th>
<th>Day I Exercise</th>
<th>Day II</th>
<th>Day III</th>
<th>Mean ± SD</th>
<th>Mean ± SD</th>
<th>Mean ± SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Resting</td>
<td>10.53 ± 3.44</td>
<td>11.11 ± 3.54</td>
<td>12.10 ± 2.45</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.5 min</td>
<td>12.68 ± 2.95</td>
<td>14.21 ± 2.35</td>
<td>13.89 ± 3.04</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1.5 min</td>
<td>15.32 ± 3.38</td>
<td>16.66 ± 3.93</td>
<td>15.65 ± 3.09</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T-0.5</td>
<td>47.96 ± 8.62</td>
<td>50.61 ± 9.20</td>
<td>51.37 ± 8.68</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T</td>
<td>50.66 ± 9.01</td>
<td>53.06 ± 8.09</td>
<td>52.68 ± 8.74</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Table 4: Mean and SD of oxygen uptake per minute “VO₂” (lit/min)**

<table>
<thead>
<tr>
<th>Time of recording</th>
<th>Day I Exercise</th>
<th>Day II</th>
<th>Day III</th>
<th>Mean ± SD</th>
<th>Mean ± SD</th>
<th>Mean ± SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Resting</td>
<td>0.18 ± 0.8</td>
<td>0.19 ± 0.10</td>
<td>0.20 ± 0.16</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.5 min</td>
<td>0.34 ± 0.19</td>
<td>0.36 ± 0.19</td>
<td>0.39 ± 0.39</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 min</td>
<td>0.45 ± 0.21</td>
<td>0.45±0.22</td>
<td>0.37±0.15</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1.5 min</td>
<td>0.54 ± 0.26</td>
<td>0.51 ± 0.26</td>
<td>0.45 ± 0.22</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T-0.5</td>
<td>1.11 ± 0.29</td>
<td>1.01 ± 0.28</td>
<td>1.09 ± 0.31</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T</td>
<td>1.14 ± 0.30</td>
<td>1.09 ± 0.34</td>
<td>1.12 ± 0.36</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Table 5: Mean and SD values of carbon dioxide expired per minute (VCO₂) (lit/min)**

<table>
<thead>
<tr>
<th>Time of recording</th>
<th>Day I Exercise</th>
<th>Day II</th>
<th>Day III</th>
<th>Mean ± SD</th>
<th>Mean ± SD</th>
<th>Mean ± SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Resting</td>
<td>0.18 ± 0.16</td>
<td>0.16 ± 0.08</td>
<td>0.17 ± 0.07</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.5 min</td>
<td>0.29 ± 0.16</td>
<td>0.31 ± 0.17</td>
<td>0.28 ± 0.14</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 min</td>
<td>0.38 ± 0.26</td>
<td>0.38 ± 0.22</td>
<td>0.35 ± 0.22</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1.5min</td>
<td>0.45 ± 0.27</td>
<td>0.43 ± 0.24</td>
<td>0.40 ± 0.27</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T-0.5</td>
<td>1.10 ± 0.44</td>
<td>1.09 ± 0.24</td>
<td>1.09 ± 0.27</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T</td>
<td>1.15 ± 0.43</td>
<td>1.22 ± 0.29</td>
<td>1.11 ± 0.28</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Table 6: Mean and SD values of respiratory quotient (R)**

<table>
<thead>
<tr>
<th>Time of recording</th>
<th>Day I Exercise</th>
<th>Day II</th>
<th>Day III</th>
<th>Mean ± SD</th>
<th>Mean ± SD</th>
<th>Mean ± SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Resting</td>
<td>0.81 ± 0.12</td>
<td>0.89 ± 0.14(p&lt;0.05)</td>
<td>0.86 ± 0.11(p&lt;0.05)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.5 min</td>
<td>0.79 ± 0.08</td>
<td>0.87 ± 0.13(p&lt;0.05)</td>
<td>0.86 ± 0.09(p&lt;0.05)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 min</td>
<td>0.78 ± 0.12</td>
<td>0.83 ± 0.10(p&lt;0.05)</td>
<td>0.83 ± 0.10(p&lt;0.05)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1.5 min</td>
<td>0.82 ± 0.14</td>
<td>0.82 ± 0.18</td>
<td>0.85 ± 0.15</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T-0.5</td>
<td>1.00 ± 0.14</td>
<td>1.02 ± 0.15</td>
<td>1.03 ± 0.11</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T</td>
<td>1.02 ± 0.13</td>
<td>1.03 ± 0.13</td>
<td>1.05 ± 0.13</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Experimental Protocol**

All patients were studied for three days in a week at the same time of day trying to keep the ambient conditions of temperature, humidity etc. the same.

**Day-I**

Height and weight of the subjects, room temperature (°C) and barometric pressure (millibar) were recorded. Body surface area (BSA) was calculated from Nomogram based upon Dubois formula using height and weight. Normal Oxygen consumption under basal condition was calculated (VO₂) from BSA as suggested by ECSR.
Results were tabulated and analysed statistically with paired t tests

Observations

As shown in Graph 1, most of the patients (n=11) were in age group of 30-34 years. Only one patient was in the age group 40-45 years. Totally, 72% were males (n=18) and 28% (n=7) were females among the study subjects.

As depicted in graph 2, FEV₁ decreased immediately after inhalation on day II and day III. It increased gradually after that on day II and day III and reached its maximum level 30 minutes after inhalation. Increase in FEV₁ is more on CPM day. After exercise FEV₁ fell on all the days and fall was more 5 minutes after exercise. Fall in FEV₁ is less on day III compared to previous days.

Graph 3 depicts the effect of CPM on Peak Expiratory Flow Rate (PEFR). PEFR increased gradually after CPM inhalation and was maximum 30 minutes after inhalation. The PEFR decreased just after exercise and there was maximum fall of PEFR 5 minutes after completion of exercise on all the test days. Fall in PEFR was less with prior treatment with CPM (day III) compared to previous days.

FEF₅₀% decreased just after inhalation of CPM and it increased gradually on day III and reached its maximum level 30 minutes after inhalation compared to placebo day. FEF₅₀% fell just after exercise on all the three days and maximum fall was 5 minutes after exercise. Fall in FEF₅₀% was less comparatively with prior treatment with CPM (day III) compared to previous days, depicted in graph 4.

Table 2 shows change in Spirometric indices after inhalation of CPM and Placebo. There was significant increase in FEV₁, PEFR and FEF₅₀% (P<0.01, 0.05, 0.05 respectively) which was seen 30 minutes after inhalation of CPM aerosol compared to placebo.

Significant fall in FEV₁, PEFR and FEF₅₀% was seen 5 minutes after exercise in comparison to pre-exercise levels on placebo and drug day. On CPM day, fall was less compared to placebo day but it was NOT significant, as shown in Table 2.

Resting and exercise values of Minute Ventilation (VE) on all the three days was comparable and was statistically NOT significant by the end of exercise as shown in Table 3.

Table 4 depicts changes in Oxygen uptake with exercise and placebo, exercise and CPM. Resting and exercise values of oxygen uptake VO₂ were comparable on all the three days and the change was statistically NOT significant during rest and end of exercise.

As observed in Table 5, resting and exercise values of carbon dioxide expired were comparable on all the three days and statistically NOT significant during rest and end of exercise.

Table 6 shows the variation of respiratory quotient (R) during the test days. Resting and initial values (1 min) during exercise of R were significant. But it becomes comparable and statistically NOT significant at the end of exercise.

Discussion

Chlorpheniramine Maleate (CPM) and other anti-histamines are very effective in many allergic disorders and are ingredients of many anti-allergic preparations. They are commonly used along with bronchodilators in patients with bronchial asthma. But when given alone, how far they are effective in bronchial asthma is still not clear. Present study was conducted on twenty-five established cases of bronchial asthma on three days in a week. Subjects were in age range of 18 to 44 years. The subjects were subjected to exercise on all the three days. On Day 1 patients were screened end exercise was performed. On Day 2 placebo was given by inhalation route to get better comparison, while on Day 3 aerosolized CPM was given.

Effect on Spirometric Functions

FEV₁, PEFR and FEF₅₀% demonstrated a drop immediately and 5 min after exercise on screening day. Most of the workers have observed Bronchoconstrictor effect between 3-15 minutes. These were compatible with typical EIA.

On Day 2 and 3 pulmonary functions were observed after placebo and CPM aerosol inhalation respectively. There was a small fall in FEV₁, PEFR and FEF₅₀% immediately after inhalation on study day 2 and there was no significant difference in the magnitude of this decrease. This may be due to mild and transient degree of bronchoconstriction caused by CPM and placebo after inhalation.

Despite the initial reduction in Spirometric indices, the effect of CPM was bronchodilatory by 30 minutes after inhalation as compared to placebo. There was significant increase in FEV₁, PEFR and FEF₅₀% compared to baseline.

Lung functions 5 minutes after exercise challenge showed a significant fall but the fall was less on day 3 than on day 2. There as significant difference between the percent fall in FEV₁, PEFR and FEF₅₀%.

Spirometric indices 5 minutes after exercise were compared to pre-exercise levels, i.e. 30 minutes after inhalation of placebo or CPM, a significant fall in FEV₁, PEFR and FEF₅₀% was noted. But the difference between the percent fall in FEV₁, PEFR and FEF₅₀% between the last 2 days was not significant. This suggests that the effect of exercise was approximately similar on both CPM and placebo days.

Our observations tally with Schacter et al. who observed that there was decrease in lung functions immediately after CPM inhalation. This may be due to local irritation caused by CPM aerosol inhalation. Our study is in conformity with Popa and Schacter who found that bronchodilation occurs sometime after inhalation of CPM inhalation. This may be due to effect on resting ‘bronchomotor tone’ in asthmatics due to local or circulating histamine (Popa et al). CPM has anti-cholinergic properties also and the bronchodilation may be due to inhibition of cholinergic activity by a secondary mechanism.

In our study when post exercise lung functions were compared with lung functions immediately before exercise on both placebo and CPM day, the difference was not significant suggesting the effect of exercise nearly same on CPM and placebo days.

Protection of EIA by other antihistamines have been observed by many workers. Comparing pre-exercise values, no significant protection was observed against. It is likely that other mediator substances released from mast cells may be involved in addition to histamine. The other possibility may be that CPM given by aerosol inhalation was inadequate to fully prevent EIA. The side effects observed were cough
Slight increase in VE on CPM day was insignificant on all the three days. This may be due to local irritation caused by CPM aerosol inhalation (Byrne et al. 1983). Our study is in conformity with Popa (1977) Groggins (1978), Eiser (1981) and Schacter (1985) that bronchodilation occurs sometime after inhalation of CPM, this may be due to effect on resting broncho motor tone in asthmatics due to local or circulating histamine. Schacter et al. (1985) also observed that CPM causes blunting of EIA due to improvement in baseline lung functions rather than a direct effect on mechanism EIA.

**Effect on Gas Exchange**

VE, VCO₂, VO₂, and ‘R’ were recorded during exercise on all the three days. VO₂ and VCO₂ values on three days remained comparable and not significant during rest and exercise. On day 2, VE when compared to day 1 was not significant during rest but was slightly significant by the end of exercise. On day 3 VE was slightly significant during rest and became not significant with start of exercise. On day 2 and 3, ‘R’ as compared to that of day1 was slightly significant during rest and initial minutes of exercise but became insignificant after that till the end of exercise.

From our observations it is apparent that change in VO₂ and CO₂ were insignificant on all the three days. Slight increase in VE on CPM day was observed. This may be due to effect on resting bronchomotor tone as shown by resting lung volumes after CPM which became insignificant by the end of exercise. Change in ‘R’ during exercise was dependent on relative alteration in VO₂ and VCO₂ kinetics. It was observed that ‘R’ was significant (P< 0.05) on placebo and CPM day compared to day 1 during rest. This can be explained possibly by some psychogenic effect of drug intake, lead to hyperventilation and in turn increased CO₂ wash out and in turn increase in ‘R’. This effect disappeared during exercise.

CPM being very economical and easily available drug can definitely help in more better way for patients of EIA, however number of subjects are relatively less so further studies using higher number of subject may be conducted.

**Conclusion**

This study shows that Chlorpheniramine causes bronchodilation during resting period by acting on the circulating or tissue histamine in asthmatics which contributes to an increase in resting bronchomotor tone. The effect on resting bronchomotor tone may be due to anticholinergic properties. Along with it there may be some other mechanisms which contribute to increased bronchomotor tone in asthmatics. As there is incomplete inhibition of EIA by Chlorpheniramine, it suggests that there may be some other associated mediator release or pathogenesis of EIA other than histamine release as the sole mechanism.

We conclude that Chlorpheniramine when given by inhalation produces significant bronchodilation during rest in asthmatics. The bronchodilator response may depend upon the degree of airways obstruction present, which may be a reflective of histamine tone. The difference between pre-exercise and post-exercise lung functions were comparable on day 2 and day 3, suggesting the effect of exercise nearly same on both days.

**References**

2. Global initiative for Asthma, NH/LBI/WHO workshop Report: Global strategy for asthma, NIH publication No.02-3659 Revised 2007-8

**Dr. Vithalrao Nadgouda Best All India Annual Thesis Award**

1. The award is open to the physicians from various medical institutions / hospitals from India within one year of passing the MD / DNB examination in Medicine / General Medicine / Internal Medicine as on the last date for submission of the application for the above award 31st May 2020.
2. There shall be two awards: the first award shall comprise of Rs. 15,000/- along with a certificate and the second award shall comprise of Rs. 10,000/- along with a certificate.

Full format is available on API and JAPI websites: www.apiindia.org / www.japi.org

Dr. Mangesh Tiwaskar
Hon. General Secretary

Dr. A. M. Bhagwati
Jt. Secretary
Cross-sectional Study on Vitamin D Status in CKD Patients

Sougata Kumar Ghosh¹, Shibendu Ghosh²*

Abstract

Background: Chronic Kidney Disease (CKD) is a disease characterized by alterations in either kidney structure or function or both for a minimum of 3 months duration. New evidences have established a novel paradigm in the management of CKD patients having Vitamin D deficiency. It appears in some studies that adequate replacement of Vitamin D in deficient population can reduce premature mortality and morbidity in CKD population.

Aims and Objectives: This cross-sectional study is designed **To assess Vitamin D status in CKD patients and to correlate Vitamin D status with eGFR.**

Methodology: A retrospective cross sectional study on 100 cases of Chronic Kidney Disease patients and matched control subjects in a tertiary care hospital of Eastern India. eGFR was calculated using MDRD-EPI study equation. Vitamin D status was measured using 25(OH) vitamin D levels. Correlation was calculated by Pearson correlation analysis.

Results: Among 100 cases, 56 were male and 44 were female. Among 100 control, 53 were female and 47 were male. Among the cases, the mean eGFR was 25.15 ± 11.89. Among the control, the mean eGFR was 87.22 ± 17.82. Among the cases, the mean Vitamin D (Vit D) was 22.57 ± 9.76. Among the control, the mean Vit D was 35.24 ± 10.18. Among the cases, in non-dialysis patients the mean Vit D was 25.66 ± 8.54 and in dialysis patients the mean Vit D was 10.94 ± 2.65. Among the cases, 38 patients had Vit D deficiency (<20), 44 patients had Vit D insufficiency (20-30) and 18 patients had normal Vit D (>30). The positive correlation was found between eGFR and vitamin D level and that was statistically significant.

Conclusion: Both deficiency and insufficiency of Vitamin D were higher in CKD patients compared to control. Vitamin-D deficiency was more pronounced in advanced stages of CKD. eGFR was strongly associated with serum vitamin-D level.

Introduction

CKD is an emerging public health problem and one of the most powerful predictors of premature cardiovascular disease. Progression of CKD and many of the cardiovascular complications may be linked to hypovitaminosis D.¹ Patients with CKD have an exceptionally high rate of severe vitamin D deficiency that is further exacerbated by the reduced ability to convert 25(OH) vitamin D into the active form, 1,25 dihydroxy-vitamin D.²

The major complications related to CKD include cardiovascular disease, anaemia, infectious complications, neuropathy and abnormalities related to mineral and bone metabolism. Disturbance in mineral and bone metabolism accompanied by soft tissue and vascular calcification is one of the most common and important consequences of CKD development and progression.³ As well described in the literature, CKD is characterized by low 25(OH) vitamin D (calcidiol), low 1,25(OH)₂ vitamin D (calcitriol) as well as vitamin D resistance.⁴

According to the guidelines, serum levels of 25(OH)D between 20 and 30 ng/ml indicate vitamin D insufficiency and levels less than 20 ng/ml indicate vitamin D deficiency. Severe deficiency is defined as a 25(OH)-D level less than 10 ng/ml.⁵ KDIGO (Kidney disease improving global outcomes) guidelines recommend that the serum level of 25(OH)D should be maintained over 30 ng/ml in patients of all stages of CKD.⁶

It is well established in various studies that Patients with CKD have an higher rate of severe vitamin D deficiency.⁷ Limited studies have evaluated vitamin D status in Indian population groups and found the deficiency to be highly prevalent.⁸ No data, however, are available on the prevalence or severity of 25(OH)-D deficiency in Indian CKD patients.

Materials and Methods

It is an observational hospital based cross-sectional study on 100 cases of Chronic Kidney Disease patients and matched control subjects to study the Vitamin D status in CKD population and correlation between their serum 25-OH-vitamin D level and eGFR. Study was conducted in Vivekananda Institute of Medical sciences (VIMS), Ramakrishna Mission Seva Pratishthan (RKMSP), Kolkata for a period of 18 months (January 2017-June 2018).

100 CKD Patients were selected after proper initial screening from outdoor clinics, dialysis unit and different wards under department of General Medicine and Nephrology, RKMSP. Age and sex matched controls were selected from same study population. Ethical clearance was taken from the Institutional Ethical Committee prior to the commencement of the study.

Inclusion criteria were age of eighteen years or older and eGFR value <60 ml/min/1.73 m². Patients were excluded who were on medications known to affect vitamin D absorption and metabolism such as anticonvulsants, isoniazid, rifampicin, theophylline, glucocorticoids, bisphosphonates.

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or taking vitamin D supplements or eGFR=60 ml/min/1.73 m2. Following laboratory investigations were done- Serum urea, creatinine, 25-OH-vitamin D, electrolytes (sodium, potassium, calcium, phosphate). Ultrasonography of lower abdomen was done to assess kidney sizes.

Estimation of GFR was done using MDRD-EPI study equation: GFR (mL/min/1.73 m2) = 175 × (Scr)-1.154 × (Age)-0.203 × (0.742 if female). Vitamin D status was measured using 25(OH) vit D level and eGFR=

Table 1: Distribution of Age and sex in groups

<table>
<thead>
<tr>
<th>Group</th>
<th>Case</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female</td>
<td>44</td>
<td>53</td>
</tr>
<tr>
<td>Male</td>
<td>56</td>
<td>47</td>
</tr>
<tr>
<td>Mean age</td>
<td>60.69</td>
<td>60.81</td>
</tr>
</tbody>
</table>

Table 2: Distribution of vitamin D in groups

<table>
<thead>
<tr>
<th>Vitamin D</th>
<th>Case</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Deficiency</td>
<td>38</td>
<td>5</td>
</tr>
<tr>
<td>Insufficiency</td>
<td>44</td>
<td>33</td>
</tr>
<tr>
<td>Normal</td>
<td>18</td>
<td>62</td>
</tr>
</tbody>
</table>

Table 3: Distribution of mean vit D in dialysis vs non-dialysis patients

<table>
<thead>
<tr>
<th>Group</th>
<th>Number</th>
<th>Vitamin D</th>
<th>p.value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
<td>Minimum</td>
</tr>
<tr>
<td>Dialysis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>79</td>
<td>25.66</td>
<td>8.5476</td>
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</table>

Table 4: Distribution of mean Vit D vs. eGFR

<table>
<thead>
<tr>
<th>CKD Sub group</th>
<th>eGFR</th>
<th>Number</th>
<th>Vitamin D</th>
<th>p.value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
<td>Minimum</td>
<td>Maximum</td>
</tr>
<tr>
<td>CKD 5 &lt;15</td>
<td>23</td>
<td>11.1130</td>
<td>2.9562</td>
<td>7.8000</td>
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<td>CKD 3b 31-45</td>
<td>27</td>
<td>26.8296</td>
<td>7.3646</td>
<td>7.7000</td>
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<tr>
<td>CKD 3a 45-60</td>
<td>6</td>
<td>36.3167</td>
<td>4.9898</td>
<td>29.8000</td>
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</table>

Table 5: Correlation between vit D and eGFR

<table>
<thead>
<tr>
<th>Vitamin D Remarks</th>
<th>Correlation Coefficient (r)</th>
<th>p-value</th>
<th>Number</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>&lt;0.0001</td>
<td>100</td>
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</tbody>
</table>

The positive correlation was found between eGFR and vitamin-D level and that was statistically significant.

Discussion

This is a cross sectional, observational study of 100 cases of Chronic Kidney Disease patients in Department of Medicine and Nephrology, Vivekananda Institute of Medical Sciences (VIMS), Ramakrishna Mission Seva Pratishthan (RKMS), Kolkata, during the period of January 2017-June 2018. This study on 100 cases of Chronic Kidney Disease patients and matched control subjects is undertaken to study the prevalence of Vitamin D deficiency in CKD population and correlation between their serum 25(OH)-vitamin D level and eGFR.

Zulfikar Jabbar et al found that mean age was 39.55 ± 9.88 years in control and 40.6 ± 12.04 years in cases. We found that among cases, the mean age (mean ± s.d.) of patients was 36.31 ± 4.98. Difference of mean VitD vs eGFR was statistically significant (p<0.0001).
control, 53 (53.0%) patients had female and 47 (47.0%) patients had male.

Rozita M et al. found mean levels of 25(OH) D were comparable in the control and CKD groups (15.3 ± 4.2 ng/mL and 16.1 ± 6.2 ng/mL (p = 0.453) respectively. The proportion of subjects with 25(OH)D insufficiency and 25(OH) D deficiency were also comparable in both groups. However in 25(OH)D deficiency group, the mean levels of 25(OH)D was significantly lower in the CKD groups (11.2 (6.5) ng/mL vs 12.6 [3.7], p = 0.039). The serum 25(OH)D levels were also not different across the different CKD stages (p = 0.87).

We found that in cases, the mean Vit D (mean± s.d.) of patients was 22.57 ± 9.76. In control, the mean Vit D (mean± s.d.) of patients was 25.24 ± 10.18. Difference of mean Vit D in two groups was statistically significant (p<0.0001). We found that among cases, 38 (38.0%) patients had Vit D deficiency, 44 (44.0%) patients had Vit D insufficiency and 18 (18.0%) patients had normal Vit D. Among control, 5 (5.0%) patients had Vit D deficiency, 33 (33.0%) patients had Vit D insufficiency and 66 (66.0%) patients had Vit D normal. Association of Vit D vs. group was statistically significant (Table 2).

A.Mittal et al.11 found that majority of the hemodialysis patients (43/45 [95.5%]) were either vitamin D deficient or had insufficient levels. 40/45 (88.9%) were vitamin D deficient (levels <20 ng/ml); of these, 29/40 (64.4%) had severe vitamin D deficiency (levels <10 ng/ml) and 3/45 (6.7%) had insufficient levels (20-30 ng/ml) of vitamin D. Only 2/45 (4.4%) patients had normal levels of vitamin D.

We found that in non-dialysis patients, Vit D of patients was 25.66 ± 8.54. In dialysis patients, Vit D of patients was 10.94 ± 2.65. Difference of mean Vit D in Dialysis vs Non-Dialysis was statistically significant (p<0.0001) (Table 3).

Arulanantham R et al.12 found that the prevalence of vitamin D deficiency was much higher in stage IV and stage V CRF when compared to stage II and stage III CRF. So, as the severity of CRF increases the prevalence of vitamin D deficiency increases.

We found that in CKD stage V/ (eGFR<15) Vit D of patients was 11.11 ± 2.95. In CKD stage IV/(eGFR15-30) Vit D of patients was 24.07 ± 8.29. In CKD stage 3a/(eGFR>30-45) Vit D of patients was 26.82 ± 7.36. In CKD stage 3b/(eGFR>45) Vit D of patients was 36.31 ± 4.98. Difference of mean Vit D vs eGFR was statistically significant (p<0.0001) (Table 4 and Figure 1). The positive correlation was found between eGFR and Vitamin D level and that was statistically significant (Table 5).

Summary and Conclusion
Both deficiency and insufficiency of Vitamin D were higher in CKD patients compared to control and that is statistically significant. Vitamin D deficiency was more pronounced in advanced stages of CKD and more marked in hemodialysis patients compared to non-dialysis CKD patients. eGFR was strongly associated with serum Vitamin D level, that is also statistically significant. The positive correlation was found between Vitamin D and eGFR.

References
Comparative Analysis of Clinical and Biochemical Profile of Exertional Heat Related Illness Among Cadets in a Military Training Centre in South India: A Single Centre Experience

Sankar J1*, Lekshmi Sankar2, R Ramprasad3, Kishore Kumar4

Abstract

Background: Heat-related illnesses includes a range of manifestation starting from minor illness like heat rashes/heat cramps to more complicated illness like heat exhaustion and the most severe heat stroke. Often derangements in biochemical parameters including metabolic acidosis, respiratory alkalosis, electrolytes, transaminitis and renal dysfunction are noticed in patients with heat stroke. Objective: The present study was an attempt to compare the clinical and changes in biochemical parameters in exertional heat exhaustion and heat stroke patients among cadets from a military training centre admitted to an Armed forces hospital in South India.

Material and Methods: The present study was carried out as a cross sectional comparative study among patients with heat exhaustion (n=30) and heat stroke (n=30) in a tertiary level Armed forces hospital located in Chennai. Simple random sampling technique was used to select study participants. Clinical and biochemical parameters of the study participants were examined. Statistical analysis: Means and proportions were calculated for continuous and categorical variables respectively. Difference in proportions were tested using chi square test and a p value <0.05 was considered statistically significant.

Results: On examination most the patients had tachycardia, blood pressure and respiratory rate in normal ranges. Most of the patients were found having elevated liver enzymes (>90%). Hyponatremia was the most common electrolyte abnormality. Other abnormal biochemical parameters noted were hypokalemia and deranged renal parameters. Higher proportion of patients with heat stroke were found to have tachycardia, transaminitis and abnormal electrolyte and biochemical parameters as compared to those with heat exhaustion.

Conclusion: Tachycardia, transaminitis and hyponatremia was widely observed in patients with heat related illness and these changes occur at higher rates in patients in heat stroke as compared to heat exhaustion.

Introduction

Heat stress, a condition that results from excessive heat production (ie, metabolic heat production from the working muscles) or inhibited heat loss (ie, decreased sweating response, decreased ability to evaporate sweat) or both. The temperature in India is forecasted to increase continuously in the next decades and by the end of this century globally mean temperatures are forecasted to increase by 5.5°C.1,2 Future climate change is expected to cause substantial increases in heat-related mortality.3 Historically in the Armed Forces, ‘Exertional Heat Hyperpyrexia’, was described in the past as ‘Classic Fatigue Syndrome’ by the British troops from the days of the Crimean War and Indian Mutiny.4 Although this illness is presumably occurs in hot and humid weather, it can present itself with extreme physical exertion in the absence of extreme environmental conditions also. The first sign of heat stroke is often CNS dysfunction (eg, collapse, aggressiveness, irritability, confusion, seizures, altered consciousness)4 and can even progress to a systemic inflammatory response and multi-organ system failure unless early diagnosis and management is ensured. The risks of morbidity and mortality increases with increasing time for which an individual’s body temperature remains above the threshold (>40.5°C [105°F]) and are significantly reduced if body temperature is lowered.5 Often derangements in biochemical parameters including metabolic acidosis, respiratory alkalosis, electrolytes, transaminitis and kidney dysfunction are noticed in patients with heat stroke.6,7 There are very few studies comparing the biochemical parameters in patients with exertional heat exhaustion and heat stroke.8,9 There are very few studies comparing the biochemical parameters in patients with exertional heat exhaustion and heat stroke. The present study was an attempt to compare the changes in biochemical parameters in exertional heat exhaustion and heat stroke among the cadets from a military training centre admitted to a Armed forces hospital in South India.

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Material and Methods

The present study was carried out as a cross sectional comparative study among the cadets admitted to Armed forces hospital with features suggestive of heat stroke and heat exhaustion. Operational definition of heat stroke in the present study was central nervous system dysfunction and extreme hyperthermia (more than 40.5°C), after exertion and exposure to environmental heat and the definition of heat exhaustion considered was elevated core temperature (less than 40.5°C) with out any CNS dysfunction after exertion and exposure to heat.

The study was undertaken in a tertiary level Armed Forces hospital located in Chennai during the period from March 2018 to June 2019. The temperature and humidity levels of this region during the study period varies from 34.3 to 36.9°C and 62 to 70% respectively. Simple random sampling technique was used to select study participants from all the patients admitted to this hospital. The minimum required sample size was calculated to be 30 in each group using the software epi-info. After the onset of symptoms, the patients were taken to the emergency resuscitation room and vitals were recorded by a medical officer, after emergency resuscitation measures, they were immediately transferred to ICU.

Appropriate history from the medical assistant who provided medical cover to the training event, was obtained and physical examination was carried out simultaneously. Patients were given active cooling measures, fluid resuscitation, electrolyte replacement and other supportive measures. Biochemical parameters including electrolytes, liver enzymes, renal function parameters, haemogram and INR were evaluated for all the study patients in the same lab using the same equipment throughout the study period. Institute ethical committee approval was obtained before the study was begun and informed written consent was obtained from all the patients before including them in the study. Statistical analysis: Data entry was done using MS Excel 2013 and data analysis was performed using SPSS version 22.0. Means and proportions were calculated for continuous and categorical variables respectively. Difference in proportions were tested using chi square test and a p value ≤ 0.05 was considered statistically significant.

The table below shows the distribution of study participants based on clinical and biochemical parameters and the association between type of heat related illness and biochemical parameters.

### Table 1: Distribution of study participants based on clinical and biochemical parameters (n=60)

<table>
<thead>
<tr>
<th>Feature</th>
<th>Frequency / Mean</th>
<th>Percentage/ SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>SBP</td>
<td>101</td>
<td>9</td>
</tr>
<tr>
<td>DBP</td>
<td>70</td>
<td>8</td>
</tr>
<tr>
<td>PR</td>
<td>100</td>
<td>11</td>
</tr>
<tr>
<td>Temperature</td>
<td>100.8</td>
<td>2.2</td>
</tr>
<tr>
<td>RR</td>
<td>21</td>
<td>2.2</td>
</tr>
<tr>
<td>Anaemia</td>
<td>35</td>
<td>58.3</td>
</tr>
<tr>
<td>Raised TLC</td>
<td>28</td>
<td>46.7</td>
</tr>
<tr>
<td>Elevated serum bilirubin</td>
<td>41</td>
<td>68.3</td>
</tr>
<tr>
<td>Elevated AST</td>
<td>57</td>
<td>95.0</td>
</tr>
<tr>
<td>Elevated ALT</td>
<td>54</td>
<td>90.0</td>
</tr>
<tr>
<td>Elevated LDH</td>
<td>55</td>
<td>91.7</td>
</tr>
<tr>
<td>Elevated Blood urea nitrogen</td>
<td>45</td>
<td>75.0</td>
</tr>
<tr>
<td>Elevated serum creatinine</td>
<td>27</td>
<td>45.0</td>
</tr>
<tr>
<td>Hyponatremia</td>
<td>45</td>
<td>75.0</td>
</tr>
<tr>
<td>Hypernatremia</td>
<td>3</td>
<td>5.0</td>
</tr>
<tr>
<td>Hypokalemia</td>
<td>12</td>
<td>20.0</td>
</tr>
<tr>
<td>Hyperkalemia</td>
<td>1</td>
<td>1.7</td>
</tr>
<tr>
<td>Elevated uric acid</td>
<td>24</td>
<td>40.0</td>
</tr>
<tr>
<td>Elevated INR</td>
<td>26</td>
<td>43.3</td>
</tr>
</tbody>
</table>

### Table 2: Association between type of heat related illness and biochemical parameters (n=60)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Heat related illness</th>
<th>Total n(%): p value*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Heat exhaustion n(%)</td>
<td>Heat Stroke n(%)</td>
</tr>
<tr>
<td>Anaemia</td>
<td>19(54.3)</td>
<td>16(45.7)</td>
</tr>
<tr>
<td>Absent</td>
<td>11(44.0)</td>
<td>14(56.0)</td>
</tr>
<tr>
<td>TLC</td>
<td>7(25.0)</td>
<td>21(75.0)</td>
</tr>
<tr>
<td>Elevated</td>
<td>23(71.9)</td>
<td>9(28.1)</td>
</tr>
<tr>
<td>Normal</td>
<td>11(26.8)</td>
<td>30(73.2)</td>
</tr>
<tr>
<td>Serum Bilirubin</td>
<td>19(100.0)</td>
<td>0(0.0)</td>
</tr>
<tr>
<td>Elevated</td>
<td>27(47.4)</td>
<td>30(52.6)</td>
</tr>
<tr>
<td>Normal</td>
<td>3(100.0)</td>
<td>0(0.0)</td>
</tr>
<tr>
<td>AST</td>
<td>24(44.4)</td>
<td>30(55.6)</td>
</tr>
<tr>
<td>Elevated</td>
<td>6(100.0)</td>
<td>0(0.0)</td>
</tr>
<tr>
<td>Normal</td>
<td>27(49.1)</td>
<td>28(50.9)</td>
</tr>
<tr>
<td>Serum creatinine</td>
<td>16(35.6)</td>
<td>29(64.4)</td>
</tr>
<tr>
<td>Elevated</td>
<td>14(93.3)</td>
<td>1(6.7)</td>
</tr>
<tr>
<td>Normal</td>
<td>6(22.2)</td>
<td>21(77.8)</td>
</tr>
<tr>
<td>Sodium</td>
<td>22(48.9)</td>
<td>23(51.1)</td>
</tr>
<tr>
<td>Low</td>
<td>8(66.7)</td>
<td>4(33.3)</td>
</tr>
<tr>
<td>Normal</td>
<td>0(0.0)</td>
<td>3(100.0)</td>
</tr>
<tr>
<td>Potassium</td>
<td>3(25.0)</td>
<td>9(75.0)</td>
</tr>
<tr>
<td>Low</td>
<td>26(55.3)</td>
<td>21(44.7)</td>
</tr>
<tr>
<td>Normal</td>
<td>1(100.0)</td>
<td>0(0.0)</td>
</tr>
<tr>
<td>Serum uric acid</td>
<td>15(62.5)</td>
<td>9(37.5)</td>
</tr>
<tr>
<td>Elevated</td>
<td>15(41.7)</td>
<td>21(58.3)</td>
</tr>
<tr>
<td>Normal</td>
<td>5(19.2)</td>
<td>21(80.8)</td>
</tr>
<tr>
<td>INR</td>
<td>25(73.5)</td>
<td>9(26.5)</td>
</tr>
<tr>
<td>Total</td>
<td>30(50.0)</td>
<td>30(50.0)</td>
</tr>
</tbody>
</table>

### Results

On examination most the patients had tachycardia, blood pressure and respiratory rate in normal ranges. Anaemia was observed in 58% of the patients. Most of the patients were found having transaminitis (>90%). Hyponatremia was the most common electrolyte abnormality that is observed.
in 75% of the patients. Other biochemical parameter disturbances noted were hypokalemia (20%), elevated blood urea nitrogen (75%), elevated serum creatinine (45%), elevated serum uric acid (40%) and elevated INR (43.3%) (Table 1).

Higher proportion of patients with heat stroke were found to have transaminitis and abnormal electrolyte/biochemical parameters as compared to those with heat exhaustion. Also, this association was found to be statistically significant (p value <0.05). Leukocytosis and INR was also found to be significantly high among patients with heat stroke as compared to that of heat exhaustion group of patients (p value <0.05) (Table 2).

**Discussion**

Heatstroke is the most severe form of heat-related disorders that include mild heat intolerance, heat exhaustion and heat stress. The present study was an attempt to compare the changes in biochemical parameters in exertional heat exhaustion and heat stroke among cadets in military training centre, admitted to an Armed forces hospital in South India. Even after extensive literature search, it was noted that available published material on comparative analysis of biochemical profile for patients with exertional heat related illnesses among young cadets are minimal. Some of the important known biochemical changes observed in patients with heatstroke are elevated urea, creatinine, cardiac and skeletal muscle enzymes, myoglobin and troponin. Elevated liver enzymes, renal parameters, derangements in serum electrolytes were noted in a study among 78 patients with exertion heat stroke carried out between 2003 and 2014, the common electrolyte disturbances were hypokalemia (71.2 %), hypophosphatemia (59.1 %), hypernatremia (53.0 %), hypocalcemia (51.5 %), and hypomagnesemia (34.9 %). The observed proportions in the above study were in comparable ranges with that of the findings noted in the present study. Absence of control group to clearly delineate the heat stroke illness patients with abnormal biochemical profile remained one of the important limitation of the present study. The study population mainly comprised of young cadets who are healthy with out any co morbidities, as compared to that of general population, thereby limiting the generalization of the present study findings. However, it is also assumed that biochemical variations noted in such healthy subjects will also be expected, in similar proportions or higher, in other subjects with different demography considering the pathophysiology of the disease.

**Conclusion**

This study is unique in the sense that only very few studies mentioned in literature comparing the effects of heat exhaustion and heat stroke particularly among exertional heat related illness which are different from effects of classical non exertional heat stroke in the elderly. Tachycardia, transaminitis and hyponatremia was widely observed in patients with heat related illness and these changes occur at higher rates in patients in heat stroke as compared to heat exhaustion. These abnormalities should be suspected and corrected in all patients with heat related illnesses. Prompt identification of patients with heat exhaustion and immediate resuscitation including cooling measures, intravenous fluids and correction of electrolyte abnormalities are required to prevent further progression to devastating heat stroke.

**References**

Role of MRI in Evaluation of Spectrum of Liver Lesions in Cirrhotic Patients

Anagha Joshi\(^1\), Sukhada Kulkarni\(^2\*\), Ankita Shah\(^2\)

Abstract

MRI provides better intrinsic soft-tissue contrast with more enhanced depiction of even subtly different tissue properties making lesion evaluation easy. Faster sequences which capture arterial sequences better, lack of ionizing radiation and simultaneous evaluation of background liver parenchyma and the liver lesions are additional advantages of using MRI as the imaging technique of choice. Comprehensive liver imaging using MRI now includes T1, T2-weighted imaging and in- and opposed-phase, in addition to dynamic post-contrast imaging with proper breath holding techniques. Wider variety of liver specific contrast agents is available for use in MR imaging with the gadolinium based agents being considered the most useful and practical, particularly for lesion characterization.

Aims and Objectives: To evaluate MRI spectrum of liver lesions in cirrhotic patients, Role of MRI in focal liver lesion evaluation and to differentiate benign versus malignant lesions.

Materials and Methods: A prospective study of OPD or IPD patients who underwent imaging tests like Ultrasonography, or CT scan for suspected chronic liver disease was done. A total 35 patients were investigated (June 2014 - November 2016) with MRI abdomen done with the patient in supine position on a Philips Achieva 3.0T MRI scanner. Standard MRI abdomen protocol, including T2W TSE in axial and coronal plane, T2W fat suppressed (SPAIR) images in axial and coronal plane, T1W TFE, in- and out-of-phase imaging and Diffusion-weighted imaging (DWI) in axial plane along with pre-contrast baseline fat-suppressed T1W imaging in at least one plane was acquired. Breath-holding was required in few sequences. 0.1 mmol/kg Gadolinium based contrast (Gadobenate) was injected at the rate of 2.5 ml/sec followed by saline flush and dynamic contrast enhanced MRI (DCE-MRI) with post-contrast fat-suppressed T1W imaging was acquired.

Results and Conclusions: In cirrhosis, there is development of nodules which are initially only microscopically detectable. With progression of cirrhosis, there is development of radiologically detectable regenerative nodules, dysplastic nodules and hepatocellular carcinoma. Amongst these regenerative nodules are completely benign lesions whereas dysplastic nodules, though benign, are considered premalignant; and hepatocellular carcinoma is a malignant condition. Differentiation of benign versus malignant lesions is possible on the basis of enhancement pattern in dynamic contrast enhanced MRI. The signal characteristics of focal lesions and other findings like portal vein thrombosis are helpful, give additional clue to the diagnosis and also helpful in assigning LI-RADS grade to a lesion. Also, MRI characterization after gadolinium based contrast injection was found to be similar to the previous imaging based on non-gadolinium contrast agents.

Introduction

Liver cirrhosis is defined as diffuse process characterized by fibrosis and conversion of normal liver architecture into structurally abnormal nodules. Cirrhosis has become the 12th leading cause of death by 2013. Cirrhosis is the main cause of HCC which accounts for 70% to 85% of primary liver cancers and is the 4th most common cancer in males in India.\(^1\) Cirrhosis is characterized by the formation of bridging fibrous and parenchymal nodules, which range from small (<3 mm) in diameter i.e. micronodules, to large (>1 cm) in diameter i.e. macronodules. Well defined dysplastic nodules are generally larger, may be > 2 cm whereas regenerative nodules are usually < 2 cm. There is step-wise progression from regenerative nodules (RN) to hepatocellular carcinoma (HCC) along the pathway of RN, low grade dysplastic nodules (LGDN), high grade dysplastic nodules (HGDN) and finally HCC.

Modalities In Evaluation of Liver Cirrhosis

“Cirrhosis” per se is a pathological diagnosis. However clinical, biochemical and radiological examination can be used in evaluation. In patients with cirrhosis, an elevated AFP level is a marker for increased risk of HCC, however serum AFP level measurement has poor accuracy for diagnosis of HCC, and patients with infiltrative HCC may have normal AFP levels. Hence, the use of AFP level does not qualify it as a screening test for HCC. With more advanced HCC, AFP testing is occasionally helpful to confirm a radiologic diagnosis mainly in patients in whom there is some uncertainty about the diagnosis and biopsy is not possible. Patients with later stage disease are more likely to have markedly elevated AFP levels.

Amongst the radiological investigations, MRI is better imaging modality because of high quality
imaging with high intrinsic soft tissue contrast, faster sequences which capture arterial sequences better, lack of ionizing radiation and simultaneous evaluation of background liver parenchyma and the liver lesions. Moreover, gadolinium based liver specific contrast agents are being considered to be the most useful and practical, particularly for lesion characterization. MRI is more sensitive for diagnosis of cirrhotic nodules, with its most important role in cirrhotic patient being the diagnosis and follow up or progression of cirrhotic nodules. Sensitivity of MRI varies with tumor size; however, it has been estimated to be about 100% in HCCs larger than 2 cm.

Nodules and fibrosis- the two main features of cirrhosis, combined in varying proportions result in a wide spectrum morphologic appearances. Liver may be normal in size, may be enlarged early in the disease or shrunken in late disease and shows heterogeneous architecture with surface irregularity, nodularity. Sometimes, there is relative segmental hypertrophy of caudate lobe and left lobe segments II, III; atrophy of the right hepatic lobe and reduction in the transverse diameter (< 3 cm) of the medial segment of left lobe i.e. segment IV.

Regenerative nodules (RN)

Regenerative nodules vary in appearance and can be T1 hypo, iso, or hyper-intense while these are usually T2 hypointense, smaller than 2 cm and show similar pattern of enhancement as the normal hepatic parenchyma. Fat containing nodules can be large (> 1.5 cm). The presence of numerous nodules < 1 cm suggests benignity.² T1 hyperintensity may be because of the presence of lipid, protein, or possibly copper.³ The fibrous septa surrounding RNs appear T1 hypointense and T2 hyperintense.

Dysplastic nodules (DN)

Dysplastic nodules, previously called adenomatous hyperplastic nodules are premalignant, usually T1 hyperintense, while being iso or hypointense on T2W images. Low-grade dysplastic nodules (LGDNs) are not considered premalignant, whereas high-grade dysplastic nodules are premalignant, progress to HCC more frequently, and may even be associated with increased alpha-fetoprotein levels.⁴ LGDNs show same enhancement characteristics as that of the background liver parenchyma on all dynamic phases. HGDNs tend to show early homogeneous arterial enhancement post gadolinium contrast enhancement and fade to isointensity but do not show washout.

Hepatocellular carcinoma (HCC):

HCC is reported to develop in dysplastic nodule when “nodule within a nodule” appearance i.e. a focus of T2 hyperintensity within a T2 low signal intensity nodule is noted. Arterial phase hypoenhancement is the most common, sensitive and important imaging finding in the diagnosis of HCC, but can also be seen in HGDNs, AP shunts and in a variety of benign and malignant hepatic lesions. The key distinguishing feature of HCC from other lesions is the development of delayed “washout”; defined as arterially enhancing nodules becoming “hypointense” compared to the background liver on the delayed phase imaging. HCCs greater than 2 cm in size have high diagnostic sensitivity as they tend to show washout. However, HCCs smaller than 2 cm may not show washout. Hypovascular HCCs are uncommon.²

HCCs exhibit hypointensity on hepatobiliary phase images, except for well differentiated HCCs which may retain the contrast agent. Delayed pseudocapsule enhancement of hepatic nodules aids in the diagnosis of HCC, and is particularly helpful in lesions that do not show classical features of HCC on dynamic imaging.

HCC may demonstrate slow growth hence only nodules that are stable for 2 years are considered benign. HCCs can be focal (nodular), massive, and diffuse/infiltrative² with the nodular type being most common and further classified as solitary or multi-focal. A rare variant of nodular subtype shows rim enhancement on arterial phase imaging,² more progressive behavior with rapid interval growth, requiring short-term follow-up and prompt therapy. Diffuse HCCs are usually large, have ill-defined boundaries, almost always associated with portal venous thrombus; which can be bland or most of the time tumoral in nature and usually have very high alpha-fetoprotein levels. A very close differential of diffuse HCCs are the areas of confluent fibrosis which has similar signal intensity and enhancement features as fibrotic septa but unlike neoplasms, it typically has a wedge like or geographic shape with straight or concave borders, radiating from the portal hilum to contact the liver surface, retracts the overlying hepatic capsule, shows progressive contrast enhancement and is associated with progressive volume loss if follow-up studies are performed (6).

International guidelines regarding radiological diagnosis of HCC

In the setting of liver cirrhosis, international guidelines have set the noninvasive criteria for HCC diagnosis; which relies on post-contrast dynamic imaging techniques with at least three different phases (arterial, portal venous, and equilibrium phases). Functional imaging like DWI and hepatobiliary specific MR contrast agents are useful in the detection and characterization of borderline hypovascular lesions. HCC diagnosis is established by the detection of contrast hyperenhancement in the arterial phase (wash-in) and hypoenhancement in the portal or delayed phase (wash-out) with dynamic MDCT or MRI. This behavior is defined as “HCC radiological hallmark” (7).

Eastern guidelines state that irrespective of the dimensions of the nodules, HCC diagnosis can be established by the typical enhancement pattern even in lesions smaller than 1 cm (8). According to the updated American Association for the Study of Liver Diseases (AASLD) guidelines, the detection of the typical enhancement pattern at one single imaging modality in nodules larger than 1 cm suffices for diagnosing HCC (9). Recent European Society for the Study of the Liver (EASL) guidelines reinforced that although a single imaging modality is considered sufficient for diagnosing HCC in nodules above 2 cm, nodules of size 1–2 cm should be investigated by two imaging modalities (7). Both EASL and AASLD guidelines suggest biopsy for all atypical nodules larger than 1 cm.

Standardization of reporting

To reduce the interobserver variability and inconsistency in interpretation and reporting of findings at liver imaging, scoring systems have been developed. In 2012, American College of Radiology developed the
A total number of 35 consecutive patients with liver cirrhosis diagnosed by clinical / biochemical / imaging criteria (USG / CT) were included in the study.

Maximum number of patients belonged to age group of 41-50 years and the mean age of our study population was 40.70 years. 23 patients (62.86 %) were male and 12 patients (37.14 %) were female. The most common presenting symptom was abdominal pain, followed by abdominal distension. Amongst the study population, 10 patients (28.6 %) had history of alcohol intake, 8 patients (25.72 %) were HBsAg positive while 3 patients (8.6 %) were HCV positive. Of these, 16 patients had got AFP levels done, of which, 7 patients (43.75 %) had normal AFP levels of which 4 had no cirrhotic nodules, 2 had hepatocellular carcinoma of grade LR-5B (1 focal and 1 diffuse) and 1 had hepatocellular carcinoma of grade LR-4A. Of the 9 patients (56.25 %) having raised AFP level, 6 had hepatocellular carcinoma of grade LR-5B (3 focal and 2 diffuse), 1 had diffuse hepatocellular carcinoma of grade LR-4B and 3 had dysplastic nodules of grade LR-3.

Amongst the study population, 27 patients (77.15 %) had focal liver lesions detected in MRI (20 patients i.e. 74.1 % had cirrhotic nodules, whereas 7 (25.9 %) patients had other pathologies) and 8 patients (22.85 %) did not have any MRI detectable lesions. Out of the 20 patients with cirrhotic nodules, the dominant lesion in 12 patients was hepatocellular carcinoma (7 focal and 5 diffusely infiltrating), 5 had regenerative nodules (including 2 which were lipid rich and 1 showing atypical enhancement pattern) whereas 3 had dysplastic nodules. In addition to the dominant lesion, multiple other cirrhotic nodules (regenerative nodules or dysplastic nodules) were noted in 12 patients. 6 patients had Budd-Chiari syndrome (5 of them also having other cirrhotic nodules and 1 without other cirrhotic nodules) while 7 patients did not have any other lesion.

**Lesion characteristics:** Out of the 12 patients having hepatocellular carcinoma, 7 had focal while 5 had diffusely infiltrating hepatocellular carcinoma. All hepatocellular carcinoma cases were confirmed either histologically, or correlated with imaging on CT or with raised AFP values.

**Out of the 7 patients with focal hepatocellular carcinoma,** 3 lesions were T1 hyperintense, 2 were isointense, and 1 was iso-hyperintense while 1 lesion was a hyperintense with a hypointense component within. 3 lesions were T2 hyperintense, 1 was isointense, 1 was iso-hyperintense and 1 was hypo-isointense while 1 lesion was isointense with a hyperintense component. 2 lesions showed restricted diffusion with corresponding low ADC values while 1 lesion had patchy restriction and 4 lesions did not show restricted diffusion. There was no significant change in signal intensities in dual FFE sequence. In post-contrast sequence, 2 of the lesions showed portal venous phase enhancement without washout, whereas 1 lesion showed arterial phase enhancement without washout. 1 lesion showed atypical enhancement pattern with no significant arterial phase enhancement and patchy portal phase enhancement without washout.

**Out of the 5 patients with diffuse hepatocellular carcinoma,** 2 lesions were T1 hypointense, 2 were hyperintense, and one was isointense. 3 lesions were T2 hyperintense and 2 were hypointense. 3 lesions had restricted diffusion with corresponding low ADC values while 2 lesions had patchy restricted diffusion. None of the lesions showed significant change in signal intensities in dual FFE sequence. In post-contrast sequence, 1 of these lesions showed typical arterial phase enhancement with delayed phase washout, 3 showed arterial phase enhancement without washout while 1 lesion showed peripheral enhancement.

**Out of the 3 patients with Dysplastic nodules,** 2 lesions were T1 hyperintense and 1 was isointense. 2 lesions were T2 hyperintense and 1 was hypointense. None of the lesions showed restricted diffusion. None of the lesions showed significant change in signal intensities in dual FFE sequence. In post-contrast sequence, 2 of the lesions showed portal venous phase enhancement without washout, whereas 1 lesion showed arterial phase enhancement without washout.

**Out of the 5 patients with Regenerative nodules,** 2 lesions were T1 hyperintense, 1 was iso-hyperintense and 2 lesions were isointense. 3 lesions were T2 iso-intense and 2 lesions were hypointense. None of the lesions showed restricted diffusion. 2 of the lesions showed loss of signal in out-of phase scan s/o lipid deposition. In post-contrast sequence, 2 of the lesions were isoenhancing to rest of the liver parenchyma, 2 were non-enhancing while 1 lesion was hypoenhancing.

**Portal Vein Thrombosis:** 5 patients (14.3 %) had portal vein thrombosis, of which, 3 had definite tumor thrombus, 1 had probable tumor thrombus and 1 had bland thrombus.

**LIRADS Grade of various lesions:** Out of the study population, 8 patients did not have any MRI detectable lesions hence LIRADS grade was not applied. Out of the 27 patients having MRI detectable liver lesions, the dominant lesion was characterized under LIRADS grading system. 10

### Table 1: The pattern of nodules was as following

<table>
<thead>
<tr>
<th>MRI detected liver lesions</th>
<th>No. of cases</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Regenerative nodules only</td>
<td>5</td>
<td>25</td>
</tr>
<tr>
<td>Dysplastic nodules only</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>HCC only</td>
<td>6</td>
<td>30</td>
</tr>
<tr>
<td>Regenerative nodules with dysplastic nodules</td>
<td>3</td>
<td>15</td>
</tr>
<tr>
<td>Dysplastic nodules with HCC</td>
<td>3</td>
<td>15</td>
</tr>
<tr>
<td>Regenerative nodules with HCC</td>
<td>1</td>
<td>5</td>
</tr>
<tr>
<td>Regenerative nodules, dysplastic nodules and HCC</td>
<td>2</td>
<td>10</td>
</tr>
</tbody>
</table>

Liver Imaging—Reporting and Data System (LI-RADS) for standardizing terminology and criteria for interpreting and reporting findings of CT and MRI examinations of the liver in patients with cirrhosis or increased risk of HCC. The LI-RADS classifies lesions to five categories ranging from definitely benign to definitely HCC on the basis of several criteria, such as mass-like configuration, increase in size, arterial phase hyperenhancement, portal venous phase or later phase hypoenhancement, presence of tumor capsule, and vein involvement. In the latest 2013.1 version, LI-RADS and UNOS OPTN categorizations have been unified. This version applies to multiphase CT and MRI examinations performed with conventional extracellular contrast materials. It currently, does not apply to hepatobiliary specific gadolinium-based agents.

**Observations**
lesions (28.57 %) were LR-1, of which, 2 were regenerative nodules and 8 (29.6 %) were other pathologies. 2 lesions were LR-2 and LR-4A each 3 were LR-3 and LR-4A each while 7 (20 %) were LR-5B. LIRADS distribution of the lesions is as follows (Table 2).

USG was done in all patients. USG was able to identify 14 (51.85 % of the lesions) amongst the 27 patients in whom lesions were identified on MRI. CT was done in 11 patients, of which 10 patients had focal lesions detected in MRI. CT was able to identify 8 (80 %) amongst these 10 lesions while 2 (20 %) were not detectable (regenerative nodules and a small cyst).

**Results and Discussion**

The observations and results were tabulated under various headings and then correlated with various past studies.

With respect to the mean age and gender distribution, our observations were concordant with the previous studies (10, 3).

In our study, maximum i.e. 15 patients (42.9 % of the cases) were recently diagnosed cases of liver cirrhosis, followed by 8 patients (22.9 % of the cases) who were diagnosed within last 5 years. 6 patients belonged to 6-10 yrs duration group, 3 patients in 11-15 yrs group, 2 patients in 16-20 yrs group and 1 patient in 21-25 yrs group. 

To the best of our knowledge, there is no significant literature available pertaining to the duration of diagnosed cirrhosis in patients with radiologically diagnosable liver changes. Although the duration of diagnosed cirrhosis observed in our study population was less, this is most likely spurious. The proposed factors contributing to this false result are – The center being a tertiary care hospital, patients referred to this hospital are almost always treated for a significant duration of time outside, majority of them getting only symptomatic treatment without much workup, and thus causing delay in the actual diagnosis. Also, patients coming to our hospital were from lower socio-economic strata hence negligent about health conditions.

No significant correlation was observed with raised or normal AFP values as similar lesions were observed in both the groups. This is in concordance with the other studies (11, 12).

Out of the 27 patients having focal lesions detected in MRI, 20 (74.1 %) patients had cirrhotic nodules, whereas 7 (25.9 %) patients had other pathologies. Out of the 20 patients with cirrhotic nodules, the dominant lesion in 12 patients was hepatocellular carcinoma (7 focal and 5 diffusely infiltrating), 5 patients had regenerative nodules (including 2 which were lipid rich and 1 showing atypical enhancement pattern) whereas 3 patients had dysplastic nodules. Out of the 20 patients with cirrhotic nodules, in addition to the dominant lesion, multiple other cirrhotic nodules (regenerative nodules or dysplastic nodules) were noted in 12 patients, 6 patients had Budd-Chiari syndrome (5 of them also having other cirrhotic nodules and 1 without other cirrhotic nodules) while 7 patients did not have any other lesion.

**Lesion characterization**

**Hepatocellular carcinoma:** (Figures 2, 3, 4). Findings in our study were correlated with previous studies and were consistent regarding T2 signal intensity. Our study differs in having a considerable number of hepatocellular carcinoma, which were T1 hyperintense. However T1 hypointensity in hepatocellular carcinoma is well known to occur and is usually associated with better tumor grade than T1 hypointense hepatocellular carcinomas (13). The contrast enhancement pattern is similar for focal hepatocellular carcinoma but differs in diffuse hepatocellular carcinoma, many of which showed arterial phase enhancement but no washout (1 patient had arterial phase enhancement with delayed phase washout, 1 patient had peripheral enhancement while 3 patients had arterial phase enhancement but persistent delayed phase enhancement without washout) (3, 14, 15, 16).

**Dysplastic Nodules:** (Figure 5): As compared to previous study done by Quaia et al (3), our study revealed similar (consistent) signal intensities in unenhanced scans and contrast enhancement pattern in 2 patients but different contrast enhancement pattern (arterial enhancement) in 1 patient. However even this patient did not have delayed phase washout hence was consistent with the results of previous studies e.g. done by JA Marrero et al.14

**Regenerative nodules:** (Figure 6) Signal characteristics in our study group are similar on T2 weighted images but differ from this observation on T1 weighted images. However the observations in our study are consistent with the literature stating that regenerative nodules can be iso-hyperintense on T1 weighted images. These differences can be attributed to less number of sample size for regenerative nodules. Enhancement pattern was classical in two of the lesions whereas atypical in the other three. 2 of the lesions were fat containing, one of which showed no enhancement.

**Portal vein thrombosis:** Out of the study population of 35 patients having liver cirrhosis, 4 patients (11.4 % of the cases) had portal vein thrombosis and 31 patients (88.6 % of the cases) did not have any portal vein thrombosis. All the 4 patients having portal vein thrombosis had diffuse type of hepatocellular carcinoma (amongst total of 5 patients having diffuse hepatocellular carcinoma). Our findings were consistent with the previous results (14, 15).

**LIRADS:** Out of the study population of 35 patients having liver cirrhosis, 27 patients (77.15 % of the cases) had MRI detectable liver lesions (cirrhotic nodules as well as other pathologies which are considered) and 8 patients (22.85 % of the cases) did not have any MRI detectable lesions.

![Fig. 1: Pattern of nodules and percentage amongst total patients having nodules](image_url)
lesions detected in MRI, 10 (28.57 %) were LR-1, of which 2 were regenerative nodules and 8 (29.6 %) were other pathologies and 7 (20 %) were LR-5B (Hepatocellular carcinomas).

To the best of our knowledge, there is no significant literature available pertaining to exact number or prevalence of different LIRADS lesions in cirrhotic patients.

Our results were consistent with the observations in previous studies regarding detection of lesions in USG or CT (17, 18).

**Conclusion**

The spectrum of liver changes in cirrhotic patients in MRI includes heterogeneity, surface nodularity,
selective lobe atrophy and development of focal lesions like regenerative nodules, dysplastic nodules and hepatocellular carcinoma. Development of portal vein thrombosis, associated findings of portal hypertension like splenomegaly, ascites and collaterals may be found.

Cirrhotic nodules are initially only microscopically detectable with progression to development of radiologically detectable nodules later. Regenerative nodules are completely benign lesions, dysplastic nodules though benign, are considered premalignant; and hepatocellular carcinoma, is clearly a malignant condition. Hence, differentiation of

Fig. 4: An ill-defined T1 hypointense, T2 hyperintense lesion in segments VI, VIII showing patchy areas of early arterial enhancement, increasing in portal phase and appearing isointense to rest of the parenchyma in venous and delayed phase without washout. Also seen is hyperintense filling defect showing arterial enhancement in branches of portal vein with non-opacification in portal phase suggestive of tumor thrombus

Fig. 5: Few T1 hyperintense, T2 hypointense lesions showing early arterial enhancement, appearing hyperintense to rest of the liver parenchyma in portal venous and venous phases but isointense in delayed phase i.e. no washout
benign versus malignant lesions is possible on the basis of enhancement pattern in dynamic contrast enhanced MRI.

MRI best characterizes focal cirrhotic liver lesions. USG can detect focal lesions but cannot reliably characterize them. CT can reliably characterize the focal lesions and differentiate between regenerative nodules and hepatocellular carcinoma, but may not be able to reliably differentiate dysplastic nodules from regenerative nodules or from hepatocellular carcinoma. Hence CT is still less sensitive as well as specific than MRI. MRI is most reliable investigation for suspected hepatocellular malignancy— in detection and also for monitoring of patients in whom the lesions are detected previously. Although ultrasound is used for monitoring the patients in early stages of cirrhosis, MRI has high sensitivity and specificity. The signal characteristics of focal lesions and other findings like portal vein thrombosis are helpful, give additional clue to the diagnosis and also helpful in assigning LIRADS grade to a lesion.

Abbreviations


References

Relevance of Asymptomatic Electrocardiographic Abnormalities at High Altitude

Yatharth Dixit¹*, Dennis Abraham², Vishnu Prasad³

Abstract
Background: Cardiovascular diseases, especially coronary artery disease, are epidemic all over the world. Globally, CVD led to 17.5 million deaths in 2012.¹ More than 75% of these deaths occurred in developing countries.² In contrast to the developed countries, where mortality from CVD is rapidly declining, an increasing trend has been noted in the developing countries.² India is a large and socioeconomically diverse country and is home to 17% of the world’s population. In India, more than 10.5 million deaths occur annually and it was reported that CVD led to 20.3% of these deaths in men and 16.9% of all deaths in women.³ The striking features of CVD epidemiology in India are high mortality rates, premature CAD, and increasing burden.⁴

Introduction
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Regions above 1500 m are termed as High altitude (HA).⁷ Illnesses associated with HA are commonly observed above an altitude of 2500 m; therefore regions above 2500 m are considered as HA for all practical purposes. Upon ascent to HA, an individual’s body undergoes a series of adaptive changes to maintain normal performance in daily activities. This process is known as acclimatization.⁷ A recent estimate suggests that nearly 140 million people live at an altitude greater than 2500 m which includes the populations of South America, Central Asia, and Eastern Africa. These highlanders are chronically exposed to relative hypoxia, which has important consequences on the cardiovascular system.⁸

One of the most important effects of prolonged stay in HA is pulmonary hypertension leading to right ventricular hypertrophy. The first direct measurement of increased pulmonary arterial pressure by cardiac catheterization was done in Peru (4540 m) in 1956.⁹ Penaloza et al. established the connection between chronic hypoxia and pulmonary hypertension for the first time in 1962.¹⁰ Since then numerous studies have confirmed this fact. This also propelled researchers to study the pattern of ECG abnormalities at HA. A study conducted by Rotta and Lopez on 120 healthy highlanders suggested four common patterns of ECG namely, (1) right ventricular hypertrophy, (2) suggestive of right ventricular hypertrophy (S1, S2, S3), (3) incomplete and complete heart block and (4) normal pattern.¹¹ In another study conducted by Penaloza et al. in 13 healthy lowlanders who were temporarily taken to high altitude for four weeks, main changes seen in the ECG were clockwise rotation

Results: Out of 54 subjects, mean age was 40.6 yrs. Mean BMI was 24.28 Kg/m². Most common ECG abnormality was T wave inversion in inferiorly directed frontal plane leads seen in 16 (29.6%) subjects followed by T wave inversion in both inferiorly directed frontal plane leads and precordial leads noted in 13 (24%) subjects. Next most common ECG abnormality was T wave inversion in the precordial leads seen in 10 (18.5%) subjects. Only three subjects turned out to be positive for inducible ischemia. Coronary angiography however showed normal coronaries in all the three subjects.

Conclusions: Our study suggests that majority of ECG abnormalities in high altitude are transient/benign in nature and do not suggest an increased risk of cardiovascular disease whether evaluated by Framingham Risk Score or structural/functional evaluation by 2D Echocardiography/Treadmill Test.

Abstract
Method: A total of 54 subjects were included in the study. All of them underwent acclimatization before ascent to high altitude. Subjects were selected if they were detected to have ECG abnormality in high altitude. Various parameters such as height, weight, BMI, and multiple laboratory parameters were also recorded.

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Conclusions:

- Our study suggests that majority of ECG abnormalities in high altitude are transient/benign in nature and do not suggest an increased risk of cardiovascular disease whether evaluated by Framingham Risk Score or structural/functional evaluation by 2D Echocardiography/Treadmill Test.
Healthy males inducted to HA

ECG screening for age > 35 years during acclimatization

ECG abnormality in HA (study population) (54 subjects screened)

Admitted in hospital

Risk factor assessment
(Age, smoking, alcohol, dyslipidemia, obesity) (Haematological, biochemical, radiological and urinary investigations)

2D Echo & TMT

Any abnormality further evaluated by CAG and cardiologist consultation

Fig. 1: Flowchart depicting study procedure

Fig. 2: Frequency of subjects with ECG abnormality according to the duration spent in high altitude

around the long axis of the heart with backward rotation of the apex and T wave inversions in right precordial leads. 10

The aim of the present study was to study the clinical profile of subjects with ECG abnormalities on ascent to HA and to identify the importance of ECG abnormalities in HA with relevance to CAD.

Material and Methods

The present study was conducted in a secondary care hospital having basic specialties and investigation facilities, located in the eastern sector of the country at an altitude of 2000 m. The study was carried out as a cross-sectional study over a period of one year (Nov 2017-Nov 2018). Study population consisted of all subjects meeting the eligibility criteria (healthy males between 20-60 years age, meeting the ECG abnormality criteria on ascent to HA and no previous comorbidity). All subjects with past history of ECG abnormality and previous comorbidities like Hypertension, Type 2 Diabetes Mellitus, Cerebrovascular Accident etc were excluded from the study. Sample size was calculated to be 54 based on the formula:– (Zα)2 x p(1-p)/d2; where Zα= 1.96 for 95% confidence interval, p= 0.036 proportion of asymptomatic subjects with ECG abnormality, d= acceptable deviation. Convenience sampling technique was used to select the study participants. Study protocol was approved by institutional ethics committee and performed in accordance with the Declaration of Helsinki. Informed written consent was obtained from all the participants before including them in the study.

Brief Procedure

All the study participants were transferred from Medical Establishments co-located with HA posts. All subjects more than 35 years of age were screened for ECG abnormality. All those who were detected to have ECG abnormality in HA were admitted to these Medical Establishments and subsequently transferred to our hospital located at a lower altitude (2000 m) for further evaluation. All subjects with ECG abnormality in HA were interviewed about family history of sudden death, consumption of tobacco and alcohol, continued exposure to certain drugs (beta blockers, calcium channel blockers), history of thyroid disorder and history of prior chronic illnesses. A complete physical examination was carried out including pulse, blood pressure, respiratory rate, temperature, height, weight, body-mass index, thyroid examination and complete systemic examination. 12 lead ECG was recorded by 12 channel Bionet ECG machine model No – 9108. All the study participants were then subjected to necessary haematological, biochemical and radiological investigations. Haematological investigations consisted of complete hemogram (to exclude polycythemia). Biochemical investigations included blood urea, serum creatinine and urine examination (to rule out kidney disease), serum potassium (to screen for electrolyte abnormality), thyroid profile (to screen for thyroid disorder) and liver function tests (to rule out liver disease). These subjects also underwent structural and functional study of the heart by 2D Echo and TMT. Those found to have a positive TMT underwent Coronary Angiography (CAG) and further risk stratification was subsequently carried out. A flow chart depicting the study procedure is shown in Figure 1.

Statistical analysis

The data was analysed using SPSS (Statistical Package for Social Sciences) version 22.0 software. Descriptive and inferential statistics were performed.

Results

A total of 54 subjects were included in the study. Mean age of the subjects was 40.6±3.7 years. Of these 51 (94.4%) subjects were detected to have ECG abnormality in the first stage of acclimatization. ECG abnormalities seen in HA are depicted in Table 1. Most common ECG abnormality was T wave inversion in frontally directed frontal plane leads seen in 16 (29.6%) subjects followed by T wave inversion in both inferiorly directed frontal plane leads and precordial leads noted in 13 (24%) subjects. Next most common ECG abnormality was T wave inversion in the precordial leads seen in 10 (18.5%) subjects. Other common abnormalities seen were Complete Right Bundle Branch Block (RBBB), Incomplete RBBB, ST depression in both frontal plane and precordial leads and Right Axis Deviation (RAD). Obesity was noted among 17 (31.5%) participants. and
Table 1: Frequencies of ECG abnormalities in high altitude

<table>
<thead>
<tr>
<th>ECG abnormality</th>
<th>Frequency</th>
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<tbody>
<tr>
<td>T wave inversion in limb leads</td>
<td>29.6%</td>
</tr>
<tr>
<td>T wave inversion in limb and precordial leads</td>
<td>24%</td>
</tr>
<tr>
<td>T wave inversion in precordial leads</td>
<td>18.5%</td>
</tr>
<tr>
<td>Complete RBBB</td>
<td>7.4%</td>
</tr>
<tr>
<td>Incomplete RBBB</td>
<td>3.7%</td>
</tr>
<tr>
<td>Right axis deviation</td>
<td>3.7%</td>
</tr>
<tr>
<td>ST depression and T wave inversion in limb leads</td>
<td>3.7%</td>
</tr>
<tr>
<td>ST depression and T wave inversion in limb and precordial leads</td>
<td>1.85%</td>
</tr>
<tr>
<td>Left bundle branch block</td>
<td>1.85%</td>
</tr>
<tr>
<td>Left ventricular hypertrophy</td>
<td>1.85%</td>
</tr>
<tr>
<td>Premature ventricular complexes</td>
<td>1.85%</td>
</tr>
<tr>
<td>Left anterior hemiblock</td>
<td>1.85%</td>
</tr>
</tbody>
</table>

18 (33.3%) participants were noted to be consuming tobacco in some or the other form. Nearly 25 (46.3%) subjects had spent less than 30 days in HA (Figure 2). Out of 54 only three (5.5%) subjects were found to be positive for inducible ischemia on Treadmill Test. All the three subjects however turned out to have a normal coronary angiogram. Only two (3.6%) subjects had abnormal 2D Echocardiography out of which one (1.8%) subject was detected to have reduced ejection fraction and was finally diagnosed to have Coronary Artery Disease. Only one (1.8%) subject had high risk of general cardiovascular disease and nine (16.6%) subjects had intermediate risk of general cardiovascular disease according to Framingham Risk Score. Out of these 10 subjects only one subject was found to be positive for inducible ischemia on TMT. However he also turned out to have a normal coronary angiogram.

Discussion

The present study was an attempt to document ECG abnormalities on ascent to HA, in asymptomatic healthy individual without any previous ECG changes and correlation of these changes with CAD. All the subjects underwent ECG evaluation before ascent to high altitude. This allowed us to document ECG abnormality occurring on reaching HA which could not be attributed to preexisting illnesses. In our study mean age of the subjects was 40.6 ± 3.7 years which could be attributed to the selection procedure itself since only asymptomatic individuals more than 35 years of age were included in the study. 54 (94.4%) subjects were found to have ECG abnormality in the first stage of acclimatization. This could be due to the effect of high altitude itself. This has been observed in a previous study in which 100% subjects developed ECG abnormality at HA. However they were directly inducted to an altitude of 4500 meter. It has also been observed that there is significant association between ECG abnormality and altitude. Odds ratio for abnormal ECG was found to increase significantly with every 1000 m increase in altitude. It was observed in the present study that the most common ECG abnormality was T wave inversion in inferiorly directed frontal plane leads. This was followed by T wave inversion in both inferiorly directed frontal plane leads and precordial leads. Another common abnormality seen was T wave inversion only in the precordial leads. These changes are likely due to overloading of the right ventricle because of changes in the pulmonary circulation and hypoxia. This finding is supported by previous studies conducted in HA. However a recent study conducted on highlander natives of Nepal concluded that ECG abnormalities were present on both sides of the heart, on the left side of the heart for Mustang participants (Tibetan origin) and on the right side of the heart for Humla participants (Indo-Aryans). The principal finding of our study was that the majority of ECG abnormalities in high altitude are transient/ benign and do not suggest an increased risk of cardiovascular disease since only three out of 54 subjects turned out to be positive for inducible ischemia on TMT evaluation and none of them were found to have any abnormality on coronary angiogram. Study conducted by Aryal et al. also concluded that HA populations of Humla and Mustang districts in Nepal had a prevalence of CHD comparable with that seen in low-altitude populations. It was also found that there is no association between ECG abnormality in HA in temporary residents and Framingham risk score since only one out of 54 subjects was found to be in high-risk category and only nine out of 54 subjects were found to be in the intermediate risk category. Only one out of these 10 subjects turned out to be positive for inducible ischemia on TMT but again had a normal coronary angiogram. This is in accordance with the latest US Preventive Services Task Force (USPSTF) recommendation which concluded that for asymptomatic adults at low risk of CVD events (individuals with a 10-year CVD event risk less than 10%), it is very unlikely that the information from resting or exercise ECG (beyond that obtained with conventional CVD risk factors) will result in a change in the patient’s risk category as assessed by the Framingham Risk Score. The authors have also observed that the majority of T wave inversions involving inferiorly directed frontal plane leads and right sided precordial leads reverted to normal within three to ten days of descent to a lower altitude. This observation is also supported by a previous study conducted on 202 healthy lowlanders inducted to HA, which concluded that ECG changes reverted to normal in 100% of individuals after descent to a lower altitude.

Conclusion

ECG abnormalities in high altitude are transient/ benign in nature and do not suggest an increased risk of cardiovascular disease whether evaluated by Framingham Risk Score or structural/ functional evaluation by 2D Echocardiography/ Treadmill Test.

Acknowledgements

Authors would like to thank their spouses, teachers, colleagues, nursing staff and most importantly the patients who participated in the study.

Declarations

Ethical approval

The study was approved by the Institutional Ethics Committee.

References

Serum Heart Type Fatty Acid Binding Protein Levels in Prediabetes-An Invaluable Cardiovascular Biomarker

Priyamvadha Ramesh¹, Ajay Chauhan²*, Parul Goyal³, Amrinder Singh⁴, Ayushi Singhal¹, Asmita Gupta¹

Abstract

Background: The pathophysiological effects of diabetes on the heart and the rest of the cardiovascular system begins much earlier in its precedent stage of prediabetes and one major underlying defect is insulin resistance. Heart-type fatty acid binding protein (H-FABP) is a recently studied molecule inherent to the cardiac myocytes found to rise in both coronary and non-coronary heart diseases. The utility of the molecule in prediabetes and its relationship with insulin resistance is being studied.

Objective: The aim of the study is to compare serum levels of H-FABP in prediabetics and controls and correlate them with Homeostatic model assessment – insulin resistance (HOMA-IR).

Methods: 50 prediabetic patients and 50 age, sex and BMI matched controls were employed in the case control study. Serum fasting and postprandial blood sugars, glycosylated hemoglobin (HbA1c), fasting insulin levels were measured in cases and controls. HOMA-IR index was calculated from fasting glucose and insulin values. Serum H-FABP was measured in both cases and controls using Immunoturbidimetric method with anti- H-FABP coated latex reagent kits. The values were compared between both the groups.

Results: The mean serum fasting insulin level among cases was 12.22mIU/ml and that of the control group was 5.37mIU/ml (p value <0.0001). HOMA-IR mean values were 3.31 ± 1.56 and 1.16 ± 0.44 in cases and controls respectively (p<0.001). The mean serum levels of H-FABP among cases and controls were 6.38± 2.76ng/ml and 3.24 ± 2.47 ng/ml respectively (p<0.0001). The correlation between the two variables, HOMA-IR and H-FABP was also found to be strongly positive (r=0.675). Linear regression analysis showed that for 1 unit increase in HOMA-IR, H-FABP increased by 1.095 and for 1 unit increase in fasting insulin, H-FABP increased by 0.038.

Conclusion: Prediabetics have a higher risk of cardiovascular morbidity when compared to normoglycemics with insulin resistance being the single most important contributor. Serum H-FABP levels are elevated in prediabetes representing a marker of subclinical cardiovascular disease (CVD).

Introduction

The Diabetes mellitus spectrum includes a group of disorders with hyperglycemia resulting from defects in either secretion or action of insulin or in some cases, both. Almost always a predecessor of type 2 diabetes (the most common type), prediabetes is a state of intermediate hyperglycemia and comprises of impaired fasting glucose (IFG) and impaired glucose tolerance (IGT). A study from South Asia found that there was an incidence of 29.5 for every 1000 person years for prediabetes and that the conversion degree of prediabetes to diabetes was 58.9%.¹

All components of the metabolic syndrome have found to be associated with an increased risk for coronary heart disease (CHD) worldwide but the so called ‘Asian Indian phenotype’ adds to the risk. Similar to diabetic heart disease, prediabetic cardiovascular morbidity is also on the rise. Studies on prediabetes and cardiovascular disease (CVD) show that the estimated relative risk (RR) was 0.97 to 1.30 for IGT and 1.12 to 1.37 for IFG.²

Heart-type fatty acid binding protein (H-FABP) belongs to a group of intracellular lipid chaperones, found abundantly in the cytosol of cardiomyocytes, and released into the bloodstream when the myocardium is injured.³ H-FABP has been studied as a diagnostic marker for acute coronary syndrome (ACS) and in other CVD like cardiomyopathy, heart failure, pulmonary embolism and atherosclerosis. Glatz JF et al also reported that experimentally induced...
diabetes causes a significant increase of the FABP content of rat heart and suggests that this finding could be due to the enhanced fatty acid utilization by a diabetic heart compared to a non-diabetic heart.4

Thus with the growing incidence of micro and macrovascular complications in diabetes, it becomes important to assess and diagnose the same in the preceding prediabetic state and undertake early interventions. The aim of this study is to measure the serum levels of H-FABP in prediabetics and thus CVD risk at an earlier stage and compare them with normoglycemics and also look for a possible correlation with insulin resistance parameters.

**Materials and Methods**

The study was conducted in the Departments of Medicine and Biochemistry at Post Graduate Institute of Medical Education and Research, Dr. RML Hospital, New Delhi.

Study Design: A case control study.

Sample Size The study group consisted of 50 consecutive patients of prediabetes and 50 control subjects from Medicine OPD, Medicine Wards and Medicine Emergencies of Dr. Ram Manohar Lohia Hospital after fulfilling all inclusion and exclusion criteria and matched for age, sex and ethnicity.

Study period: 1st November 2017 to 31st March 2019

**Calculation of Sample Size**

**Primary Objective**

To compare the levels of H-FABP in prediabetics and controls.

To achieve the primary objective, the input for statistical sample size calculation was taken from the study by Basek Karbek et al,2011.

Patients with impaired glucose tolerance showed a mean (±SD) of 32.5±34.2ng/dl and controls showed a mean ± SD of 16.8±14.9ng/dl.

With the above inputs, we considered a minimum difference of about 50% in H-FABP levels in prediabetics and controls.

With this information, the sample size was calculated as follows.

\[ n = \left( \frac{Z_{1-\alpha} + Z_{1-\beta}}{\text{difference}} \right)^2 \times \text{SD}^2 \]

We require a sample size of 49 on each side (for convenience, 50) to achieve the primary objective of comparing H-FABP between prediabetics and controls.

**Inclusion Criteria**

- 50 Cases of Prediabetes of age 18-65 years as defined by fasting plasma glucose between 100 to 125 mg/dL OR 2 hour postprandial glucose/2 hour oral glucose tolerance test (OGTT)(after 75 gm of glucose solution ingestion) between 140 to 199 mg/dL OR HbA1c = 5.7-6.4% (American Diabetes Association 2016).
- 50 control subjects, matched for age, gender, ethnicity and body mass index and with fasting blood glucose of less than 100mg/dl and 2 hour postprandial glucose/2 hour OGTT of less than 140mg/dl and with no known co-morbidities as per exclusion criteria.

[An informed bilingual written consent was taken from each of the patient/relatives for inclusion].

**Exclusion Criteria**

- Known Hypertensives.
- Known Diabetics
- Chronic smokers
- Chronic alcoholics
- Known cases of cerebrovascular accidents or transient ischemic attacks [TIA]
- Known hypothyroid or hyperthyroid patients.
- Known established cases of stroke, angina pectoris, myocardial infarction.
- Known cases of peripheral vascular disease and history of intermittent claudication.
- Patients with history of pulmonary embolism
- Known cases of chronic renal failure.
- Known cases of cardiomyopathy and heart failure.
- Known cases of Systemic Lupus Erythematosus (SLE), Vasculitis, malignancy and connective tissue disorders.
- Known retrovirus positive patients
- Patients on drugs like statins and other anti hyperlipidemic drugs and anti platelet or anti thrombotic drugs.

**Methods**

All the cases and controls underwent the following examinations and tests:

**Clinical Examination**

The study participants were called to the Department of Medicine, Dr. RML hospital and asked to fill a pre-determined questionnaire which included baseline data about age, sex, race, ethnicity and family history of diabetes or hypertension.

They then underwent a detailed clinical examination including measurement of height (using stadiometer), weight (using a weight measurement scale) and waist circumference at the upper borders of both hip bones (using a standard measuring tape). Body mass index (BMI) was calculated as weight (in kg) divided by the square of height (in meters). Resting systolic and diastolic blood pressures were recorded twice using an automated sphygmomanometer after a 5-min rest and average was calculated.

**Laboratory Investigation**

Around 10 mL of fasting blood sample was collected after venipuncture. Samples were taken in EDTA vial for glycated hemoglobin measurements. Plain (Red) vials were used to take samples for serum biochemistry including baseline biochemical parameters and separately for H-FABP.

Investigation done on the patients were

- Fasting plasma glucose,
- Post prandial plasma glucose
- Glycated haemoglobin (HbA1c),
- Fasting serum insulin levels, measured by Chemiluminiscence Immuno Assay (CLIA) onVitros ECiQ by Orthoclinical Diagnostics.

All of the samples were analyzed on a fully automated clinical chemistry analyzer in the Department of Biochemistry, PGIMER and Dr. RML hospital, New Delhi.

- Samples for H-FABP were
The basal state insulin resistance of the individual was calculated using the HOMA-IR (homeostatic model assessment of insulin resistance) using the formula, HOMA-IR =fasting plasma glucose (mg/dl)* fasting serum insulin (mIU/ml)/ 22.5.

**Serum Heart Type Fatty Acid Binding Protein**

Serum H-FABP kits were imported from Randox Laboratories, India. Separate kits for cases and controls along with the buffer agents and anti H-FABP latex coated reagents were used- Catalogue number: FB 4025 and FB 4026. The stored serum samples were analysed as a whole by immunoturbidimetric method.

**Principle of the Test**

The samples were assayed on the principle of immunoturbidimetry with the help of a H-FABP calibrator series. The samples were allowed to react with a buffer and anti H-FABP coated latex reagents and the formation of antigen-antibody complex during the reaction resulted in an increase in turbidity, the extent of which was measured as the amount of light absorbed at 700nm. By constructing a standard curve from the absorbance of the standards, H-FABP concentration in the sample was measured.

Measuring range of the kits was 0.747 – 120 ng/ml.

**Statistical Analysis**

Categorical variables were presented in number and percentage (%) and continuous variables were presented as mean ± SD and median. Normality of data was tested by Kolmogorov-Smirnov test. If the normality was rejected then non parametric test was used.

Quantitative variables were compared using Independent t test/ Mann-Whitney Test (when the data sets were not normally distributed) between the two groups. Qualitative variables were correlated using Chi-Square test/Fisher’s Exact test. Spearman rank correlation coefficient was used to find out the correlation of various parameters with each other. Univariate linear regression was used to find out the cause and effect relationship between various parameters. A p value of <0.05 was considered statistically significant. The data analysis was done using Statistical Package for Social Sciences (SPSS) version 21.0.

**Results**

The aim of our study was to assess the serum levels of the molecule H-FABP in patients with prediabetes and compare with the same in normoglycemics. It was a case-control study and after calculating the sample size (50) as per statistical analysis, 50 cases and 50 controls were enrolled. Matching with respect to age, sex, BMI, blood pressure and BMI was ensured. The following observations were made (Tables 1, 2).

We infer that for 1 unit increase in HOMA-IR, H-FABP increases by 1.095 and for 1 unit increase in Fasting insulin, H-FABP increases by 0.38.

---

**Table 1: Demographic and anthropometric characteristics among cases and controls**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Cases (n=50)</th>
<th>Controls (n=50)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>AGE (mean ± SD)</td>
<td>35.96 ± 4.48</td>
<td>35.94 ± 4.27</td>
<td>0.982</td>
</tr>
<tr>
<td>SEX (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Males</td>
<td>48(n=24)</td>
<td>54(n=27)</td>
<td>0.548</td>
</tr>
<tr>
<td>Females</td>
<td>52(n=26)</td>
<td>46(n=23)</td>
<td></td>
</tr>
<tr>
<td>BMI (mean ± SD)</td>
<td>24.07 ± 2.71</td>
<td>24.08 ± 2.70</td>
<td>0.99</td>
</tr>
<tr>
<td>Waist circumference (mean ± SD)</td>
<td>82.02 ± 9.22</td>
<td>80.11 ± 13.03</td>
<td>0.775</td>
</tr>
<tr>
<td>Systolic blood pressure (mean ± SD)</td>
<td>116.56±17.08</td>
<td>114.8±9.00</td>
<td>0.521</td>
</tr>
<tr>
<td>Diastolic blood pressure (mean ± SD)</td>
<td>73.76±14.25</td>
<td>73.52±5.68</td>
<td>0.811</td>
</tr>
</tbody>
</table>

---

**Table 2: Biochemical parameters among cases and controls**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Cases (n=50)</th>
<th>Controls (n=50)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fasting blood sugar</td>
<td>110.86±9.79</td>
<td>86.68±7.14</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Postprandial blood sugar</td>
<td>161.3±21.97</td>
<td>119.68±12.1</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>HbA1c</td>
<td>6±0.21</td>
<td>4.9±0.46</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Fasting insulin levels</td>
<td>12.22±5.42</td>
<td>5.37±1.95</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>HOMA-IR index</td>
<td>3.31±1.56</td>
<td>1.16±0.44</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Serum H-FABP</td>
<td>6.38±2.76</td>
<td>3.24±2.47</td>
<td>&lt;.0001</td>
</tr>
</tbody>
</table>
rather than plasma insulin levels, is disease. Hyperglycemia associated cardiovascular conditions, hence proving as a cardiac biomarker of diagnostic metabolic conditions, the increase in the levels noticed by the increase in the levels correlated with HOMA-IR indices, a subjects. The levels also positively prediabetics compared to normal increase in Fasting insulin, H-FABP increases by 1.095 and for 1 unit increase in HOMA-IR, H-FABP increases by 1.095, for 1 unit increase in HOMA-IR, H-FABP increases by 0.038. (Table 6).

Discussion

The study shows evidence of increased levels of H-FABP in prediabetics compared to normal subjects. The levels also positively correlated with HOMA-IR indices, a measure of insulin resistance. This signifies an alteration in the normal cardiovascular function in such patients as noticed by the increase in the levels of the molecule in various coronary and non coronary heart diseases and metabolic conditions, hence proving as a cardiac biomarker of diagnostic and prognostic significance for the hyperglycemia associated cardiovascular disease.

It was studied that insulin sensitivity, rather than plasma insulin levels, is associated with early atherosclerosis in diabetes and prediabetes. Studies report a link between the molecular pathways of insulin signaling and inflammation. The progression of IR to diabetes parallels the progression of endothelial dysfunction to atherosclerosis. The downregulation of the antiatherogenic phosphatidylinositol-3-kinase-mediated insulin receptor-signaling pathway, and maintained activity of the proatherogenic mitogenic-activated protein kinase pathway in insulin-resistant states, leads to accelerated atherosclerosis.

Factors like increased oxidative stress, coagulability, endothelial dysfunction, mitochondrial dysfunction are found associated with insulin resistance in diabetic humans and animals and are supposedly due to the metabolism of excess glucose and fatty acids in the hyperglycemic state contributing to the development of chronic inflammation and CVD.

H-FABP is a recently detected biomarker found to be released into the bloodstream in cases of myocardial injury, as researched in multiple studies. Okamoto et al and Azzazy HM et al proposed that H-FABP was an excellent biochemical marker for the diagnosis of acute Myocardial Infarction (MI) in the early phase and also in predicting further cardiac events in such patients. Farooq Ghani et al suggested that the magnitude of the increase in plasma H-FABP, released also might demonstrate a good correlation with the size of the infarction. Pelsers MM et al noticed that H-FABP proves to be an excellent early cardiac marker in detecting minor myocardial injury in heart failure and unstable angina, apart from ACS. Puls M and his colleagues concluded that H-FABP might be a promising indicator of early right ventricular injury in acute PE.

H-FABP has also been studied in pump-related clinical contexts like dilated and hypertrophic cardiomyopathy, endocardial fibroelastosis, Chronic Obstructive Lung Diseases (COPD) with cor pulmonale and left heart failure, showing significant differences in values pre- and post- treatments, with comparable or probably better results to pro-Brain Natriuretic Peptide (pro-BNP) and troponin T in heart failure syndromes.

Apart from the primary cardiac diseases, studies have been done in various metabolic conditions. Akbal et al researched that serum H-FABP levels were significantly higher in patients with both diabetes and metabolic syndrome thus representing latent cardiac injury. Oktay B and team hypothesised that H-FABP could be used as a marker of cardiac injury in the early asymptomatic period of obstructive sleep apnoea syndrome.
Başar Ö found that H-FABP levels were elevated in patients with Non-Alcoholic Fatty Liver Disease (NAFLD) and that they correlated positively with BMI, carotid intima-media thickness (CIMT) and HOMA-IR. Although there is quite a number of research done worldwide, there are limited Indian studies done on the molecule in diabetes and metabolic syndrome states.

The results of our study are in par with a similar study done by Basek karbek et al performed at the Endocrinology Department of Diskapi Yildirim Beyazit Training and Research Hospital in Turkey that showed that serum H-FABP levels significantly were increased in people with IGF and IGT when compared with the controls.20

Thus ours is probably the first case-control study of its kind in the Indian subcontinent to gauge the CVD risk in prediabetics through H-FABP and its correlation with markers of insulin resistance.

The spectrum of diabetes mellitus and its pathological effects is one of the major global health challenges in today’s world and identifying the disease and its major adverse effects at an early stage is the mainstay of primary and secondary prophylaxis of its complications. We, based on the results propose that the molecule, H-FABP can represent early asymptomatic heart disease in the form of coronary diseases (myocardial infarction, angina) and non-coronary diseases (heart failure, cardiomyopathy etc.) in these patients. Proactively identifying the marker in their serum before the patients develop the clinical disease would pave way for the physicians to diagnose CVD in dysglycemic patients earlier and manage them with diet, lifestyle and pharmacological measures, whenever necessary.

Further studies are required in a wider and mixed population to establish a relationship bringing ethnicity, geographical distribution into account and find how they affect individually, the values of H-FABP in prediabetics. Follow up studies are also essential to propose the prognostic utility in cardiac diseases in these patients. Studies on the employment of H-FABP as therapeutic targets for metabolic disorders like obesity, diabetes and atherosclerosis are ongoing and these promise future benefit.

Conclusion

Diabetes, or rather the entire spectrum of dysglycemic disorders comprising of Impaired fasting glucose (IFG), Impaired glucose tolerance (IGT) and Diabetes mellitus is associated with CAD, atherosclerosis and systolic and diastolic heart failures and insulin resistance plays a main causative role. H-FABP levels are increased in prediabetics, correlated with insulin resistance and thus predict early subclinical atherosclerosis and heart disease in them. It is imperative to have a high suspicion of such events in any patient with dysglycemia and strategies to devise methods to diagnose the same are warranted in the current scenario.

References

In T2DM, START EARLY with Glycomet®-GP 0.5 mg SR + Glimipride 0.3 mg

In uncontrolled T2DM, STEP UP with Glycomet®-GP 1 mg SR + Glimipride 1 mg

ACROSS THE SPECTRUM OF T2DM MANAGEMENT

FOREVER WITH YOU AS A GUIDING LIGHT

Data on file
In T2DM Patients

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Jalra-M

Vildagliptin 50 mg + Metformin 500 mg/850 mg/1000 mg

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CONTINUING THE LEGACY WITH >15 MILLION PATIENTS

Jalra

Jalra is an anti-diabetic medicine approved for the treatment of Type 2 Diabetes Mellitus (T2DM) as monotherapy or in combination with pioglitazone. It contains Vildagliptin, a DPP-4 inhibitor, which enhances incretin, and Metformin, which improves glucose disposal. Clinically proven benefits include faster achievement of glycaemic targets and improved HbA1c levels.

In T2DM Patients

Glycomet-S.R.

Metformin Hydrochloride Sustained Release Tablets 500 mg/850 mg/1000 mg

The Gold Standard Metformin

Let Glycomet be a part of Journey of every Insulin Resistant patient either alone or in combination

The only Metformin in India with widest range and 100% availability

**INDICATIONS:**
- Treatment of Type 2 Diabetes Mellitus
- Prevention of Macrovascular and Microvascular complications under the supervision of a physician

**DOSAGE AND ADMINISTRATION:**
- For Adults:
  - Initial dose: 500 mg once daily, increasing to 1000 mg once daily
  - Maximum dose: 2000 mg once daily
  - If lower dose required, may be given twice daily
  - Geriatric patients: Initial dose: 250 mg once daily, increasing to 500 mg once daily
  - Children: In patients weighing 50 kg or more: 500 mg once daily
  - In patients weighing less than 50 kg: 250 mg once daily

**CONTRAINDICATIONS:**
- Hypersensitivity to metformin or any other component
- Severe renal impairment (CrCl <30 ml/min)
- Severe hepatic impairment
- Lactic acidosis

**WARNINGS:**
- Monitor renal function regularly
- Avoid use in patients with history of hypoglycemia
- Monitor for weight gain and body mass index
- Monitor for hypoglycemia
- Consider discontinuing if adverse effects occur

**ADVERSE REACTIONS:**
- GI: Nausea, vomiting, diarrhea, abdominal pain
- Metformin: Lactic acidosis, severe hypoglycemia, severe hepatic impairment

**PRECAUTIONS:**
- Use with caution in patients with hepatic impairment
- Use with caution in patients with limited renal function
- Use with caution in patients receiving other drugs that may cause hypoglycemia

**INTERACTIONS:**
- Caution with use of drugs that may cause hypoglycemia
- Use with caution in patients with history of liver disease

**PREGNANCY:**
- Category B
- Use during pregnancy only if clearly needed

**NURSING MOTHERS:**
- Use with caution

**DOSE FOR DIABETIC KETOACIDOSIS:**
- Use with caution

**OVERDOSAGE:**
- Monitor for hypoglycemia

**HOW SUPPLIED:**
- Tablets of 500 mg, 850 mg, and 1000 mg

**PHARMACOLOGICAL CATEGORY:**
- Biguanide

**INFORMATION FOR PATIENTS:**
- Avoid alcoholic beverages
- Avoid strenuous exercise
- Consult healthcare provider before initiating or discontinuing treatment

**REFERENCES:**

**NOT FOR USE IN PATIENTS WITH SEVERE LIVER DYSFUNCTION OR IN PREGNANCY.**
The Most Economical & Widely Available Statin Combination

For Primary & Secondary Prevention

**Active 4 for Active Heart**

- **Ecosprin AV 75**
  - Enteric Coated Aspirin 75 mg + Atorvastatin 10 mg

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  - Enteric Coated Aspirin 75 mg + Atorvastatin 20 mg

- **Ecosprin AV 150**
  - Enteric Coated Aspirin 150 mg + Atorvastatin 10 mg

- **Ecosprin AV 150/20**
  - Enteric Coated Aspirin 150 mg + Atorvastatin 20 mg
IT TAKES A *rose-vala statin*
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Roseday®-10
Rosuvastatin 10 mg

Rapid & Robust Plaque Stabilization
Rosuvastatin 10mg > Atorvastatin 20mg¹

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¹ Based on clinical studies. *Roseday®-10mg & Roseday 20mg are bioequivalent to the branded drug.*
In type 2 diabetes uncontrolled on dual therapy,

Choose Glycomet® Trio
Glimepiride+Metformin+Voglibose

Choose

\[
\begin{align*}
1000 & \quad 2000 \\
1000/1000 & \quad 1000/1000 \\
& \quad 1000/1000 \\
& \quad 1000/1000 \\
\end{align*}
\]

Forte 1000
Forte 2000

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with CONVENIENCE

---

In Primary and Secondary Prevention of CVD,

Ecosprin 75 150 325
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An Ecosprin a day, keeps heart attack away

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By India - Of India - For India

A step towards CAD THE SOCIETY

*IMS MAT Dec 2018. # AIOCD MAT Jan 2020*
Role of Pulse Oximetry and Ankle Brachial Index in Diagnosis of Lower Limb Artery Disease (LEAD) in Patients with Coronary Artery Disease

Anoop Jain¹, Ganesh Seth²*, Sanjay Parmar³, Harikishan Srivastava⁴, Sarita⁵

Abstract

Background: Lower extremity arterial disease is a common cardiovascular disease that is estimated to affect approximately 202 million individuals worldwide¹ and increases with aging. LEAD is associated with significant morbidity, mortality, and quality of life impairment². LEAD esp. when symptomatic is more prevalent in men in high-income countries but in low and middle-income countries it is more prevalent in women.¹ Although the prevalence of critical limb ischemia is low (0.4%), the total number of individual having LEAD is increasing with a 23% increase in the prevalence in last decade as a result of total population increase, aging, increased incidence of diabetes and smoking worldwide.¹ In India, Peripheral artery disease of the lower extremity is an important cause of morbidity and affects 10 million peoples.³

Atherosclerosis is the most common cause of LEAD worldwide; and since it is a generalized disorder and involves medium and large sized arteries. Many patients with symptomatic peripheral artery disease (PAD) have evidence of coronary artery disease (CAD) based on clinical presentation and electrocardiogram and coronary angiography. The high prevalence of combined CAD and PVD has been confirmed in two large international studies—the REACH (Reduction in Atherothrombosis for Continued Health) registry and the AGATHA (A Global Atherothrombosis Assessment) study in which 16 to 35% of patients (with established atherosclerotic disease or three or more risk factors) had polyvascular disease.¹,² The presence of combined lower extremity PVD and CAD is associated with nearly doubled all-cause mortality, to 4.6% per year, compared with either disease alone.⁴

The diagnosis of PAD begins with clinical suspicion in the typical patient population. Increased rates of PAD have been demonstrated in patients with coronary artery disease, cerebrovascular disease, diabetes, and renal failure.²,⁴ In 75% cases peripheral vascular disease is asymptomatic. In 25% cases peripheral vascular disease is symptomatic with intermittent claudication, coldness and numbness of feet, weakness of lower limb, dependent rubor, non-healing ulcer and gangrene. The most commonly ascribed symptom that develops as a result of PAD is intermittent claudication (IC). Most epidemiologic studies have used a noninvasive measurement, the ankle-brachial index (ABI), to diagnose PAD. The ABI is the ratio of ankle to brachial systolic blood pressure.

Pulse oximetry measures peripheral blood hemoglobin saturation of oxygen (SaO₂). Pulse oximetry is a well-established method for non-invasive evaluation of arterial oxygenation. As the blood flow to the limb distal to stenosis decreases the limb develop coldness and numbness along with other ischemic changes like gangrene and ulcer because of hypoxia of limb. There are few studies that have shown that SaO₂ measurement by pulse oximetry can detect LEAD.

Introduction

Lower extremity artery disease is a common cardiovascular disease that is estimated to affect approximately 202 million individuals worldwide¹ and increases with aging. LEAD is associated with significant morbidity, mortality, and quality of life impairment². LEAD esp. when symptomatic is more prevalent in men in high-income countries but in low and middle-income countries it is more prevalent in women.¹ Although the prevalence of critical limb ischemia is low (0.4%), the total number of individual having LEAD is increasing with a 23% increase in the prevalence in last decade as a result of total population increase, aging, increased incidence of diabetes and smoking worldwide.¹ In India, Peripheral artery disease of the lower extremity is an important cause of morbidity and affects 10 million peoples.³

¹Senior Professor and Ex-HOD, Cardiology, SMS, Jaipur, Rajasthan; ²Associate Consultant, Interventional Cardiology, Medanta, Lucknow, Uttar Pradesh; ³Associate Consultant, Interventional Cardiology, Shri Balaji Action Medical Institute, New Delhi; ⁴Consultant Cardiologist, Popular Hospital, Varanasi, Uttar Pradesh; ⁵Resident, B.B.D.C.O.D.S., Lucknow, Uttar Pradesh; *Corresponding Author Received: 05.10.2018; Accepted: 20.12.2019
My study aims at establishing the role of ABI and pulse oximetry in detection of LEAD.

Methods

This study is hospital based observational study. The patients with admitted to department of cardiology S.M.S. Medical College and hospitals were enrolled. Study duration was 12 months.

Exclusion criteria’s were patients with (1) Patients with renal failure, (2) digital necrosis/gangrene of an toe hampering spo2 measurement, (3) cardiogenic shock or COPD having decreased saturation in all four limbs, (4) Absent pulsetile waveform in limb in spo2 probe and (5) B/L upper limb PAD.

Oxygen saturation (SaO2) of index figure of upper limb and 2nd or third toe in lower limb was measured with the patients in the supine position and at 12-in elevation of the foot, using a pulse oximeter at room air. Before measurement patient advised to wash hands and feet and allowed to dry at room temperature and nail polish if applied was removed. ABI was calculated as ratio of ankle to brachial systolic blood pressure. Ankle pressure was measured by pneumatic cuff placed around the ankle is inflated to suprasystolic pressure. Ankle pressure was measured by pneumatic cuff placed around the ankle and subsequently deflated while the onset of flow is detected with a Doppler ultrasound probe placed over the dorsalis pedis or posterior tibial arteries, thus denoting ankle systolic blood pressure.

Definitions

Abnormal pulse oximetry was defined as a SaO2 value of more than 2% lower in the toes than finger value in supine or a decrease of more than 2% on 12-inch elevation of the leg (decrease from the value at the supine position). An abnormal ABI was defined as less than 0.9. For the combination of ABI and pulse oximetry, we defined a positive test result as either an ABI of less than 0.9 or a decrease in SaO2 of more than 2%, as described herein; a negative test result for the combination was an ABI of 0.9 or more and an SaO2 decrease of 2% or less. Significant LEAD was defined as the presence of monophasic waveforms at any one of the lower extremity arteries during Doppler waveform analysis and/or more than 50% stenosis of aortoiliac or CFA disease on CTA.

Statistical analysis

Sensitivity, specificity, and likelihood ratios were derived for abnormal pulse oximetry and ABI results to detect LEAD and for the combination of the two were calculated.

Results

We enrolled total 224 patients (448 limbs) in the study. Detailed history and examination was performed. Patient characteristics are given in Table 1. Mean age of patients was 54.4±12.3 years. Most of the patients, 206 (92%) were smoker and male 197 (88%). Out of 56 patients 36 patients were diabetic, 64 were hypertensive.

We found that significant LEAD was found in 152 limbs (34%) on the basis of CTA and Doppler examination. Pulse oximetry and ABI data is given in Table 2.

As indicated in the tables, the ABI test had better test characteristics but with 95% CIs that overlapped with the pulse oximetry test results.

Pulse oximetry has a Sensitivity of 60.5% (95%CI; 52.2-68.3%), Specificity of 95.9% (95%CI; 93-98%), and Positive likelihood ratio 14.93 (95%CI; 8.45-26.3%) and Negative likelihood ratio 0.41 (95%CI; 0.34-0.5%). ABI has a Sensitivity of 69.7% (95%CI; 61.7-76.9%), Specificity of 97.3% (95%CI; 94.7-99%), and Positive likelihood ratio 25.8 (95%CI; 12.9-51.5) and Negative likelihood ratio 0.32 (95%CI; 0.12-0.40%).

So, in our study, ABI was found more sensitive than pulse oximetry in the detection of LEAD. However when the both tests are used in combination, Sensitivity increases to 84.2% (95%CI; 77.4-89.6%), Specificity decreases to 91.9% (95%CI; 88.2-94.8%), and Positive likelihood ratio 10.32 (95%CI; 7-15.33%)
and Negative likelihood ratio 0.17 (95% CI: 0.12-0.25%).

Our study suggests that although inferior to ABI, pulse oximetry also has the sensitivity of 60% and specificity of 95% for detection of LEAD and when used in combination with ABI sensitivity increases and there was more chances of accurately identifying the patients with LEAD.

Discussion

In our study, we found that difference in the oxygen saturation between fingers and toes assessed by pulse oximetry in the supine or 12-inch elevation of lower limb is at least as accurate as ABI in detection of lower limb arterial disease. However the combination of both has better sensitivity than when used alone.

LEAD is a risk factor for increased total mortality, morbidity and QOL impairment.9-10 This risk seems to persist for more than 10 years in patients with peripheral arterial disease.19 Jawahar et al. compared the pulse oximetry in symptomatic LEAD and normal individuals and had negative results and concluded that oximetry is not very sensitive test for asymptomatic LEAD.20

Our study suggests that pulse oximetry is at least as accurate as ABI and is an effective additional method for the screening of LEAD. However when used in combination with ABI the sensitivity for the detection of LEAD increases. Pulse oximeters are widely available in patient care areas and easy to use. The technique of measuring SaO₂ is well known, simple, noninvasive, and inexpensive tool, which gives quick result and thus makes it a good screening tool.

The limitations of this study are as follows: (1) the small number of patients; (2) performance of the tests on a specific patient population group and study population does not represent general population overall so results may not be generalized.

In conclusion, these results suggest that pulse oximetry may be a useful additional tool to screen for LEAD in high-risk patients. It has a sensitivity and specificity nearly similar to the ABI. Larger studies are needed to confirm how it compares with the ABI. When combined with the ABI, the results for the combination of the two tests are superior to the ABI or pulse oximetry alone in detecting LEAD in these patients.

References

Relationship between Serum Levels of Pregnancy Associated Plasma Protein A and Coronary Artery Disease in Males

Prattay Guha Sarkar 1*, Gabjender Ranga 2

Abstract

Objectives: The availability of a sensitive and specific early marker of plaque instability, whose levels become elevated before or even in the absence of myocardial necrosis, should improve diagnostic and therapeutic decision making in Acute Coronary Syndromes. This analytic cross-sectional study was designed to estimate the serum levels of Pregnancy Associated Plasma Protein A (PAPP-A), highly sensitive C reactive protein (hs-CRP) and creatinine phosphokinase MB (CPK-MB) in patients of old myocardial infarction, unstable angina, non ST elevation and ST elevation myocardial infarction and to assess their correlation with plaque instability.

Methods: Male patients of Coronary Artery Disease aged between 40 to 60 years were recruited in to the four study groups: Healthy controls; Old Myocardial Infarction, not having features of acute coronary syndrome; Unstable Angina, non ST elevation myocardial infarction and ST elevation Myocardial Infarction. Appropriately timed blood sample collection was done and serum levels of PAPP-A, hs-CRP and CPK-MB were estimated. Qualitative cardiac troponin T was done in all patients. Appropriate statistical tests were applied and intergroup comparison was done.

Results: Serum levels of PAPP-A were found to be significantly different in all the four groups (p<0.001) with highest values observed in patients of ST elevation myocardial infarction (26.38 ± 4.10 IU/l) as compared to controls (3.29 ± 0.93). The serum levels of PAPP-A has a statistically significant positive correlation with the mean serum levels of CPK-MB with a correlation coefficient (R²) of 0.781 and a p value of <0.001. Thus, it may be useful in diagnosing ACS, especially in cardiac troponin T negative patients.

Conclusion: Serum levels of PAPP-A is a sensitive and specific early marker of plaque instability, whose levels become elevated before or even in the absence of myocardial necrosis. This marker can improve diagnostic and therapeutic decision making in Acute Coronary Syndromes.

Introduction

Indian subcontinent is facing an epidemic of coronary artery disease (CAD). It is house to nearly 70 million patients suffering from atherosclerotic cardiovascular disorders. A Acute coronary syndromes – Unstable angina, Non ST elevation myocardial infarction (NSTEMI) and ST elevation myocardial infarction (STEMI) are major causes of death in patients with CAD. B Unstable atherosclerotic plaque is a major mechanism of development of acute coronary syndrome (ACS) from stable CAD. Several biomarkers of ACS have been identified. These include creatinine phosphokinase-MB (CPK-MB), cardiac troponin T (cTnT), brain natriuretic peptide, high sensitive C-reactive protein (hs-CRP), myeloperoxidase, pregnancy associated plasma protein-A (PAPP-A), metalloproteinase-9 etc. These biomarkers play important role in risk stratification and treatment strategies in patients with ACS. The availability of a sensitive and specific early marker of plaque instability, whose levels become elevated before or even in the absence of myocardial necrosis, should improve diagnostic and therapeutic decision making.

Pregnancy Associated Plasma Protein-A is one such marker and its serum levels have been shown to rise further with the severity of ACS. Thus there is room for improvement regarding the available early diagnostic and risk assessment approaches used in the management of coronary patients. PAPP-A is a screening marker for Down’s syndrome pregnancies. It is also present in human fibroblasts and released during rupture of atherosclerotic plaque. Since PAPP-A was found to be elevated in patients of ACS in 2001, its role as either a diagnostic or prognostic marker for CAD has been an interesting area of research. The hypothesis behind current study is that the process of transformation from stable to unstable plaque might be reflected by increase in levels of PAPP-A. Unlike Troponin T or I, PAPP-A has fewer causes of false positivity, so it can be used for the accurate diagnosis of ACS.

Methods

Subjects and design

This study used an analytic cross-sectional design. Written informed consent was taken from both patients and controls prior to enrollment into the study. The study comprised of the following four groups with 30 males in each group between age 40-60 years. Group A: Healthy controls. Group B: Old myocardial infarction, not having features of acute coronary syndrome. Group C: unstable angina and non ST elevation myocardial infarction (UA/NSTEMI). Group D: ST elevation myocardial infarction (STEMI). Patients with renal disease [blood urea > 40 mg/dl, serum creatinine levels >1.5mg/dl] or post real transplant patients, inflammatory conditions on clinical history and examination, terminal
**Table 1: Comparison of serum hs-CRP levels in study groups**

<table>
<thead>
<tr>
<th></th>
<th>Group A (Control) (n=30)</th>
<th>Group B (Old MI) (n=30)</th>
<th>Group C (UA/NSTEMI) (n=30)</th>
<th>Group D (STEMI) (n=30)</th>
<th>p values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean ± SD</td>
<td>2.44 ± 0.63 (2.4-4.1)</td>
<td>4.20 ± 0.98 (3.1-6.9)</td>
<td>5.52 ± 1.81 (3.0-8.1)</td>
<td>8.80 ± 1.60 (7.1-12.1)</td>
<td>A vs B = 0.01</td>
</tr>
<tr>
<td>Range</td>
<td>1.97-2.95</td>
<td>3.67-5.10</td>
<td>7.37-9.12</td>
<td></td>
<td>C vs B &lt; 0.001</td>
</tr>
</tbody>
</table>

p values significant at <0.05 and highly significant at <0.001; All values have been described as mean ± SD and range

**Table 2: Comparison of serum CPK-MB in study groups**

<table>
<thead>
<tr>
<th></th>
<th>Group A (Control) (n=30)</th>
<th>Group B (Old MI) (n=30)</th>
<th>Group C (UA/NSTEMI) (n=30)</th>
<th>Group D (STEMI) (n=30)</th>
<th>p-values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean ± SD</td>
<td>18.27 ± 4.04 (11-24)</td>
<td>19.93 ± 3.67 (11-24)</td>
<td>77.67 ± 75.85 (11-221)</td>
<td>396.57 ± 163.70 (166-876)</td>
<td>A vs B = 0.487</td>
</tr>
<tr>
<td>Range</td>
<td>15-21</td>
<td>16.75-21.25</td>
<td>21-154.50</td>
<td>257.25-458.50</td>
<td>C vs D &lt; 0.001</td>
</tr>
</tbody>
</table>

p values significant at <0.05 and highly significant at <0.001; All values have been described as mean ± SD and range

**Table 3: Comparison of serum levels of PAPP-A in study groups**

<table>
<thead>
<tr>
<th></th>
<th>Group A (Control) (n=30)</th>
<th>Group B (Old MI) (n=30)</th>
<th>Group C (UA/NSTEMI) (n=30)</th>
<th>Group D (STEMI) (n=30)</th>
<th>p-values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean ± SD</td>
<td>3.29 ± 0.93 (1.99-5.23)</td>
<td>6.66 ± 1.13 (7.2-11.11)</td>
<td>16.02 ± 4.11 (11.23-23.4)</td>
<td>26.38 ± 4.10 (19.09-32.0)</td>
<td>A vs B = 0.001</td>
</tr>
<tr>
<td>Range</td>
<td>2.22-4.01</td>
<td>7.86-9.64</td>
<td>12.38-19.82</td>
<td>23.65-29.68</td>
<td>C vs D &lt; 0.001</td>
</tr>
</tbody>
</table>

p values significant at <0.05 and highly significant at <0.001; All values have been described as mean ± SD and range

**Table 4: Correlation of serum levels of PAPP-A with hs-CRP and CPK-MB in study groups**

<table>
<thead>
<tr>
<th></th>
<th>CPK-MB (n=120)</th>
<th>hs-CRP (n=120)</th>
<th>P value PAPP-A vs CPK-MB</th>
<th>P value PAPP-A vs hs-CRP</th>
</tr>
</thead>
<tbody>
<tr>
<td>PAPP-A</td>
<td>0.781</td>
<td>0.840</td>
<td>&lt; 0.001</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

p-value significant at <0.05 and highly significant at <0.001

Statistical Analysis

One way ANOVA was used to calculate p-values for separate groups of parametric data. Kruskal-Wallis and Wilcoxon W test was used to calculate p-value for separate groups of non-parametric data. Spearman’s rank order correlation was used to determine coefficients for nonparametric measures of association. A p-value < 0.05 was considered to be statistically significant and a p-value < 0.001 was considered to be highly significant.

Results

Serum level of hs-CRP was found to increase with the severity of coronary artery disease. Mean value of hs-CRP in group A (controls), B (old myocardial infarction), C (UA/NSTEMI) and D (STEMI) were found to be 2.44 ± 0.63 mg/dl, 4.20 ± 0.98 mg/dl, 5.52 ± 1.81 mg/dl and 8.80 ± 1.60 mg/dl respectively. There was statistically significant difference in the serum level of hs-CRP in all the four groups (p < 0.05) (Table 1).

Serum level of CPK-MB was also found to increase with the escalating severity of coronary artery disease. It was normal in controls, patients of old myocardial infarction and patients of unstable angina. Mean values of CPK-MB in group A (controls), B (old myocardial infarction), C (UA/NSTEMI) and D (STEMI) were found to be 18.27 ± 4.04, 18.93 ± 3.67, 77.67 ± 75.85 and 396.57 ± 163.70 IU/l respectively. There was statistically significant difference in the serum level of CPK-MB in all the four groups (p < 0.001) (Table 2).

Serum levels of PAPP-A were found to be significantly different in all the four groups. Highest values were observed in patients of ST elevation myocardial infarction. Mean values of PAPP-A in group A (controls), B (old myocardial infarction), C (UA/NSTEMI) and D (STEMI) were found to be 3.29 ± 0.93, 8.66 ± 1.13, 16.02 ± 4.11 and 26.38 ± 4.10 IU/l respectively (Table 3).

The serum levels of PAPP-A had a statistically significant positive correlation with the mean serum levels of CPK-MB with a correlation coefficient (R^2) of 0.781 and a p value of <0.001. Furthermore, the serum levels of PAPP-A also has a statistically significant positive correlation with the serum levels of hs-CRP with a correlation coefficient (R^2) of 0.840 and a p value of <0.001. (Table 4)

Intergroup analysis of correlation between CPK-MB and PAPP-A revealed that serum levels of PAPP-A correlated strongly with the serum levels of CPK-MB in patients of UA/NSTEMI and STEMI. Correlation coefficient (R^2) calculated in patients of UA/NSTEMI is 0.777 and in patients of STEMI is 0.812. However, the correlation of serum levels of PAPP-A with CPK-MB was not significant statistically in patients of old myocardial infarction and healthy controls. Mean serum levels of PAPP-A correlated weakly with the mean serum levels of hs-CRP in patients of UA/NSTEMI and patients of STEMI.
Table 5: Intergroup correlation of serum PAPP-A, CPK-MB and hs-CRP

<table>
<thead>
<tr>
<th>Serum PAPP-A</th>
<th>Serum PAPP-A</th>
<th>Serum PAPP-A</th>
<th>Serum PAPP-A</th>
<th>p values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group A (n=30)</td>
<td>0.014</td>
<td>0.011</td>
<td>0.777</td>
<td>0.812</td>
</tr>
<tr>
<td>Group B (n=30)</td>
<td>0.014</td>
<td>0.011</td>
<td>0.777</td>
<td>0.812</td>
</tr>
<tr>
<td>Group C (n=30)</td>
<td>0.014</td>
<td>0.011</td>
<td>0.777</td>
<td>0.812</td>
</tr>
<tr>
<td>Group D (n=30)</td>
<td>0.014</td>
<td>0.011</td>
<td>0.777</td>
<td>0.812</td>
</tr>
</tbody>
</table>

p-value significant at <0.05 and highly significant at <0.001 (Table 5).

Further, mean serum levels of PAPP-A were found to correlate directly with the size of infarct in patients with STEMI. It was found to be highest in patients with anteroseptal STEMI compared to patients of inferior wall STEMI and anterior wall STEMI. Serum PAPP-A levels had a very strong correlation with mean serum CPK-MB levels in all patients of STEMI. Mean serum levels of PAPP-A were found to be highest in NYHA class IV patients compared to patients in other functional classes. Furthur, mean serum level of PAPP-A was higher in cTnT positive patients compared to cTnT negative patients and the difference was statistically significant.

Discussion

The results of our study show that all patient groups of CAD had a higher mean serum level of PAPP-A. Interestingly the levels increased progressively as the severity of CAD increased. On intergroup comparison it was found that the mean serum levels of PAPP-A were significantly different of all patient groups of CAD had a higher mean serum level of PAPP-A. hs-CRP levels were significantly different as well.

On intergroup comparison it was found that the mean serum levels of PAPP-A show a progressive rise with the increase in unstable plaque burden in patients of CAD. The results of our study show a progressive rise with the increase in unstable plaque burden in coronary artery disease. The results of our study are in accordance with the pioneering work done by Bayes-Genis et al. They had observed substantially and significantly higher PAPP-A levels in acute myocardial infarction and in unstable angina than in control subjects (20.6 mIU/L vs. 14.9 mIU/L vs. 7.4 mIU/L) with a p-value of <0.01.

Further, using a cut off value of 10 mIU/L it was possible to identify ACS patients with a sensitivity of 89.2% and specificity of 81.3%. The results of our study further highlight the value of PAPP-A as a robust biomarker for the diagnosis of ACS, as all our patients had values greater than 10 mIU/L. The lowest value in our patients of UA/NSTEMI was 11.23 mIU/L. A significantly lower serum level of PAPP-A was found in the control subjects of our study. If we use a cut off value of 10 mIU/L then the sensitivity of the test, according to our study, is 100%. It was found that the serum levels of PAPP-A was significantly higher in patients of CAD as compared to other study subjects. Patients of UA and NSTEMI had serum levels of PAPP-A lower than patients of STEMI. Patients of old myocardial infarction with stable CAD had further lower serum levels of PAPP-A. Lowest serum levels of PAPP-A was found in the control subjects.

This progressive rise in the serum level of PAPP-A may be because of its release from unstable plaque and progressive increase in the plaque instability in patients of severe CAD and ACS. In view of the available data and the results of our study, it can be concluded that serum PAPP-A level is a highly sensitive and specific biomarker for ACS. The serum levels of PAPP-A correlate with the severity of ACS and can be used to predict the outcome of ACS.

A progressive increase in the serum levels of hs-CRP was noted with the increase in the severity of CAD. hs-CRP levels correlate with the clinical severity of coronary artery disease and with coronary events in both acute and sub-acute phase of myocardial ischemia. Patients who are hospitalized for treatment of acute coronary syndrome have and have raised CRP levels have significantly more ischemic episodes during hospital stay than patients with lower CRP levels.

Sub-group analysis also revealed that statistically significant correlation between the serum levels of PAPP-A and CPK-MB was present only in patients of UA/NSTEMI and STEMI. There was no statistically significant correlation found in healthy controls and patients of old myocardial infarction. Our results are in accordance with those of You et al. In stable CAD patients, CPK-MB levels do not increase, but as is evident from the results of our study, serum PAPP-A levels increase in the patients of stable CAD as compared to controls, reflecting the presence of potentially unstable plaque.

So it may be concluded from our study that PAPP-A in peripheral blood may reflect the instability of plaque. It can help to accurately make diagnosis of ACS in Troponin negative patients or in patients with false positive Troponins. Future studies are required to assess further the serum levels of PAPP-A as a potential biomarker for plaque instability. It has to be seen whether it can predict plaque rupture in future. Larger studies with greater number of subjects are required to further confirm our observations.

References

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Physician Burnout: Cause and Prevention Strategies

Umesh Sharma¹, Shashank R Joshi², Amit Ghosh³

Abstract
Ongoing evolution in healthcare places physicians under an ever-increasing pressure to consistently perform at a higher level, leading to a significant number of physicians including those in training feeling “burnt-out”. Burnout is a result of interplay between personal characteristics and environmental factors. Unaddressed physician burnout negatively affects the individual, work environment and most importantly patient care. Individual and environmental changes are needed to assess and effectively manage burnout. Stigma and fear of professional consequences, especially among regional doctors appears to be an important barrier to access services and address burnout. There is an ever increasing need to expand the Triple Aim (enhancing patient experience, improving population health, and reducing costs) to a Quadruple Aim that goal of improving the work life of health care providers, including clinicians and staff.

Introduction
Caring for the patient is a fundamental reason why people including physicians choose to work in the healthcare profession. Healthcare has been undergoing tremendous evolution as a result of various factors like increased demand for services for an aging population, changing payer mix with reducing reimbursements, electronic medical records, newer regulations and compliance responsibilities. This places physicians under an ever-increasing pressure to consistently perform at a higher level, hence creating a demoralizing misalignment of physician’s values and need for quality patient care causing a “moral injury”. Unaddressed moral injury eventually leads to burnout. Burnout is affecting a significant number of physicians including those in training and has created an epidemic that needs to be acutely addressed. ¹

It is vital to understand why physicians burn out, manage burn out and create strategies and tactics to prevent burnout to engage and retain a vital and productive workforce.

Understanding Burn Out
Maslach and Jackson in 1981 defined burnout as an occupation stress in human service professionals (teachers, doctors, nurses etc.) causing emotional exhaustion.²

Burnout can be characterized by three components which include depersonalization, emotional exhaustion and low personal accomplishment/experience of ineffectiveness. Burnout is now a well-recognized syndrome and has the potential of creating a negative reaction to one’s work, it most time comes with a feeling of dissatisfaction, hatred and complain.²

World Health Organization has now defined burn-out as a syndrome resulting from chronic workplace stress that has not been successfully managed. It is characterized by three dimensions: 1) feelings of energy depletion or exhaustion; 2) increased mental distance from one’s job, or feelings of negativism or cynicism related to one’s job; and 3) reduced professional efficacy. Burn-out refers specifically to phenomena in the occupational context and should not be applied to describe experiences in other areas of life.³

Donald Berwick has stated that a clash between a new era of measurement and accountability targeting quality, errors, costs, inequities and a traditional physician autonomy lies at the root of this growing crisis.⁵

Prevalence of burnout
Although, the prevalence varies amongst different specialties, it affects clinicians from all specialties including medical students and residents. Physicians who work in the front line like emergency department, primary care, neurology etc. tend to have higher rates of burnout. A nationwide survey by Shanafelt et.al, revealed a 54.4% prevalence of at least one burnout symptom amongst 6880 US physicians from various specialties with about 7.6% decline in work-life in a 3-year period from 2011-2014.⁶ A 2018 survey of US physicians by Merritt Hawkins reported that 55% of physicians have a somewhat or very negative morale while 78% often, sometimes or always experience feeling of burnout.⁷ Emergency medicine physicians tend to suffer from some of the highest levels of burn out.⁸ Some potential reasons include: heavy work load with resultant inability of physicians to fully perform their duties to patients and not be able to give 100% attention to patients, high patient turnover, and resource limitations.⁹

High level of burn out is not only limited to Emergency medicine, but also prevalent in non-front line departments like Physical Medicine and Rehabilitation (PM&R). A national survey by Sliwa et. al, showed 50.7% of 1,536 physiatrists met the definition of burnout. Increasing regulatory demands, workload and job demands, practice inefficiency and lack of resources was again identified as top factors.¹⁰

Every one point (on a seven point scale) increase in burnout is associated...
with 30–40% increase in likelihood that physicians will reduce their workhours and professional exit in next two years. Burn out has even started to affect future physicians including medical students and residents because of added stress of study in addition to work.

Medicine is a team sport that includes interaction with nursing colleagues, who unfortunately are also facing burn-out. Burnout in nursing staff tends to negatively affect their work-satisfaction, quality of care and their intent to leave their job.

Physicians identify physician patient relationship as the most satisfying part of medical practice, while loss of autonomy, time with patient, and EHR are the greatest source of professional dissatisfaction that negatively affects quality of care, patient interaction and efficiency.

Factors causing burnout

Burnout is a result of interplay between personal characteristics and environmental factors as mentioned in Table 1. Individual factors like having no spouse, work-life imbalance and personality traits like being self-critical, compulsiveness, perfectionism, or delayed gratification can create additive stress in an otherwise already stressful workplace. Hobbies and interests can also help provide a mechanism for delaying gratification, and practicing skills that can be easily mitigated, and existential burnout that is linked to how residents view themselves within the context of their developing role as physicians and needs intervention.

Table 1: Factors predisposing to burnout

<table>
<thead>
<tr>
<th>Individual-related</th>
<th>Environmental-related</th>
</tr>
</thead>
<tbody>
<tr>
<td>Personality traits: compulsiveness, perfectionism</td>
<td>Unmanageable workloads</td>
</tr>
<tr>
<td>Delayed gratification,</td>
<td>Lack of autonomy and involvement in decisions affecting the practice</td>
</tr>
<tr>
<td>Social support</td>
<td>Chaotic and inefficient work environment</td>
</tr>
<tr>
<td>Hobbies and interests</td>
<td>Lack of alignment amongst physicians and executives regarding mission, values, purpose and compensation</td>
</tr>
<tr>
<td>Optimism and emotional regulation</td>
<td></td>
</tr>
</tbody>
</table>

Unaddressed physician burnout negatively affects the individual, work environment and most importantly patient care. Burnout can lead to an individual feeling tired, exhausted, inattentive, and depressed, leading to substance abuse, practice departures, and potentially suicidality. Physician turnover can lead to avoidable physician-replacement costs to the practice and also lead to sub-optimal interpersonal work relationships. Patient care can be adversely affected by increased medical errors, malpractice, reduced patient satisfaction, and poor quality and outcomes.

Similarly trainees can experience professional development limitations, personal consequences including suicide, and can affect patient care adversely. Burnout and stress can lead to hypertension, depression, and anxiety amongst our nurse colleagues.

A recent study estimated that the cost of physician burnout in US around $4.6 billion a year.

This cost was attributable to physician turnover, reduced productivity, and estimated price of advertising for the vacated position, hiring and training. At the organizational level it was estimated that the annual burnout cost was estimated around $7600 per physician per year.

Studies have shown that aside from the anxiety, depression, insomnia, emotional and physical exhaustion, and loss of cognitive focus associated with physician burnout, an estimated 300 to 400 U.S. physicians take their own lives every year. Physician suicide rates are higher than the suicide rate for the general public by 40 percent for men and 130 percent for women.

Diagnosis

Burnout is evident when one sees a variation in performance in an otherwise good performer, leading to suboptimal clinical interactions or interpersonal interactions. Being proactive is better than being retroactive while managing this critical issue. Many standardized surveys are available like Maslach Burnout inventory, Oldenburg Burnout Inventory, Copenhagen Burnout Inventory etc.

Prevention and management of physician burnout

In recent years there has been substantial research and evidence on prevention and management of burnout. Organizations can support restructuring of physician workflow and provide resources to promote focus groups, wellness programs, and reduce work and administrative responsibilities. Linzer et.al have recommended a 10-step approach to prevent physician burnout. These focus on individual and institutional priorities.

Since individual characteristics like difficulty in balancing personal and professional life, paying little or no attention to wellness, work-alcoholism, and genetic factors increase an individual’s susceptibility to burnout, hence seemingly if these issues are checked, there should be a decrease in burnout. Emotional regulation either by self or taught or interventions like mindfulness have been reported to be beneficial for burnout management.

In order to reduce the level of burnout, an individual has to be mindful about it and try to check the factors that led to it. Some suggested strategies include implementation of regulations, working space and time, and pursue opportunities that are of value to the physician. Research of academic internal medicine faculty by Shanafelt et.al demonstrated an inverse relationship of time spent on meaningful work activity (> 20%) and burnout.

Self-limited circumstantial burnout is reversed by resolving the triggering workplace challenge like conflict, nurturing personal lives, and taking time-off from work. While existential burnout that arises from uncertain professional role or loss of meaning in medicine needs the following: feeling validated, connecting with
Table 2: Strategies to prevent and manage burnout

<table>
<thead>
<tr>
<th>Individual (physician wellness)</th>
<th>Social support</th>
<th>Hobbies and interests outside work</th>
<th>Environmental (Organization, Regulatory)</th>
<th>Improve EMR-usability</th>
</tr>
</thead>
<tbody>
<tr>
<td>Healthy lifestyle</td>
<td>Professional support (Focus group, Wellness programs)</td>
<td>Physical activity like sports</td>
<td>Application Programming Interface (API) will allow third parties to develop apps</td>
<td></td>
</tr>
<tr>
<td>Self care skills</td>
<td>Employee assistance programs</td>
<td>Travel, Volunteering</td>
<td>AI to allow third parties to develop apps</td>
<td></td>
</tr>
<tr>
<td>Emotional regulation skills</td>
<td>Statewide physician health programs</td>
<td>Meditation</td>
<td>AI to support clinical documentation and quality and regulatory compliance</td>
<td></td>
</tr>
<tr>
<td>Resiliency training</td>
<td>Wellness programs with effective Chief Wellness Officers</td>
<td>Manageable workflows</td>
<td>Safe Haven non-reporting of appropriate treatment for mental health and substance abuse</td>
<td></td>
</tr>
<tr>
<td>Social and family interactions</td>
<td></td>
<td>Effective workflows</td>
<td>API to allow third parties to develop apps</td>
<td></td>
</tr>
<tr>
<td>Professional support</td>
<td></td>
<td>Flexibility and autonomy in job</td>
<td>AI to support clinical documentation and quality and regulatory compliance</td>
<td></td>
</tr>
<tr>
<td>(Focus group, Wellness programs)</td>
<td></td>
<td>Career development opportunities</td>
<td>Safe Haven non-reporting of appropriate treatment for mental health and substance abuse</td>
<td></td>
</tr>
</tbody>
</table>

Table 2 further summarizes strategies to combat burnout.

**Barriers to implementation**

Stigma and fear of professional consequences, especially among regional doctors appears to be an important barrier to access services and address burnout. Although there has been increased awareness and research in psychosocial and behavioral interventions, the quality of evidence remains low. There is also a rising concern that efforts are focussed more on increasing resilience and wellness rather than managing the uncontrolled evolution and practice of current era medicine. Hence, we may be treating the symptom rather than the disease.

**Conclusion**

Burnout not only affects the physicians personally but has been a factor in patient harm, hence health care organizations have an inherent responsibility to prevent and manage physician burnout. Healthcare organizations need to invest in the psychological health of their physician and other employees, since a resilient and non-burnt workforce would be able to adequately handle the physical and emotional needs of patients they care for. Hence, there is an ever increasing need to expand the Triple Aim (enhancing patient experience, improving population health, and reducing costs) to a Quadruple Aim that goal of improving the work life of health care providers, including clinicians and staff.

Many organizatos like Mayo Clinic have come up with comprehensive strategies to address burnout. Some key features include: recognizing burnout as a threat to healthcare, use common metrics and identify drivers of burnout using staff surveys, implement strategies to mitigate these factors and share best available evidence.

**References**


8. Rothenberger DA. Physician Burnout and Well-Being. A.

Colleagues and patients, finding meaning in medicine, and redefining a professional role and identity.

Volunteering, which is supposed to improve mental health, has been postulated as a strategy to combat burnout. According to Iserson, many physicians feel like they are not fulfilling their roles like they ought to, hence short-term global medicine experiences may reinvigorate and reengage clinicians who are suffering or at high risk of persistent burnout syndrome while simultaneously befitting medically underserved populations.

Healthcare organizations can modify environmental factors that contribute to burnout. Autonomy within workplace, career development opportunities positively correlate with workplace engagement and resiliency. Addressing communication, workflow challenges and initiating quality improvement projects that target clinician concerns can help improve burnout and retention.

Burnout focus group maybe be able to come up with some practical strategies that require minimal resources to implement like: compulsory daily coffee breaks, increasing self- and organizational awareness of the risks of burnout and mentoring or buddy systems. Workplace wellness programs that are led by an executive-level chief wellness officers help employees with early recognition of burnout and create effective strategies and tactics to provide social and organizational support to sustain behavior change.

Other organization supported strategies could include utilization of nurse practitioners or medical assistants to decrease physician workload, mitigate stresses contributing to burn-out, and reallocate more physician time to procedures. Organizations can optimize career fit and promote physician satisfaction and help to reduce attrition among academic faculty physicians.

State Medical societies like Massachusetts can create statewide physician health programs that reach out to hospitals and physicians and provide confidential mental healthcare. The Federation of State Medical Boards (FSMB) has called on state medical boards to offer “safe haven” non-reporting of physicians who have received appropriate substance abuse and mental health treatment and remain in good standing.

Innovative ways will be needed to reduce EHR burden and increase usability. Use of open health care Application Programming Interface (API) will allow third parties that can improve EHR usability and efficiency. Artificial intelligence (AI) technologies will need to be developed to support clinical documentation, quality and regulatory compliance.

Many organizations like Mayo Clinic have come up with comprehensive strategies to address burnout. Some key features include: recognizing burnout as a threat to healthcare, use common metrics and identify drivers of burnout using staff surveys, implement strategies to mitigate these factors and share best available evidence.
doi/10.1377/hblog20180914.711688/full/.
Congenital malformations of the heart can range from complex malformations which are fatal to innocuous structural anomalies with no clinical consequences. Clinicians should be aware of the different varieties so as to decide on the correct prognosis and advise further treatment and follow up for the patients. We here describe a benign congenital structural abnormality of the heart in a young female.

A 12 year old girl was brought to the outdoor clinic before her school sports event. She had participated in athletic sports in the past without any significant problems. But this time, she complained of some non-specific chest discomfort, not related to exertion and was brought in for a check-up. Clinically, she was normal with regular pulses, normal heart sounds and normal blood pressure. There were no stigmata of congenital heart disease.

As a part of the routine check-up, she underwent screening for dyslipidemia and diabetes, both of which came out to be normal. An electrocardiography was done, which was also normal. Finally an echocardiography was done, which revealed (Figure 1) a net-like flimsy structure in the right atrium which revealed (Figure 1) a net-like fenestrated structure found infrequently near its junction with the inferior vena cava. The structure was mobile, not prolapsing into any chamber and not attached with any vegetation. There was no regurgitation of the tricuspid valve. Atrial septum was intact. After review by two experts, this was diagnosed as Chiari network, a congenital anomaly of the heart. The girl was declared fit for any sports event and she participated in athletics without any symptoms.

Chiari network is a net like fenestrated structure found infrequently in the right atrium.1 This is embryonic remnant of valves of sinus venosus, and hence usually lie in close relation with the inferior vena cava (IVC).1 In our case also, the structure was found near junction of the IVC. First described in 1897, this structure has been found to be present in the heart in a variable proportion (2-13%) of the general population.2 Usually it is of no clinical significance and only rarely, it is associated with infective endocarditis, arrhythmia or thromboembolism.2 One other rare complication of the Chiari network is mechanical obstruction to invasive cardiac procedures. Other cardiac structural defects may be associated with the Chiari network, the most common being patent foramen ovale and atrial septal aneurysm.3

Usually no treatment is needed for the Chiari network. If it is a site of embolism or arrhythmia, it may be resected through right atriotomy.4

Echocardiography is usually adequate to diagnose a chiari network.5 The condition is usually asymptomatic and diagnosed incidentally during echocardiographic screening for other purposes. The network is well visible in all standard echocardiographic windows like apical four-chamber, parasternal long axis and subcostal views.5 Sometimes it may be confused with vegetations or cardiac tumour. Cardiac MRI may be done for better characterisation.5 But this is not routinely needed and experienced echocardiologists can diagnose it with confidence. Routine screening of athletes, as in our case, may reveal Chiari network rarely. But it is not considered a contra-indication to athletic participation.5

We present this case to sensitize clinicians to this benign echocardiographic finding. Knowledge of the benign nature of this embryonic remnant will help to avoid unnecessary investigations and anxiety for the patient.

References

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A Tale of Three Nodules
Amanda Dave\(^1\), Vishisht Mehta\(^2\), Carrie Valenta\(^2\)

**Introduction**

Panic attacks are common and typically present with episodes of spontaneous and acute fear that lasts a variable length of time, up to one hour. Somatic features may appear, and agoraphobia is also commonly associated with panic attacks. Due to somatic features and the diversity of presentations, panic attacks can mimic other disease states such as hyperadrenalism and hyperthyroidism. Substance abuse is also commonly considered in the differential. Thus, it is imperative in the evaluation of a patient in acute distress to consider all possible diagnoses.

**Case Report**

We report a case of a 45-year old Caucasian female with a past medical history of fibromyalgia, depression, and a benign right adrenal tumor removed 3 years prior. She presented to the emergency department with a five-day history of weakness, cold sweats, shaking, dizziness, visual changes and headaches. She also described a severe headache with non-radiating pressure-like pain alleviated by rest and exacerbated by movement. Vital signs were significant for an elevated blood pressure (166/37 mm Hg) and tachycardia (122 bpm). An initial EKG revealed sinus tachycardia. On examination, the patient was visibly agitated and shaking. Neurologic examination demonstrated bilateral horizontal nystagmus and bilateral patellar hyperreflexia. In the emergency department, she received two doses of lorazepam which alleviated her agitation.

Two weeks prior to admission, gabapentin was discontinued due to suicidal ideations and the patient had begun duloxetine for fibromyalgia.

At this juncture, the differential included serotonin syndrome, pheochromocytoma, thyroiditis, adrenal tumor, and carcinoid syndrome. Due to her recent medication changes, serotonin syndrome was high on the differential; gabapentin, duloxetine and tramadol were discontinued (Table 1). The Hunter criteria for serotonin syndrome requires the presence of at least one of the following features: spontaneous clonus, tremor and hyperreflexia, hypertonia, or inducible clonus with agitation or diaphoresis, or a fever above 100.4 ° F (38° C). The patient did have hyperreflexia but did not have tremors; nor did she have spontaneous or inducible clonus. While the patient had bilateral nystagmus, which can be mistaken for ocular clonus, the two are separate entities. She was also afebrile. As the patient did not meet the Hunter criteria, serotonin syndrome was ruled out.

With a family history of thyroid disease and the possibility of thyroid pathology, further workup was pursued. Initial evaluation with an ultrasound of the thyroid revealed a 1.3 cm isoechoic posterior mid-inferior indeterminate thyroid nodule with minimal internal vascularity. The TSH level was 0.15 U/mL. A 24-hour thyroid uptake scan (Figure 1) revealed

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**Fig. 1**: Thyroid Uptake Scans: At four hours, uptake - 1.3% (normal 5-15%) and at twenty-four hours was 1.2% (normal 15-35%). The impression of very low uptakes indicated a subacute thyroiditis in the setting of subclinical hyperthyroidism

**Fig. 2**: CT scan revealed a 1.2x1.1 cm right adrenal nodule highly suggestive of a lipid poor adrenal adenoma

**Fig. 3**: CT scan revealed a normal sized liver with a 6mm hypodense lesion within the lateral aspect of the hepatic segment, suggestive of a possible cyst

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Panic attacks can present with abrupt onset of extreme trepidation that can last for minutes up to an hour. A panic disorder is diagnosed when panic attacks are recurrent without expectation or with more than a month of anxiety or changes in behavior due to fear of attacks. There is a two-fold risk of panic disorders in women compared to men; having first degree relative or a twin with panic attacks also increases an individual’s risk.  

Panic disorders can present in different ways and can co-exist with other conditions. It is imperative for the clinician to have a broad differential. 

Physiologic symptoms of a panic attack include but are not limited to: sweating, feelings of choking, chest pain/discomfort, chills, fear of dying, and paresthesia. There are a number of symptoms associated with panic attacks, but at least four must occur to be considered a panic attack (II). Panic attacks can also cause hyperventilation, trembling, dizziness, and chest pain (3). Agoraphobia may develop secondary to panic attacks, and individuals with panic attacks are at an increased risk for suicide attempts and substance abuse. 

The emergency department frequently becomes the first stop for patients with recurrent panic attacks. This can result in redundant and expensive work ups; patients at risk for panic attacks should be identified to preserve resources and improve patient care. 

Considerations on the differential 

Paroxysmal supraventricular tachycardia (PSVT) can be confused for panic disorders. In a study that assessed 107 patients with PSVT, symptoms were initially attributed to panic or anxiety in 54% of the patients. In a pair of case reports, two patients had both PSVT and panic disorders; panic disorders were not terminable by vagal maneuvers, and patients were able to identify when they were having a panic attack as opposed to PSVT. 

Pheochromocytoma, a catecholamine producing tumor, was considered on the differential as well. Pheochromocytomas are found on the adrenal medulla, while secreting paragangliomas are found on extra-adrenal chromaffin cells. A pheochromocytoma should be suspected in a patient who has sweating, tachycardia, and a headache; early-onset hypertension or hyperadrenergic spells can also increase suspicion. Secreting paragangliomas tend to be more asymptomatic as compared to pheochromocytomas, but patients can present with an increase in catecholamine secretion; it can also be an incidental finding on imaging. Laboratory evaluations to investigate if a patient has a pheochromocytoma or a secreting paraganglioma include measuring urinary and plasma catecholamines and fractionated metanephrines. Furthermore, a pheochromocytoma or paraganglioma can be identified through imaging if symptoms or laboratory testing warrant it. 

Subacute granulomatous thyroiditis usually presents with neck pain and hyperthyroidism, which then progresses to euthyroidism and subsequently hypothyroidism. A hyperfunctioning thyroid nodule, or ‘hot’ nodule, can also mimic panic attacks or other etiologies in our differential. Thus, thyroid disease was an important consideration. 

Paroxysmal hypertension could also be considered on the differential. Patients with paroxysmal hypertension, also known as pseudopheochromocytoma, have surges in sympathetic activity without an underlying organic cause. In such patients, it is critical to reassure the patient that a catastrophic event is unlikely. Patients with carcinoid syndrome experience wheezing and abdominal pain as well as diarrhea; laboratory values will show elevated levels of blood serotonin and urine 5-hydroxyindoleacetic acid. 

Management of Panic Attacks 

Psychotherapy, such as cognitive behavioral therapy, is encouraged to help patients cope and to decrease the frequency of attacks. Pharmacologic interventions for panic attacks include SSRIs, SNRIs, and benzodiazepines.  

Medication reconciliation and appropriate communication with different members of the healthcare team is of vital importance. Medication reconciliation prior to discharge has been shown to decrease medication changes at discharge as well as the need for discussions with the hospitalist after discharge. Such practices reduce the likelihood of medication interactions, of which serotonin syndrome can be a dangerous and unwanted consequence. Medication reconciliation is especially important in cases where adverse effects of medications are part of the differential. In our case, the use of duloxetine was a red flag for consideration of serotonin syndrome as the culprit for the constellation of symptoms. 

Conclusion 

In cases of complicated patient presentation, it is important to systematically rule out differential diagnoses. Panic attacks are common and can mimic a myriad of other
Sine Scleroderma

Gurdeep Kaur1, Sweta Banka2, Baldev Meena3, Avinash Kulkarni4, Rajesh Prajapat4, Jeevraj Dhaka4

Abstract

Systemic sclerosis (SSc) is a connective tissue disorder of unknown aetiology. A small subset (10%) of patients with limited systemic sclerosis have all other features of the disease without any skin involvement and is known as systemic sclerosis sine scleroderma (ssSSc). Severe Critical Limb Ischaemia is rare in sine scleroderma. The present case showed severe critical limb ischaemia with severe PAH, Esophageal dysmotility, Glomerulonephritis (a rare association) with hypertension. Although skin thickening is considered as a hallmark of systemic sclerosis, there should be a high index of clinical suspicion in patients presenting with possible manifestations of systemic sclerosis without sclerodermatous cutaneous involvement because early diagnosis and treatment can reduce the morbidity and mortality in it.

Introduction

Systemic sclerosis (SSc) is a connective tissue disorder of unknown aetiology. Skin thickening is considered as a hallmark of it, which distinguishes it from other connective tissue disorders. On the basis of pattern of skin involvement, it is broadly classified into diffuse and limited variety. Diffuse systemic sclerosis (dcSSc) involves skin of extremities, face and trunk while limited systemic sclerosis (lcSSc) involves only distal extremities and face with no involvement of trunk. A small subset (10%) of patient with limited systemic sclerosis has all other features of the disease without any skin involvement and is known as systemic sclerosis sine scleroderma (ssSSc).

Case Report

A 70 year old female presented to emergency department of R.N.T. medical college with complaints of blackish discoulouration of fingers of hand over last 4 months. It started from ring finger of left hand, gradually progressing to involve middle finger of right hand and then middle finger of left hand. Past history of bluish and reddish discoulouration of fingers on exposure to cold water, cold wind since 2 years, suggestive of Raynauds phenomena. History of easy fatiguability since 3

Fig. 1: Dry gangrene involving right index finger (upto pip), left hand ring finger (uptopip), middle finger right hand (middle phalanx). Flexure contracture of right middle finger. Normal skin pinching. No signs of thickening of skin

Fig. 2: X-ray showing – distal osteolysis

References

months. No past history of any medical or surgical disease. No history of similar complaints amongst any family members. Patient was non-alcoholic and non-smoker.

**On examination**

General examination—pulse rate 84/min, regular, normal volume, no radio radial delay, no radio femoral delay, arterial wall normal, all peripheral pulses present and equally palpable. Blood pressure 200/100 in right arm, sitting posture; respiratory rate 20/min and she was afebrile. Her JVP was raised. Pallor was present. No edema, icterus, clubbing. Dry gangrene of right index finger and middle finger and left ring finger of present (Figure 1A and B).

Cardiovascular examination revealed loud P2 with no murmur. Rest systemic examination revealed no abnormality.

Blood parameters revealed HB=9.0g/dl, ESR=35, TC=5,000/mm3, platelet=2.26 lacs/mm3, SE sodium=135, SE potassium =6.0, SE urea=48, SE creatinine=0.38, LFT=WNL, CRP+(11.57, upper limit being 5).

Urine examination: positive for protein (1+), RBCS (20-22/HPF), pus cells (10-20/HPF), calcium oxalate crystals ++, 24 hours urine albumin = 0.81gm/day (significantly greater).

X-ray showed distal osteolysis (Figure 2).

USG abdomen: mild cholelithiasis, rest findings were normal.

Her echo revealed: mild concentric LVH, normal LV systolic function (EF=60%), type 1 diastolic dysfunction, severe PAH, no clot/veg/embolus.

Colour doppler study of bilateral upper and lower limbs was normal.

CECT chest: fibrotic changes in bilateral upper lobes.

All these investigations suggested vasculitis, we got her ANA profile done with following results—positive for anticientromere antibodies by EIA (200 RU/ml, normal range from laboratory being 0-20 RU/ml). Other autoimmune conditions were ruled for overlap syndrome (RF/DS-DNA/APLA/SCL-70/RNP/SSA/SSB/ANCA).

We also got a skin biopsy done which had normal hpe findings.

Upper GI endoscopy revealed pangastropathy, barium swallow study—lower esophageal dysmotility (Figure 3).

Finally she was diagnosed to have sine scleroderma. She was started on losartan 50 mg OD, nifedepin 20 mg BD. After 2 weeks of followup she still complained of pain in her fingers. We added sildenafil 50 mg BD. After consultation with rheumatologist and dermatologist she was given cyclophosphamide pulse therapy (500 mg once in every 4 weeks). Patient’s symptoms have improved considerably with no further progression of ischaemia. She was also given a CTVS opinion for amputation of gangrenous digits for which she refused and was willing to wait for autoamputation.

**Discussions**

Systemic sclerosis is a chronic connective tissue disease that typically affects skin and internal organs by widespread micro vascular damage and excessive deposition of collagen. Annual incidence of it in USA is about 20 cases per million adults. Women are around 4 times more likely than men to develop it. To facilitate its accurate diagnosis, American College of Rheumatology has given preliminary classification criteria in 1980, according to which there is one major and three minor criteria. Major criteria include skin thickening proximal to MCP joints whereas minor criteria include sclerodactyly, digital pitting scars and bibasilar pulmonary fibrosis. Utility of these criteria is to distinguish it from other connective tissue disorders. It’s further classified into limited and diffused variety based on the presence and extent of skin involvement.
Limited systemic sclerosis involves skin distal to elbow and knees only, whereas diffuse variety involves proximal extremities and/or trunk in addition to distal thickening. Face can be involved in both forms. In diffuse variety systemic complications like interstitial lung disease and renal crisis are more common whereas in limited variety pulmonary arterial hypertension is more common. Most of these patients have positive antinuclear antibody by indirect immunofluorescence (85-90%).

Amongst scleroderma specific antibodies, anti-Topoisomerase (Scl-70) and antiRNA polymerase III is more specific for diffuse variety whereas anti-Centromere is more specific for limited variety. Systemic sclerosis sine scleroderma is a variant of limited systemic sclerosis which has all other features of this disease except the skin involvement. The first report of it was published by Abrahm et al. in 1954. This disease is not a separate entity but a part of a single disease spectrum. Compared to limited cutaneous systemic sclerosis it has no significant difference in internal organ involvement, antibody type or prognosis but there is a greater frequency of pulmonary artery hypertension in it. According to Poormoghim et al. its diagnosis should be considered if he or she has all of following: 1) Raynaud’s phenomenon, 2) Positive ANA, 3) Any one of following- distal oesophageal hypomotility, small bowel hypomotility, pulmonary interstitial fibrosis, pulmonary artery hypertension, cardiac involvement typical of scleroderma or scleroderma renal crisis and 4) no other defined connective tissue or other diseases as a cause of 1), 2), or 3). This diagnosis would be more convincing if ANA specificity was due to systemic sclerosis associated autoantibody. Most frequently associated serum autoantibody associated with it is anticientromere antibody. There are scarce data in the literature for systemic sclerosis sine scleroderma.

A 2014 case report published in JAPI Edition December 2014 showed Pulmonary artery hypertension as a presenting feature of it. A recent case showed severe critical limb ischaemia with severe PAH, Esophageal dysmotility, Glomerulonephritis (a rare association) with hypertension.

In conclusion, although skin thickening is considered as a hallmark of systemic sclerosis, there should be a high index of clinical suspicion in patients presenting with possible manifestations of systemic sclerosis without sclerodermatous cutaneous involvement because early diagnosis and treatment can reduce the morbidity and mortality in it.

References

Erratum
In the March 2020 issue of JAPI, Announcement entitled “Nomination for Member Board of PRF” the Announcement should read as follows:
1. On page 12 in, the last date for withdrawal of nomination is ‘08th March, 2020’, should be read as ‘08th April, 2020’.
Spontaneous Bilateral Subdural Hematoma in a Patient with Falciparum Malaria

Madan Mahesh Singh¹, Ratti Lal Meena², Rohit K Garg³, Mehul M Prajapati¹, Neera Samar⁴, Chirag Trivedi¹, Mayank Sharma³, Sourav Shristi³, Ankur Mittal³

Abstract
A 70-year-old female presented with complaints of fever with chills, headache for 15 days and altered sensorium for 7 days. Peripheral blood smear showed ring form of P. falciparum and CT brain revealed bilateral subdural hematoma. Patient received Artesunate based combination therapy and recovered completely without surgical intervention within 8 days of admission.

Introduction
Malaria is a protozoan disease transmitted by the bite of infected Anopheles mosquitoes. The most important of parasitic disease of humans.¹ India, along with Ethiopia, Pakistan and Indonesia accounts for 80% of all malarial cases worldwide. Infections with plasmodium falciparum and plasmodium vivax are the most prevalent.

Here we are reporting a case of P. falciparum malaria associated with unusual subdural hematoma (SDH) and thrombocytopenia that recovered without surgical intervention.

Case Report
A 70-year-old female presented with complaints of fever, chills, headache for 15 days and altered sensorium for 7 days was admitted to MBGH, Udaipur. There was no rash, petechiae or bleeding observed. There was hepatosplenomegaly on systemic examination. PBF smears showed a severe degree of thrombocytopenia (8000/microL). Detailed Microscopic Examination of Giemsa stained thin and thick PBF smears revealed infested RBC with ring form of P.falciparum. Serum analysis for liver function revealed elevated levels of total bilirubin (2.4 mg/dl), direct bilirubin (1.65 mg/dl), AST (85 U/L) and ALT (312 U/L). Serology for HIV, Salmonella and Dengue infections were negative. The patient was given parenteral Artesunate (2.4 mg/kg stat iv followed by 2.4 mg/kg at 12 and 24 h and then daily for 6 days) and parenteral clindamycin (10 mg/kg iv BD for 7 days). NCCT brain was done to rule out the cause of headache and altered sensorium. It revealed bilateral SDH (Figure 1). Neurosurgeon advised to manage the patient conservatively. Our patient improved completely with ACT regime. Patient became fully conscious and oriented within 5 days of admission and recovered completely.

Discussion
As per WHO proposed definition the features of severe malaria includes cerebral malaria, pulmonary oedema, circulatory collapse, DIC, anemia and hepatitis.² Unusual complication such as bilateral SDH is extremely rare and has been reported only in few cases like in falciparum malaria³⁴ or with cerebral malaria.⁵ Our case is being reported to emphasize the occurrence and amalgamation of severe clinical manifestation in p. falciparum. It is likely that the occurrence of SDH in this case is a secondary complication to thrombocytopenia.

Conclusion
An intrusive approach is required in diagnosing and recognizing multiple complications, which provides a complete and reliable picture of severe plasmodium infections allowing appropriate treatment and management.

References
1. Nicholas J White, Joel G Breman. Malaria 1368-1384.
Percy Lavon Julian

Pradeep Rangappa

Percy Lavon Julian (9 April 11, 1899 – April 19, 1975) was an American research chemist and a pioneer in the chemical synthesis of medicinal drugs from plants. He was the first to synthesize the natural product physostigmine and was an American pioneer in the industrial large-scale chemical synthesis of the human hormones, steroids, progesterone, and testosterone, from plant sterols such as stigmasteryl and sitosterol. His work would lay the foundation for the steroid drug industry’s production of cortisone, other corticosteroids, and birth control pills. He later started his own company to synthesize steroid intermediates from the Mexican wild yam.

During his lifetime he received more than 130 chemical patents. Julian was the second African American to receive a doctorate in chemistry. He was the first African-American chemist inducted into the National Academy of Sciences, and the second African-American scientist inducted from any field.

Reversal of muscle relaxants: Non-depolarizing neuromuscular block can be reversed by anti-cholinesterases. The first anticholinesterase to be used clinically was physostigmine, which was isolated from the calabash bean by Fraser in 1864; he called it “Eseria”. Physostigmine was synthesized by Percy Lavon Julian in 1935 along with Joef Pikl at De Pauw University and confirmed its structural formula. Robert Robinson of Oxford University was the first to publish a synthesis of physostigmine, but Julian noticed that the melting point was wrong for Robinson’s end product. When Julian completed his synthesis, the melting point matched the correct one for natural physostigmine from the calabash bean. By this time the synthetic anti-cholinesterase, neostigmine (prostigmine), was investigated clinically. After the advent of d-tubocurarine, neostigmine was found to be superior at reversing curare-like neuromuscular blocking agents. Used with atropine it remains the usual reversal agent worldwide.

Steroids: Julian’s research at Glidden changed in 1940 when he began work on synthesizing progesterone, estrogen and testosterone from the plant sterol stigmasteryl. Further, Julian isolated sitosterol from soybean oil by a foam technique he invented. At that time clinicians were discovering many uses for the newly discovered sex hormones. However, only minute quantities could be produced from the extraction of hundreds of pounds of spinal cords, testicles or ovaries.

In 1940 Julian was able to produce 100lb of mixed soy sterols daily, which had a value of $10,000 in sex hormones. Julian was soon ozonising 100 pounds daily of mixed sterol dibromides. The result was the female hormone progesterone which was put on the American market in bulk for the first time. Production of other sex hormones followed.
Introduction

Hypertension (HTN), a major cardiovascular (CV) risk factor, affects millions of individuals globally. A linear relationship has been reported between blood pressure (BP) and adverse CV outcomes. Although HTN manifests with diverse symptoms, such as headache, dizziness, shortness of breath, and palpitations, most HTN patients remain asymptomatic and are diagnosed incidentally. Occasionally, asymptomatic HTN may be severe enough to be declared as a hypertensive emergency and is seen in adults as well as in school children. Thus, screening of HTN is necessary across all age groups.

In India, HTN prevalence is colossal. Recent evidence indicates HTN prevalence of 25.3% in India. This necessitates screening for HTN in asymptomatic adults. The Ministry of Health and Family Welfare (MOHFW) of India has undertaken a project for HTN, diabetes, and cancer screening in individuals aged 30 years and above. However, this age cut-off excludes adults aged 18–30 years from screening. Conducting screening in this age group is essential as increasing prevalence of HTN individuals below 30 years has been reported. Additionally, other aspects of HTN screening like the rescreening interval remain unclear. Therefore, to guide the screening of individuals for HTN in India, a group of experts involved in HTN management provided their opinions to develop a unified consensus. This paper elucidates the consensus recommendations from 94 experts, which can guide healthcare professionals for performing effective HTN screening in asymptomatic individuals.

Need for a consensus

In India, there is an immense need to reduce increasing prevalence of HTN. However, HTN awareness, treatment, and control remain low. Increasing awareness can improve the control of HTN. Furthermore, the increasing prevalence of HTN in young adults (<40 years) and in school children (6–16 years) mandates early interventions in this age group to derive long-term benefits. Thus, to identify undiagnosed and asymptomatic HTN...
Moreover, the guidelines of the European Society of Hypertension (ESC/ESH) were referred to when discussing the approach to and statements. 14 Overall, 94 experts participated in the discussion by highlighting the key questions along with supporting evidence. After discussing each key question, the experts provided their opinion which was scored on a Likert scale ranging from 1 to 9. A mean score was calculated after voting by all the experts. A consensus statement was accepted if a mean score of 7 or higher was obtained from voting of more than two-thirds (66.6%) of the experts for each key statement. The consensus development process is summarised in Figure 1. The manuscript draft incorporating all the consensus statements was sent to all the experts who provided their comments. The final draft of the manuscript was reviewed, edited, and finalised by the core group experts.

**Consensus recommendations**

A discussion of the consensus recommendations from the expert panel is provided in following sections. Table 1 summarises all the expert recommendations and presents their mean scores on the Likert scale.

1. **Is screening for HTN in asymptomatic adults necessary?**

HTN is a growing epidemic in India. In a meta-analysis, Anchala et al. reported an overall prevalence of 30% and the prevalence rates of 33%–35% and 16%–33% in urban and rural settings, respectively. 9 A study conducted in New Delhi reported significantly increasing trends for HTN. The authors of that study reported results from two surveys conducted at a 20-year interval (1991–1994 and 2010–2012); they found that the prevalence of HTN significantly increased from 23.0% to 42.2% in urban settings and from 11.2% to 28.9% in rural settings. Similar increments were reported in pre-hypertension (Pre-HTN). Further, the highest rate of HTN increase was found in the youngest age group (35–44 years), with odds ratios (ORs) of 5.0 and 2.7 in urban and rural populations, respectively. 17 These results suggest the increasing prevalence of both pre-HTN and HTN in young individuals and has also been supported by multiple studies in India. 18-20 Additionally, most adults remain unaware of their HTN. In adults aged above 18 years, a prevalence of 26% for undiagnosed HTN has been reported. 19 Lower awareness has

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**Table 1: Summary of consensus recommendations**

<table>
<thead>
<tr>
<th>Key Area</th>
<th>Recommendation</th>
</tr>
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<tbody>
<tr>
<td>Screening</td>
<td>Screening for HTN in asymptomatic adults necessary.</td>
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<tr>
<td>Approach</td>
<td>A discussion of the consensus recommendations from the expert panel is provided.</td>
</tr>
<tr>
<td></td>
<td>Table 1 summarises all the expert recommendations and presents their mean scores on the Likert scale.</td>
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</table>
Table 1: Final consensus recommendations

<table>
<thead>
<tr>
<th>SN</th>
<th>Key question</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Screening for HTN in asymptomatic adults is necessary in India</td>
<td>8.7</td>
</tr>
<tr>
<td>2</td>
<td>Active screening for HTN can reduce the community burden of HTN and its associated complications</td>
<td>8.4</td>
</tr>
<tr>
<td>3</td>
<td>Appropriate age to initiate HTN screening should be ≥18 years</td>
<td>7.8</td>
</tr>
<tr>
<td>4</td>
<td>Targeted screening required in high-risk individuals</td>
<td>7.8</td>
</tr>
<tr>
<td>5a</td>
<td>Electronic BP recorder should be used for measuring BP during screening</td>
<td>8.2</td>
</tr>
<tr>
<td>5b</td>
<td>At least two BP readings are essential to identify HTN during screening</td>
<td>8.3</td>
</tr>
<tr>
<td>6a</td>
<td>In asymptomatic adults with BP &lt;130/85 mmHg, rescreening should be conducted every 3–5 years</td>
<td>7.1</td>
</tr>
<tr>
<td>6b</td>
<td>In asymptomatic adults with BP 130–139/85–89 mmHg, rescreening should be conducted annually at least</td>
<td>7.2</td>
</tr>
<tr>
<td>7</td>
<td>Universal screening for HTN targeting the entire population can be cost effective even in resource-limited settings</td>
<td>7.7</td>
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</table>

resulted in lower HTN treatment seeking behaviour, thereby contributing to the lower rates of HTN control. Thus, the increasing prevalence of HTN and pre-HTN, especially in young individuals, demands the careful screening of the entire population for the early detection of HTN. Screening for HTN is advocated globally by various organisations, including the World Health Organization, the World Hypertension League, and the MOHFW of India. Although screening has been recommended, the actual Indian population undergoing HTN screening remains unclear, which is in contrast to Thailand with a population coverage rate of 54.6% under HTN screening. Therefore, screening for HTN in the Indian asymptomatic adult population is urgently required. Voting from the 94 experts provided a mean score of 8.7, favouring the need for screening for HTN.

- Recommendation: Screening for HTN in asymptomatic adults is necessary in India.

2. Would active screening reduce HTN development and its associated complications and reduce the community healthcare burden?

Recently, the SPRINT trial provided evidence that reducing systolic BP intensively to a target of 120 mmHg was associated with lower rates of fatal and nonfatal major CV events and death from any cause. Some researchers question the methodology of the SPRINT trial, because BP was measured in the absence of a doctor or nurse. Nonetheless, the benefits of reducing BP to <140/90 mmHg are well established. However, scarce evidence has been provided for the benefits of screening. Population screening for abdominal aortic aneurysm, peripheral arterial disease, and HTN in Danish men (65–74 years) was associated with lower mortality rates than non-screening. In a study from Canada, 39 mid-sized communities in Ontario with residents aged 65 years and above were evaluated. Twenty communities received the intervention of Cardiovascular Health Awareness Program (CHAP), whereas 19 communities did not. Over 12-month follow-up, there was a 9% reduction in the relative risk of the composite end-point of hospital admissions for acute myocardial infarction, stroke, and congestive heart failure. This translated to 3.02 fewer hospital admissions for CV disease annually per 1000 persons. Another community-wide programme in the rural county of Maine was provided to individuals as a part of CV Disease Prevention Programs and Health Outcomes. Among adults (>150,000) aged above 40 years, there was an absolute increase of 24.7% in HTN control from 18.3% in 1970 to 43.0% in 2010. This resulted in less than expected hospitalisations per capita, and the adjusted mortality was lower than predicted mortality, with decreases from 60.4 deaths per lakh population in 1970–1989 to 41.6 deaths per lakh population in 1990–2010. These findings suggest that screening is beneficial for improving HTN control and reducing the adverse CV outcomes in a community. However, the experts observed that the population included in these studies was in the middle-to-old age range. Therefore, some of the experts discussed whether screening younger individuals will translate to similar benefits. However, the panel members agreed that if screening is initiated at a young age, early interventions can be undertaken to improve the control of risk factors and reduce adverse outcomes. Moreover, the early detection of pre-HTN and elevated BP would enable early interventions to be implemented to reduce development of HTN and its complications. This would translate to the reduction of the community healthcare burden. From the voting of 91 experts, a mean score of 8.4 was obtained in favour of the consensus.

- Recommendation: Active screening for HTN has the potential to reduce the community burden of HTN and its associated complications.

3. At what age should screening be initiated?

Age is a known risk factor for HTN. It has been reported that after the age of 69 years, the prevalence of HTN increases to 50%. However, over the past few years, the declining age for HTN development and the identification of additional risk factors have raised many concerns. Urbanisation, especially in semi-urban areas, and increasing obesity were important factors identified in a study from Peru and India. In such scenario, self-screening of HTN is an effective alternative for detecting new HTN cases. Self-screening has been found to result in similar rates of HTN detection compared to other methods, but a low referral to primary care is a concern. In Indian context, increasing HTN prevalence in younger individuals coupled with low awareness makes the HTN screening essential. The age at screening is therefore an important aspect in the HTN management algorithm. For the initial age of screening, the US Preventive Task Force recommends the age of 18 years and above, whereas the MOHFW of India recommends age ≥30 years. In addition, uncertainty is observed in the initial age at screening for HTN in various recent studies conducted in India and internationally (Table 2). Given these differences in the initial age at screening, the expert panel considered this as one of
the most important issues in HTN management.

Some experts argued that the age at screening should not be too low (such as 18 years) as HTN detection at this age would require a larger population to be screened. Some experts also pointed out that there may be operational difficulties when mass population screening is planned. Other experts opined that not considering lower ages in screening would exclude the vulnerable population of the younger age group. Retrospective analysis of data of the adults aged above 20 years from a mass gathering of the Simhastha Kumbh Mela in 2015 from Balsari et al. clears some of these doubts. It was reported that 33.6% (n = 1783/5760) of adults screened positive for HTN based on a single reading taken using an electronic BP recorder. Among these positive individuals, 27.4% (n = 1580/5760) were unaware of their HTN. Therefore, even at mass gatherings, lower ages can be considered for HTN screening. Recent studies from India identified that in apparently healthy school going children and adolescents aged 5 to 15 years, prevalence of HTN ranges from 3% to 25%. Therefore, screening should be considered at the earliest ages (i.e., when they enter adulthood). The final consensus was that screening should be started from the age of 18 years and above (score: 7.8, n = 74). This falls in line with the recommendation of the US task force and is also supported by studies that incorporated the age of 18 years and above for screening HTN.

- Recommendation: Age of 18 years and above is an appropriate age to initiate screening for HTN.

4. Is targeted screening required in high-risk individuals?

In the absence of HTN, some individuals may be at a higher risk of HTN than the general population. These individuals may harbour one or more risk factors including obesity, family history of HTN (FH-HTN), and diabetes. If these risk factors are present, individuals should be screened for HTN at a clinic or hospital when they undergo follow-up for existing illnesses. After discussion, important risk factors for inclusion were FH-HTN and obesity.

FH-HTN has been established as a risk factor in several studies. Ranashire et al. observed a significantly higher prevalence of HTN in individuals (>18 years) with FH-HTN (among parents, grandparents, siblings, and children) than in individuals without it (29.3% vs 24.4%, p < 0.001). FH-HTN was associated with increased risks of HTN (OR: 1.29), obesity (OR: 1.36), and metabolic syndrome (OR: 1.19). Another study conducted in China among elderly adults (>60 years) reported a significantly higher prevalence of HTN in the study population with FH-HTN (67.5% vs 47.9%, p < 0.001). When the prevalence of HTN was assessed based on the generations affected, a graded association was found between HTN and FH-HTN, with 63.2% having HTN when the FH-HTN included a first-degree relative with HTN and 79.1% having HTN when the FH-HTN included a second-degree relative with HTN. Goldstein et al. demonstrated that in individuals aged 22–50 years undergoing 24-hour ambulatory BP measurement, the prevalence of elevated BP tended to be higher in men but not in women when both parents had HTN. However, such gender variation may not be observed when a large population is screened. These results suggest that individuals with FH-HTN should undergo targeted screening.

Obesity is an established risk factor for HTN. However, it remains unclear whether being obese or overweight at an early age influences HTN development and how long the development process takes. The John Hopkins Precursors study in 1132 men with a mean age of 23.1 years, BMI of 23.1 kg/m², and 46 years of follow-up observed that the prevalence rates of HTN increased with increasing age (0.3% at 25 years, 6.5% at 45 years, and 37% at 65 years). Being overweight and obese was associated a 1.5-times and 4-times increased risk of HTN respectively. Further confirmatory evidence was provided by the Framingham Heart Study involving 4200 men and 5645 women. Among adults aged ≥18 years (mean age at analysis: 52.1 years), a 5% increase in weight over a 4-year duration (~4 kg in men and 3 kg in women) increased the odds of HTN by 20%–30%. Thus, even a modest weight gain in early life is associated with a future risk of HTN necessitating targeted screening in such individuals.

Some panel members suggested that screening for HTN should be conducted in shift workers. A higher prevalence of HTN has been observed in shift workers. In addition, longer work hours are associated with a higher risk of HTN. Some experts also suggested that other family members of patients with HTN should undergo screening.

When discussing this aspect, few experts opined that there is no need of such targeted screening and suggested that all such individuals should undergo routine screening similar to the general population or when they accompany a family member during consultation. However, voting (n=78) revealed a mean score of 7.8, favouring the need of targeted screening in high-risk individuals.

- Recommendation: In adults with established risk factors such as diabetes, dyslipidaemia, and albuminuria, immediate screening for HTN at clinic or hospital settings should be undertaken. In individuals with FH-HTN, who are obese/overweight and those who are gaining weight, targeted screening is necessary to detect HTN at early stages.

5. What should be the approach to screening?

Screening can be performed in any setting, including community halls, workplace, clinic, hospital, mass gatherings, and shopping malls. Thus, no person should be excluded from screening for HTN because of the setting or place of screening. BP can be taken in any arm (right or left) and in the seated position with the arm and back supported. The cuff size
should be adequate, and clothing should be minimal. Individuals should be asked to empty their bladder before recording the BP. Measurement should be conducted in a quite environment, and talking by the patient should be avoided during BP measurement. Screening for HTN at large gatherings (mass screening) provides an opportunity to identify undiagnosed HTN in a short span of time. Places such as supermarkets, institutions, hospitals, schools, and workplaces may be suitable for such screening. Door-to-door opportunistic screening has also been found to be feasible in the Indian setting. Additionally, assessing the BP of individual patients who visit physicians’ clinic for other reasons is a golden opportunity. By understanding the potential hazards of HTN, healthcare professionals such as dentists can also contribute towards HTN screening.

When the experts considered the approach to BP measurement, the instrument used for BP measurement was one of their main concerns. In India, even today, most healthcare professionals use the aneroid apparatus or mercury sphygmomanometer for recording BP. However, the experts opined that electronic BP recorders are more feasible and provide results with much less assistance and without the need of expertise. They opined that the mercury sphygmomanometer should be avoided, except when in situations where an electronic BP recorder is unavailable. They pointed that aneroid-based manual BP recording requires expertise and appropriate calibration occasionally. Moreover, the MOHFW of India advises the use of either the digital or aneroid machine for measuring BP. Assessment of voting by the experts on the use of the instrument for screening revealed that 82 responded that electronic BP recorders should be used, with mean score of 8.2. This clearly suggests that the use of the electronic BP recorder should be promoted for screening HTN.

Table 2: Hypertension screening studies that considered the age of inclusion

<table>
<thead>
<tr>
<th>Study (year)</th>
<th>Country</th>
<th>Age (years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patel et al. (2010)</td>
<td>US</td>
<td>&lt;45, 45–64, &gt;64</td>
</tr>
<tr>
<td>Pastakia et al. (2013)</td>
<td>Kenya</td>
<td>&gt;18</td>
</tr>
<tr>
<td>Zallaman et al. (2013)</td>
<td>US</td>
<td>&gt;18</td>
</tr>
<tr>
<td>Saqlain et al. (2017)</td>
<td>Pakistan</td>
<td>16–30</td>
</tr>
<tr>
<td>Elaziz et al. (2014)</td>
<td>Egypt</td>
<td>&gt;18</td>
</tr>
<tr>
<td>Ranasinghe et al. (2015)</td>
<td>Sri Lanka</td>
<td>&gt;18</td>
</tr>
<tr>
<td>Selvavinayagam (2017)</td>
<td>India</td>
<td>&gt;30</td>
</tr>
<tr>
<td>Balsari et al. (2017)</td>
<td>India</td>
<td>&gt;20</td>
</tr>
</tbody>
</table>

Another point of discussion was the number of readings to be taken in a single setting. A recent meta-analysis identified that a single BP value outside the expected range should be interpreted with caution and should not be taken as a definitive indicator of clinical deterioration. The American Society of Hypertension and International Society of Hypertension guidelines have recommended the use of two BP readings 1–2 minutes apart and considered the average reading for recording. The 2018 ESC/ESH guidelines recommend that three BP measurements, 1–2 minutes apart, should be recorded. Additional measurements are to be taken only if the first two readings differ by >10 mmHg. BP is recorded as the average of the last two BP readings. Additionally, the MOHFW of India has advised that three to four readings should be taken, and that average of these measurements should be calculated for confirming HTN. After voting by the experts, 68 voted for two measurements giving a mean score of 8.3. Thus, the final consensus was that two readings are adequate for identifying HTN at screening.

- **Recommendation:** An electronic BP recorder should be used for BP measurement. Two readings, 1-2 minutes apart, should be taken, and the average of the two readings should be considered for identifying HTN. A standard protocol should be followed during BP measurement.

6. What should be the rescreening approach?

An aspect more important than just screening is the approach to rescreening among individuals detected with HTN. After HTN detection, the MOHFW of India advises yearly screening for individuals with HTN. Although the ideal rescreening interval is uncertain, it is determined by two parameters—age at screening and initial BP levels. It has been observed that the mean incidence of HTN increases with the increasing rescreening interval, and the mean incidence varies from 2.5% at 1 year to 7.7% at 2 years, 14.2% at 3 years, 12.4% at 4 years, and 13.8% at 5 years. This is expected as the number of patients developing HTN by 5 years is more than those developing HTN at 1 or 2 years of follow-up. However, a prolonged waiting period after the initial screening may lead to the non-detection of HTN in those who developed it early after the first screening. The US Preventive Task Force has advised yearly screening in adults above 40 years of age. In those aged 18–39 years with BP values <130/85 mmHg, rescreening every 3–5 years is advised. Recent ACC/AHA guidelines for HTN recommend that in adults aged above 18 years with BP 120–129/80–89 mmHg, rescreening is advised in 3–6 months. In those with stage 1 HTN (130–139/80–89 mmHg) with <10% risk of atherosclerotic CV disease, rescreening is advised every 3–6 months. However, the 2018 ESC/ESH guidelines suggest repeat BP measurements every 3–5 years in individuals with BP <130/85 mmHg and at least annually in those with BP of 130–139/85–89 mmHg. Based on this suggestion, the experts were asked to opine on two main questions. First, regarding rescreening in asymptomatic individuals aged 18 years and above who have BP <130/85. 63 voted for a 3–5-year interval providing a score of 7.1. Thus, the final consensus was that rescreening should be conducted every 3–5 years in the adult population with BP <130/85 mmHg. Regarding rescreening in asymptomatic individuals with BP of 130–139/85–89, 86 experts voted for a yearly interval (score: 7.2); thus, rescreening of these individuals should be conducted every year.

- **Recommendation:** In asymptomatic adults with BP <130/85 mmHg, rescreening...
should be undertaken every 3–5 years. In individuals with BP 130–139/85–89 mmHg, rescreening should be undertaken every year.

7. Is screening for HTN cost effective in resource-poor settings?

Analysing the cost effectiveness helps identify neglected opportunities by highlighting interventions that are relatively inexpensive yet have the potential to reduce the disease burden substantially. Determining the cost effectiveness of HTN screening in the Indian setting is important because of the growing population size and the significant prevalence of diagnosed and undiagnosed HTN in the general population. In resource-limited settings, determining cost effectiveness is more important. A recent study in Bhutan reported that expanding from opportunistic screening (70% of the target population) to universal screening (100% of the target population) was more cost effective for screening HTN and diabetes. Most panel members expressed that enhancing the population coverage in the screening programme may be cost-effective. Some experts believed that the aforementioned rescreening intervals may also be cost-effective. After the experts voted on this key question (n = 92), the calculated score was 7.7 accepting the consensus.

- Recommendation: Universal screening for HTN targeting the entire population may be cost effective even in resource-poor settings.

Strengths and Limitations

Screening for hypertension is important but often not actively pursued especially in developing countries. In absence of specific guidelines on screening hypertension in India, the expert recommendations provide opportunity for unified approach to screening of hypertension in asymptomatic individuals. This consensus will stimulate further research in establishing concrete evidence in screening for hypertension on various aspects like age to initiate screening, benefits in terms of blood pressure control or reduction in cardiovascular outcomes and appropriate rescreening and its cost-effectiveness. The limitation is that recommendations are based on expert opinions which need to be evaluated further in large controlled studies.

Conclusion

The prevalence of HTN in the general population, including adults and adolescents, is increasing. The increased incidence of CV disease, leading to higher morbidity and mortality, is a major threat to the community. In the current scenario, the diagnosis of HTN is limited to only clinic or hospital settings. Only a limited number of individuals from the general population are being screened and diagnosed with HTN. Appropriate screening of a large population is therefore necessary to identify undiagnosed HTN for implementing early interventions to reduce HTN-related healthcare burden in the community. The initial age at screening should be 18 years. Moreover, rescreening based on age and current BP levels should be appropriately and adequately performed as suggested. The aforementioned measures are expected to translate into improved health outcomes and appropriate treatment and control of HTN, thereby reducing the incidence of adverse CV outcomes. Screening for HTN in asymptomatic adults in the community is cost effective compared with no screening and should therefore be adequately and appropriately implemented by all the stakeholders providing healthcare.

Acknowledgments

It is our pleasure to acknowledge and thank our colleagues who actively participated in the meetings and provided their opinions on formulating consensus statements. The contributors are listed in the alphabetical order. Dr A K Bhalla, Delhi; Dr A Nithin, Hyderabad; Dr Achyut Sarkar, Kolkata; Dr Ajay Ajmani, Delhi; Dr Akshay Mehta, Mumbai; Dr Anand Kumar Pandey, Delhi; Dr Anunni Shrivastava, Delhi; Dr Aparna Jaswal, Delhi; Dr Arindam Pande, Kolkata; Dr Arpita Roychowdhury, Kolkata; Dr Arun Mohanty, Kolkata; Dr Asha Mahilmaran, Chennai; Dr Ashok Punjabi, Mumbai; Dr Ashwani Gupta, Delhi; Dr B Vinoth Kumar, Chennai; Dr Bhaskar Shah, Mumbai; Dr Bhavesh Vajifdar, Mumbai; Dr (Col) C P Roy, Delhi; Dr K Damodharan, Chennai; Dr Dayasagar Rao, Hyderabad; Dr Debmalya Sanyal, Kolkata; Dr Deepka Saha, Hyderabad; Dr Dhurjati Prasad Sinha, Kolkata; Dr E A Padma Kumar, Hyderabad; Dr Eric Borges, Mumbai; Dr G Ramesh, Hyderabad; Dr Gaurav Minocha, Delhi; Dr Girish Navasundi, Bangalore; Dr J V Balasubramnian, Chennai; Dr R Jayanthi, Chennai; Dr J S N Murthy, Chennai; Dr K M Suryanarayana, Bangalore; Dr K Annad, Chennai; Dr K K Saxena, Delhi; Dr Kaustubh Vaidya, Mumbai; Dr K H Srinivasa, Chennai; Dr Kiron Verghese, Bangalore; Dr K N Srinivasan, Chennai; Dr K S Subramani, Bangalore; Dr Lanka Krishna, Hyderabad; Dr Latchumanados, Chennai; Dr M K Shah, Mumbai; Dr M S Aditya, Hyderabad; Dr Manoj Mashru, Mumbai; Dr N Sridhar, Bangalore; Dr N C Krishnamani, Delhi; Dr Nagamallessh, Bangalore; Dr Nagesh Kumar Goyal, Delhi; Dr P Balaji, Chennai; Dr P G Kerkar, Mumbai; Dr P Manokar, Chennai; Dr P A Jiwani, Hyderabad; Dr Pankaj Jariwala, Hyderabad; Dr Prabhakar Koregal, Bangalore; Dr Pranab Kumar Biswas, Kolkata; Dr Prasanna Katti, Bangalore; Dr Puneet Agarwal, Delhi; Dr R C Khokhani, Mumbai; Dr R Keshav, Bangalore; Dr R Balaji, Hyderabad; Dr R R Mantri, Delhi; Dr Rajeev Rathi, Delhi; Dr Raman Raj, Kolkata; Dr Ranjan Sharma, Kolkata; Dr Ripen Gupta, Delhi; Dr S Guruprasad, Chennai; Dr S Manoj, Chennai; Dr S S Iyengar, Bangalore; Dr S V K Ramakrishna, Hyderabad; Dr Sadanand Shetty, Mumbai; Dr S Sadanand, Chennai; Dr Saket Bhardwaj, Delhi; Dr Sanjiv Sharma, Delhi; Dr Sankar Chandra Mondal, Kolkata; Dr T Sasikanth, Hyderabad; Dr Satyam Chakraborty, Kolkata; Dr Sailender Singh, Hyderabad; Dr Shamanugundar, Chennai; Dr Shiva Kumar Reddy, Hyderabad; Dr Shyam Sundar Reddy, Hyderabad; Dr Subhash Chandra, Delhi; Dr K Subramanym, Bangalore; Dr Sujeet Jha, Delhi; Dr Sumeet Sethi, Delhi; Dr Soumik Goswami, Kolkata; Dr Soumitra Kumar, Kolkata; Dr Sunil Dwivedi, Bangalore; Dr Sunil Wani, Mumbai; Dr Suvro Banerjee, Kolkata; Dr T R Raghu, Bangalore; Dr Tathagata Ghosh, Kolkata; Dr V S Ramachandra, Hyderabad; Dr Vijay Kumar, Bangalore; Dr Vijay Negalur, Mumbai; Dr Vijay Sai, Bangalore; Dr Vikram Kolhari, Bangalore; Dr Y Shiva Kumar, Hyderabad.

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Contributors

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Disclaimer

The views expressed are of individual contributors and not of any scientific body or organization.

References

Smartphone Use ‘More than Intention’: Is it Detrimental for Sleep and Behaviour of Medical Students?

Himavathy Gara K1, Dharma Rao Vanamali2, Jeneeta Baa3

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2Assistant Professor, Veer Surendra Sai Institute of Medical Sciences and Research, Burla, Odisha
3Assistant Professor, 2Prof. and HOD, GVP Institute of Healthcare Sciences and Research, Burla, Odisha

Introduction

The present age witnesses the boom of revolutionized ‘always connected’ environment attributed to smartphone, fuelled by internet. This specific human-smartphone interaction endorses behavioural constellation of cognitive absorption, immediate gratification, craving, dependence, withdrawal and tolerance symptoms, interpersonal insensitivity and disregard for its negative consequences, similar to features of internet addiction. The bi-directional relationship between smartphone overuse and poor sleep reflects as a self-perpetuating screen-sleep cycle. As medical students are vulnerable for both, the study aims to explore the prevalence of addictive behaviour of smartphone usage among medical students and its effect on their various subjective sleep quality indicators.

Methods and Materials

This institutional-based, cross-sectional study was conducted among medical students. Inclusion criteria included (1) medical students (2) age ≥18 years (3) smartphone user with internet. Exclusion criteria included (1) diagnosed case of sleep disorder/pyschiatric illness (2) drug history of hormones, steroids, sedatives, stimulants or any psychotropic drugs; etc which may affect sleep (3) pregnancy or lactation. With face-to-face interviews, following details were recorded: (1) socio-demographics (2) anthropometric measurements (3) Smartphone Addiction Scale-Short Version (SAS-SV) to predict smartphone addiction and addictive-like symptoms1 (4) Pittsburgh Sleep Quality Index(PSQI) to measure the subjective quality of sleep over past 1 month2 (5) Epworth Sleepiness Scale(ESS) to determine daytime hypersomnolence. Statistical Package for Social Sciences (SPSS) version-22 was utilized for statistical analysis.

Results

Out of 260 students, majority 158(60.77%) were females. As per SAS-SV scores, the risk of addiction was present in 130(50%), [(females (54.43%) vs males (43.14%)]. Addiction was prevalent in 113(43.46%) [males (50.98%) vs females (38.61%)]. The presence of addictive symptoms was significantly higher among smartphone addicts. Smartphone addiction had strong association with longer sleep latency [OR-2.18, 95%CI: 1.29-3.67], poor sleep [OR-2.23, 95%CI: 1.35-3.71] and with daytime hypersonsomolence [OR-2.83, 95%CI: 1.7-4.7].

Discussion

Smartphone use can have commensurate effect on sleep-wake timings, resulting in circadian rhythm desynchronisation. Blue light exposure during bedtime supresses sleepp-facilitating melatonin release, thus delaying sleep onset. Also, pre-bedtime smartphone activities like chatting, video games and continuous digital notifications cause physiological, cognitive and emotional arousals, thus artificially lengthening sleep latency and interfering with sleep architecture. Chronic sleep deprivation can affect neuronal circuits involved in regulation of emotions, impulse control and reward-punishment behaviour, thus interfering with thoughts, motivation and personality traits. Thus, problematic smartphone usage and poor sleep, both can have direct and independent implications on health and behaviour of the students. Conglomeration of time-specific data on smartphone usage and identification of potential risk factors would help to recognize affected students who can be conferred counselling and behavioural therapy. Educational interventions promoting sleep hygiene, physical activity and occasional technology ‘break’ would facilitate ratiocination towards friendly use of smartphone to avoid any deleterious implications on health, mood and cognition.

References


Table 1: Analysis of PSQI subcomponents among undergraduates with respect to SAS-SV score

<table>
<thead>
<tr>
<th>Variable</th>
<th>Total N (%)</th>
<th>No addiction</th>
<th>SAS-SV at risk of addiction</th>
<th>Presence of addiction</th>
<th>p-value</th>
<th>Odd’s ratio</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sleep latency</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤ 15 mins</td>
<td>100</td>
<td>11</td>
<td>57</td>
<td>32</td>
<td>0.003†</td>
<td>2.18</td>
<td>1.29-3.67</td>
</tr>
<tr>
<td>&gt; 15 mins</td>
<td>160</td>
<td>6</td>
<td>73</td>
<td>81</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sleep duration</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 7 hours</td>
<td>94</td>
<td>5</td>
<td>43</td>
<td>46</td>
<td>0.390</td>
<td>1.42</td>
<td>0.85-2.36</td>
</tr>
<tr>
<td>≥ 7 hours</td>
<td>166</td>
<td>12</td>
<td>87</td>
<td>67</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Use of sleep medication</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Present</td>
<td>15</td>
<td>0</td>
<td>4</td>
<td>11</td>
<td>0.049†</td>
<td>3.86</td>
<td>1.19-12.45</td>
</tr>
<tr>
<td>Absent</td>
<td>245</td>
<td>17</td>
<td>126</td>
<td>102</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Daytime dysfunction</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Present</td>
<td>171</td>
<td>6</td>
<td>79</td>
<td>86</td>
<td>0.001†</td>
<td>2.32</td>
<td>1.35-4.00</td>
</tr>
<tr>
<td>Absent</td>
<td>89</td>
<td>11</td>
<td>51</td>
<td>27</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PSQI score</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤ 5</td>
<td>157</td>
<td>14</td>
<td>87</td>
<td>56</td>
<td>0.004†</td>
<td>2.23</td>
<td>1.35-3.71</td>
</tr>
<tr>
<td>&gt; 5</td>
<td>103</td>
<td>3</td>
<td>43</td>
<td>57</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ESS score</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤ 10</td>
<td>134</td>
<td>14</td>
<td>78</td>
<td>42</td>
<td>&lt;0.001†</td>
<td>2.83</td>
<td>1.7-4.7</td>
</tr>
<tr>
<td>&gt; 10</td>
<td>126</td>
<td>3</td>
<td>52</td>
<td>71</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

†Statistically significant (p-value <0.05); †p value was calculated by Chi-square test and Fisher’s exact test depending on the distribution of data.
Asthma Control Test (ACT) Score: Effectiveness, Validation, Reliability, and Response in OPD Patients of Our Place

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¹Associate Professor, ²Lecturer, ³Professor, ⁴Junior Resident, NKP Sumer Choudhary 1, Nayse G Jaydeep 2, Place

Reliability, and Response

Effectiveness, Validation, Reliability, and Response

In present study if we compared categorical GINA asthma control with numerical scales, using recommended cut off points for uncontrolled asthma, than the numerical scale classifies significantly more patients. In this framework, the GINA criteria are unable to correctly classify all patients with uncontrolled asthma patients.

We applied Kappa coefficient to determine the level of agreement between them. As shown in Tables 1 and 2 GINA had a better agreement with ACT <15 and ACT <20 with ACQ >1.5. O’Byrne et al.² in his study comparing GINA and ACT 5 observed the Kappa value was 0.61 when compared GINA uncontrolled with ACQ-5 >1.5.

Summary

Using appropriate cut off point’s agreement can be observed between numerical and categorical scale. The choice of the scale use to evaluate asthma control has a clear effect on the amplitude of control both in an individual patient and in patient populations. This analysis proves that recommended cut off values and GINA were not in agreement and if considering GINA guidelines as a standard measure then the cut off values must be based on the representative population which is likely to undergo the test, and then the ACT score would be a reliable and effective numerical scale.

References


Table 1: Number of patients in each scales using different cut off values

<table>
<thead>
<tr>
<th></th>
<th>Initial n (%)</th>
<th>Follow up n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gina uncontrolled</td>
<td>43(38%)</td>
<td>3(2.7%)</td>
</tr>
<tr>
<td>ACT&lt;20</td>
<td>89(80.18%)</td>
<td>76(68.4%)</td>
</tr>
<tr>
<td>ACT&lt;15</td>
<td>46(41.44%)</td>
<td>3(2.7%)</td>
</tr>
<tr>
<td>ACQ &gt;1.5</td>
<td>84(75.68%)</td>
<td>79(71.17%)</td>
</tr>
<tr>
<td>ACQ &gt;0.75</td>
<td>102(91.89%)</td>
<td>103(92.79%)</td>
</tr>
</tbody>
</table>

Table 2: Kappa Agreement between different scales

<table>
<thead>
<tr>
<th>Agreement between</th>
<th>Kappa value initial</th>
<th>Kappa value follow up</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACT with Gina</td>
<td>&lt;0.02</td>
<td>&lt;0.02</td>
</tr>
<tr>
<td>ACT&gt; 20 with ACQ</td>
<td>0.59</td>
<td>0.23</td>
</tr>
<tr>
<td>cut off &lt;0.75</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACT &lt;20 with ACQ</td>
<td>0.09</td>
<td>0.59</td>
</tr>
<tr>
<td>cut off &gt;1.5</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

new or previous diagnosed case of asthma were recruited for the study from department of Pulmonary/ Respiratory Medicine, NKP Salve Institute of Medical Sciences and Research Centre and Lata Mangeshkar Hospital, tertiary treatment center situated at Vana Dongri Digdoh Hills, Hingna Nagpur. The spirometry was performed on Geratherm spirometer. Our participants were patient’s age 12 years and above, asthma diagnosed according to GINA guidelines, literate to complete questionnaire. The GINA evaluations of patients were done by asking the patients to recollect past 4 weeks symptoms and were supported by diaries and spirometry. ACT and ACQ scoring was done on standard questionaries’ in vernacular language on 5 point and 7 point rating scale respectively.

The mean age of patients was 37.5 years with majority of them male 81.1%. Most of the patients i.e. 65.8% had exposure to tobacco. Cough was the predominant symptom followed by breathlessness. History of atopy was observed in 54.1% and the mean duration of symptoms was 16.97 years. Most of the patients were on inhaled corticosteroid therapy 67.6%.

The group of patients having ACQ score >20 and ≤15 had an agreement with GINA controlled and uncontrolled group.

The group of patients having ACQ score of ≤0.75 had fair agreement with ACT score ≥20, ACQ ≥1.5 had a moderate agreement with corresponding ACT score of <20.

In present study we studied the agreement between the commonly used categorical and numerical scales used for evaluation of asthma. We compared ACT score with GINA (splitting it into uncontrolled and controlled + partly controlled groups) and ACQ. We observed a specificity of 67% with diagnostic accuracy of 65.77% with GINA and Specificity of 89.4% and Sensitivity of 68.52% with ACQ.

We observed agreement between ACT and GINA, ACT and ACQ if proper cut off points are applied. However using recommended cut off points the ACT and ACQ classified significantly more patients as uncontrolled.

In ACQ using cut off point of ≥1.5 in the uncontrolled population the sensitivity was 68.5%. One of the study suggested ACQ-5 cut off 1 while comparing GINA to obtain a balance of sensitivity and specificity for the GINA criteria, however in the present study it would escalate the number of patients in GINA uncontrolled asthma.

Fig. 1: Comparison of act score with GINA defined asthma control

Fig. 2: Comparison of act score with ACQ

Elections of API, ICP and PRF

(Full details circular No. 1 & 2/2020)

Election for Governing Body of API, Faculty Council of ICP and Board of PRF are announced for following posts:-

**Governing Body of API:**
- President-Elect – One; Vice President – One and Elected Members – Six

**Faculty Council of ICP:**
- Dean-Elect – One; Vice Dean – One and Elected Members – 4 posts

**Board of PRF**
- Director Elect – One; Board members – Two posts

Separate nominations must be submitted for each post.

### Rules Relating to Qualification for Election to Governing Body of API

1. **President Elect:** To contest for the post of President Elect the candidate should be a life member of API for at least 10 years and have completed atleast two full terms of 3 years each in any elected position in the Governing Body.
2. **Vice President:** To contest for the post of Vice President the candidate should be a life member of API for at least 5 years and should have completed atleast one continuous full term of 3 years in any elected position in the Governing Body.
3. **Governing Body Member:** To contest for the post of member of the Governing Body, continuous membership of the Association of atleast 3 years is mandatory.

### Requirements for eligibility contest of election to Board of PRF

**Director Elect:** A member of API for at least 10 years with research experience and having 10 research publications in peer reviewed indexed journals.

**Board Member:** A Member of API for at least 10 years with research experience and having 5 research publications in peer reviewed indexed journals.

The members contesting for the PRF election must attach copies of the Research Papers as mentioned above (mandatory)

Nominations shall be made on prescribed forms stating the office for which nominations are filled. The nominations for API/PRF posts shall be proposed by one valid member and seconded by another valid member of API and duly signed by them and shall also be signed by the candidate signifying his/her willingness to stand for election and serve on the Governing Body if elected.

### Requirements for eligibility for the contests of

**Dean Elect**
- A member of API for at least 15 years and
- A Founder Fellow or a Fellow of the College of 7 year standing and
- Any person who has held the position of President/ Secretary of API or served as Vice Dean for one full term or elected member of the Faculty Council for one term.

**Vice – Dean**
- A member of API for at least 12 years and
- A Founder Fellow or a Fellow of the College of 5 year standing and
- Any person who has held the position of Secretary of API or has been a Jt Secretary from HQ for one full term or a member of the Faculty Council.

**Elected Members:** A member of API for at least 10 years and a Founder Fellow or a Fellow of the college of 3 year standing.

Nominations shall be made on prescribed forms stating the office for which nominations are filled. The nominations for ICP posts shall be proposed by one valid member and seconded by another valid member of ICP and duly signed by them and shall also be signed by the candidate signifying his/her willingness to stand for election and serve on the Faculty Council of ICP if elected.

A member shall not contest simultaneously for more than one post (i.e President-Elect, Vice-President, and Member of the Governing Body) (Dean-Elect; Vice Dean and Elected Members of Faculty Council) and also (Board members of PRF) Post means not only an office-bearer but also member of the Governing Body of API or Faculty Council of ICP or Board of PRF.

Every member is supplied with a nomination form. The nomination form completed in all respects should reach the API Office not later than 1st June 2020. (31st May 2020 is falling on Sunday) For every post on the Governing Body / Faculty Council / Board of PRF, the nomination must be accompanied by a sum of Rs. 2950/- (Rupees two thousand five hundred only) nonrefundable in the form of Demand Draft payable at Mumbai. The nomination paper NOT accompanied by the Bank Draft of Rs. 2,950/- will be deemed invalid.

### Important

Canvassing in any form should not be done by the candidate for the election. Instead, they are requested to send a short bio-data NOT MORE THAN 200 words along with the nomination paper which will be printed and circulated along with the ballot paper. Excess of bio-data beyond the first two hundred words shall be deleted. Canvassing in any form or in favour of the candidate shall not be permitted.

**THE CANDIDATE WILL HAVE TO CERTIFY AND SIGN THAT THE INFORMATION PROVIDED IN HIS/HER BIODATA IS CORRECT.**

The results will be declared at the end of counting of votes and announced in the subsequent issue of JAPI. The report will be placed before the Governing Body for intimation.

### DEAD LINES OF ELECTION PROCEDURE

<table>
<thead>
<tr>
<th>Event</th>
<th>Deadline</th>
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<tbody>
<tr>
<td>Last date to receive the nomination</td>
<td>1st June 2020</td>
</tr>
<tr>
<td>at API Office</td>
<td></td>
</tr>
<tr>
<td>Last date for withdrawal</td>
<td>20th June 2020</td>
</tr>
<tr>
<td>Last date to receive ballot papers</td>
<td>31st August 2020</td>
</tr>
<tr>
<td>at API Office</td>
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</table>

The full API circular No. 2/2020, ICP circular No. 1/2020 and Board of PRF 1/2020 are on API and JAPI website

Dr. Mangesh Tiwaskar
Hon. General Secretary
Indian College of Physicians

Eligibility Criteria for the Award of Fellowship of Indian College of Physicians

5.2.1.1 Minimum experience of 10 years after Post Graduation.

5.2.1.2 Continuous membership of the Association of Physicians of India for not less than 7 yrs.

5.2.1.3 Should have made a significant contribution to research / teaching / development in the field of medicine.

5.2.1.4 Should have contributed to API by way of scientific or Organizational works.

To make the selection objective, a point system has been followed in assessing the suitability of the applications.

The Criteria used by the Credentials Committee for the award of fellowship are:

1. Qualification
2. Experience in Medical Profession
3. Publications
4. Honours / Awards
5. Research work
6. Contribution to API
7. CME & Conference (API/ICP)
8. Social welfare / community service

The Fellowship form should be proposed and seconded by Founder Fellow / Fellow of ICP only.

- The Proposer / Seconder should not propose / second more than 3 nominees for award of ICP in a particular year.
- It is responsibility of the Nominee / applicant to get the proposal completed by the proposer and seconder along with the citation.
- API Membership No. of the proposer / seconder should be entered by the proposer / seconder themselves.
- The proposer should satisfy the requirements for proposal as under:-
  - The Nominee is a life member of API
  - The Nominee has completed 10 years after post-graduation
- The Nominee should read the Form carefully before filling the columns, to project their achievements appropriately.
- The Nominee should list their achievements in appropriate columns.
- Proof of qualifications, publications, honours, awards, must be submitted as supporting data. The supporting data should be numbered parawise (eg 1., 2., 3., etc). For more than one supporting documents, the numbering should be in alphabets (eg 1 (a), (b), (c), etc).
- No hand written applications will be accepted.
- One original and seven Xerox copies to be submitted
- Last date for receiving application form is 31st May, 2020.

Dr. Mangesh Tiwaskar  Dr. A.M. Bhagwati
Hon. General Secretary  Jt. Secretary

Available on API and JAPI Websites : www.apiindia.org & www.japi.org
Format for Submission of Bio - Data of The Nominee for Consideration for Award of Fellowship of Indian College of Physicians.

1. **Name in Full (Surname First)**
   (in Block Letters)

2. **A. P. I. Membership No. and date of joining**

3. **Date of Birth**

<table>
<thead>
<tr>
<th>Address Residence</th>
<th>Address Office</th>
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4. **Tel.:**

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<th>Fax:</th>
<th>E-mail:</th>
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</table>

5. **Postgraduate degree in Medicine**

<table>
<thead>
<tr>
<th>Year of passing</th>
<th>Institute</th>
<th>University</th>
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</table>

6. **Other Professional Qualifications**

<table>
<thead>
<tr>
<th>Year</th>
<th>Speciality / Subjects</th>
<th>University / Institute</th>
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</thead>
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</table>

   a.  
   b.  
   c.  
   d.  

   Certificates Attached

7. **Experience in Medical Profession after Postgraduation in Medicine**

<table>
<thead>
<tr>
<th>Name of Hospital / Clinic / Organisation &amp; Location</th>
<th>Number of Beds (if applicable)</th>
<th>Period Served year wise (From-To)</th>
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</table>

8. **Publications: List below.** (If number of publications in Journals exceeds 8, publications which can qualify as research papers may be listed under Research section 9.)

   a) **Number of Publications in Indexed National / International Journals.**

   Attach title page / Abstract as Appendix

   b) **Number of Chapter in Books / monograms**

   c) **Editorship of National level or State level: Book /Monogram/Update Series**

8. **Honours And Awards** (list below with photocopy of proof)

   a) **Oration in National / State Association Meeting**

<table>
<thead>
<tr>
<th>Title of Oration</th>
<th>Organisation</th>
<th>Year</th>
</tr>
</thead>
<tbody>
<tr>
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<td></td>
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</tbody>
</table>
(b) Award National / International / or State level

<table>
<thead>
<tr>
<th>Title of Award</th>
<th>Organisation</th>
<th>Year</th>
</tr>
</thead>
</table>

9. Research work (list below)

(a) Research sanctioned & funded by Research Agency

Attach Letter of sanction.

(b) Departmental Research, (To qualify, the findings should be published in National/International Journal) Do not include papers already listed under Publications

Attach title page / Abstract

10. Contribution to API (list below and attach proof)

<table>
<thead>
<tr>
<th>Post held in Organisation / Meeting</th>
<th>Name of Organisation / Meeting / CME</th>
<th>National / Zonal / Under API/ICP</th>
<th>Year</th>
</tr>
</thead>
</table>

11. Participation in CME or Scientific Sessions of API or ICP as Faculty

<table>
<thead>
<tr>
<th>Speaker / Chairperson / Other</th>
<th>Title of Talk / Session</th>
<th>Name of Meeting</th>
<th>Year</th>
</tr>
</thead>
</table>

12. Social welfare / Community service. (Include under the headings given below, with documentary evidence)

(a) Emergency services during National calamities (Quakes/ Floods/Cyclones, etc)

(b) Public education Programme (Radio), TV talk / writing in news papers

(c) Service in Rural Areas

<table>
<thead>
<tr>
<th>Service</th>
<th>Evidence</th>
</tr>
</thead>
</table>

N.B : No handwritten application will be accepted. *To be typed on separate page

*One original and seven Xerox copies of sets to be submitted

Last date for receiving the application form is 31st May 2020.

Address : Turf Estate, No. 006 & 007, Dr. E. Moses Road, Opp. Shakti Mill Compound, Mahalaxmi (West), Mumbai – 400 011.
## Citation

The Fellows proposing and seconding the nomination for Fellowship of Indian College of Physicians should highlight the professional/scientific achievements of the candidate and the contribution to A. P. I. from personal knowledge in 200 words, in the format given below:

<table>
<thead>
<tr>
<th>Name</th>
<th>Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>Membership No.</td>
<td>Membership No.</td>
</tr>
<tr>
<td>Signature Proposer</td>
<td>Signature Seconder</td>
</tr>
</tbody>
</table>

Note: The Fellowship form should be proposed and seconded by Founder Fellow/Fellow of ICP only. In case there are more than 3 nominations by any proposer/seconder, the first three nominations in order of receipt in API Office and complete in all respects will be considered for award of Fellowship of ICP and the others rejected for consideration.
REDUCE STRAINING IN HYPERTENSIVE
AND DIABETIC PATIENTS

Cremaffin PLUS

Each 5 ml contains: Lactulose 1.25 ml + Milk of Magnesia 0.75 ml + Sodium Picosulphate B.P. 3.33 mg

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Switch to the better laxative:

3X faster relief

Bloat free laxative

For the use of a registered medical practitioner or hospital or laboratory only.

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2006 VIOLENT Trial
2010 OLIVUS Trial
2009 OSCAR Trial
2007 MORE Trial
2011 ROADMAP Trial
2014 COTO Trial

A Class Apart

In Stage I hypertension

Initiate

Omesar
Olmesartan Medoxomil 10 / 20 / 40 mg Tablets

Best in Class, A Class Apart

Omesar shows stronger anti-hypertensive action than other ARBs

Also Available

Omesar H
Olmesartan Medoxomil 20/40 mg + Hydrochlorothiazide 12.5 mg Tablets

Omesar-A
Olmesartan Medoxomil 20/40 mg + Amlodipine 5 mg Tablets

TriOmesar
Olmesartan 10/40 mg + Amlodipine 5 mg + Hydrochlorothiazide 12.5 mg Tablets

Omesar CH
Olmesartan Medoxomil 20/40 mg + Chlorthalidone 12.5 mg Tablets

TriOmesar CH
Olmesartan 20/40 mg + Amlodipine 5 mg + Chlorthalidone 12.5 mg Tablets

Omesar M
Olmesartan Medoxomil 20 mg + Nebivolol Succinate EL 15/40 mg Tablets

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

ARBs- Angiotensin II Receptor Blockers

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Vilpower-M
Vildagliptin 50mg + Metformin 500/1000mg Tablets

Vildagliptin Power for better outcomes
Presenting The Most Appropriate Antibiotic Power in RTI

Zostum-O
Cefitoren Pivoxil 200mg Tablets

For O utright Success

☑ Preferred Option in Cephalosporins in 12 countries
USA, Japan, Italy, Spain, Mexico, Russia, Thailand, Portugal, Egypt, China, Turkey, Indonesia.

☑ 7 International Clinical Trials in 1910 RTI Patients
- 94.4% bacterial eradication in RTI
- 100% success rate as switch over therapy

☑ Robust Indian Data in AECOPD
77.36% Clinical Success & Decreased exacerbations from > 1.5 /2 to avg. 1.3

☑ USFDA approved

Zuventus Healthcare Ltd.