A Pilot Study of Serum Parathyroid Hormone in Acute Coronary Syndrome

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Abstract:

Acute coronary syndrome (ACS) is the public health issue as it is the single most common cause of death in the world. Role of vitamin D in cardiovascular health is of much interest at present. Experimental, as well as, some observational studies suggest that vitamin D and its metabolites are integrally related to blood pressure and the rennin-angiotensin system. Vitamin D insufficiency affects almost 50% of the population worldwide. Few studies have been carried out to determine the prevalence of hypovitaminosis D in Bangladesh . 30 Patient with ACS were included in this study who had admitted in the department of Cardiology of Bangabandhu Sheikh Mujib Medical University (BSMMU) patient with in first 48 hours of the onset of chest pain. This study was conducted from 1st July'18 to 30th June'19 (One year) by Purposive sampling. Data analysis was carried out by using the statistical package for Social Science (SPSS) version 20.0 windows software. Baseline characteristics have been compared using the independent sample student t-test test where appropriate. The student t-test was used to assess the correlation between PTH levels. p-value <0.05 was taken as significant. We found an association between elevated PTH levels and ACS.

Key Words: ACS, PTH

Introduction:

Acute coronary syndrome (ACS) is the public health issue as it is the single most common cause of death in the world. The frequency of this disease is increasing. ACS accounted for approximately 1.1 million discharges in the United States in 2009. However, in Europe there has been an overall trend for a reduction in Ischaemic heart disease (IHD) mortality during the past three decades. IHD accounts for almost 1.8 million annual deaths or 20% of all deaths in Europe, although with large variations between countries. The relative incidences of STEMI are decreasing and NSTEMI are increasing. There is a consistent pattern for STEMI to be relatively more common in younger than in order people and more common in men than in women. In several recent studies have been highlighted a fall in acute and long-term mortality following STEMI in parallel with greater use of reperfusion therapy, primary percutaneous coronary intervention (PCI), modern antithrombotic therapy, and secondary prevention. Still, mortality remains substantial: the in-hospital mortality of unselected patients with STEMI in the national registries of European countries varies between 4% and 12%, while reported one year mortality among STEMI patients in angiography registries is approximately 10%. ACS occurs three to four times more often in men than in women below the age of 60, but after the age of 75, women represent the majority of patients.

Bangladesh has been experiencing epidemiological transition from communicable disease to non-communicable disease (NCD). The overall mortality rate has decreased significantly over the last couple of decades. But deaths due to chronic diseases, specially the 'fatal four' i.e. cardiovascular disease (CVD), cancer, chronic respiratory disease and diabetes, are increasing in an alarming rate.[1] CAD is an important contributor to one of the four i.e. CVD. Of all South Asian countries, Bangladesh probably has the highest rates of CVD and yet is the least studied; in the global combat against CVD, Bangladesh is a country 'missing in action'.[2] Besides epidemiological transition, widespread environmental contaminants such as arsenic in groundwater or particulate matter in air, or specific vulnerabilities in the genetic or metabolic make-up, may play important role in the etiopathogenesis of CAD in this population. Genetic predisposition, high prevalence of metabolic syndrome and conventional risk factors plays important role.

Lifestyle related factors, including poor dietary habits, excess saturated and trans fat, high salt intake, and low-level physical activity may be important as well. Some novel risk factors, including hypovitaminosis D, arsenic contamination in water and food-stuff, particulate matter air pollution may play unique role. At the advent of the new millennium, we know little about our real situation. Large scale epidemiological, genetic and clinical researches are needed to explore the different aspects of CAD in Bangladesh. The prevalence of CAD varies considerably by populations, may be up to 10 folds. [3] South Asians are unduly prone to develop CAD. [4] Most notable features of CAD in this population are the extreme prematurity and severity; 2–4-fold higher prevalence, incidence, hospitalization and mortality; 5–10 years earlier onset of first myocardial infarction (MI) and 5–10-fold higher rates of MI and death before the age of 40 years. [4] The exact prevalence of CAD in Bangladesh is not known. Only a limited number of small-scale epidemiological studies are available. Probably the prevalence of IHD was first reported in 1976, which was 0.33%. [5] More recent data indicates CAD prevalence between 1.85% [6] and 3.4% [7] in rural and 19.6% in an urban sample of working professionals. [8,9] Despite marked disparity in values, there seems to be a rising prevalence of CAD in Bangladesh. A recent study from rural Bangladesh demonstrated a dramatic increase in CVD from 1986 to 2006. The age-standardized CVD mortality rates was increased by 30-fold (from 16 deaths per 100,000 to 483 deaths per 100,000) among males and 47-fold (from 7 deaths per 100,000 to 330 deaths per 100,000) in females. [10] A nation-wide survey is needed to find out the current epidemiological aspects of CAD in the country.

Studies involving the immigrants in abroad have found that among the South Asians, Bangladeshis are even more prone to develop CAD, and are associated with higher morbidity and mortality related to CAD. Bangladeshis in New York, USA, had more extensive and severe heart disease with 53% having triple-vessel disease compared to 26% among whites. [11]

Role of vitamin D in cardiovascular health is of much interest at present. Experimental, as well as, some observational studies suggest that vitamin D and its metabolites are integrally related to blood pressure and the rennin-angiotensin system. Vitamin D insufficiency affects almost 50% of the population worldwide. Few studies have been carried out to determine the prevalence of hypovitaminosis D in Bangladesh. High prevalence of suboptimal serum 25-hydroxycholecalciferol levels

(<25 nmol/l) was described in lactating women of low socioeconomic status and those wearing Shari, a traditional ladies wear. [12] In another survey of women aged 18–60 years, serum 25-hydroxycholecalciferol levels were <40 nmol/l in 78% of university students and 83% of veiled women. [13] Betel nut chewing, which is prevalent in Bangladesh, has been reported to contribute to hypovitaminosis D by modulating the enzymes regulating circulating 1,25-dihydroxy-cholecalciferol concentration. [14] Positive correlation has been found between vitamin D deficiency and reduced level of apoA1 in Bangladeshi people in UK independent of glycemia and other dietary, anthropometric, and lifestyle related risk factors for type 2 DM and IHD. ApoA1 deficiency may in turn lead to low level of HDL, thereby increasing the risk of CAD. [15] An association between vitamin D receptor polymorphisms and insulin secretory capacity has been described among Bangladeshi Asians in UK. [16] Further researches are needed to find out the association, if any, between vitamin D deficiency and CAD in Bangladesh.

Elevated PTH levels (> 55 pg ml/L) were seen in 16% of the patients, being most frequent in patients with myocardial infarction (28%) and congestive heart failure (42%). The levels were significantly correlated with the APACHE II score (r= 0.48, P< 0.0001) and with the length of stay in hospital (r=0.26, p< 0.002). PTH was also significantly (p<0.03) elevated in non-survivors compared with survivors and was found to be a stronger predictor of mortality (p<0.01) than the APACHE II score (P<0.02 in Cox's proportional hazard analysis. [17] Gang-Yong Wu et al. found in one study in one study that the serum PTH levels correlated with Coronary artery calcification (CAC) and may thus be used as a reliable predictor of CAC in patients without renal failure. [18] The serum PTH levels were significantly raised in the AMI patients and did not normalize during the observation time. As the PTH concentrations were unexplained by infarct size, concomitant disease or medication, so their finding suggests that PTH could be an independent risk factor for AMI. [19] It has also been suggested that elevated PTH levels may be related to nonfatal atherosclerotic CVD and development of atherosclerosis in peripheral and central large arteries. [20] In a recent study, Shekarkhar et al. demonstrated elevated PTH levels have been associated with cardiac contractility, cardiomyocyte hypertrophy, and apoptosis, as well as structural and functional changes in the vascular system and low left-ventricular ejection fraction. And there is an association between PTH levels and the number of stenotic coronary arteries. This study also showed that patients with high PTH levels were more hypertensive and had lower ejection fraction. [21]

Ethical Issues:

Ethical clearance has been taken from the institutional review board of BSMMU. The study was carried out according to Helsinki Declaration for Medical Research involving Human subjects 1964. Participants have been informed in detail about the nature and purpose of the study. It was a non-interventional study. There was no physical, psychological and social risk to the subject. Each participant has been included according to their wish to participate. They were free to withdraw their participation at any stage of the study. Data taken from the participants were regarded as confidential and has kept locked under principal investigator. Data has been used only for this scientific study. Informed written consent was taken from each participant.

Materials and Methods:

Study population:

30 Patient with ACS were included in this study who had admitted in the department of Cardiology of Bangabandhu Sheikh Mujib Medical University (BSMMU) patient within first 48 hours of the onset of chest pain.

Study design:

Cross sectional observational study

Study period:

1st July'18 to 30th June'19 (One year)

Place of Study:

This study had done in the 'Heart Failure Division' Department of Cardiology, BSMMU, Shahbagh, Dhaka, Bangladesh.

Sampling Technique:

Purposive sampling

Sample Size:

30 eligible patients had included under study.

Operational Definitions:

A. *Acute coronary syndrome*:[22]

The leading symptom that initiates the diagnostic and therapeutic cascade in patients with suspected acute coronary syndromes (ACS) is chest pain. Based on the electrocardiogram (ECG), two groups of patients should be differentiated. The clinical spectrum of non-ST-elevation ACS (NSTE-ACS) may range from patients free of symptoms at presentation to individuals with ongoing ischaemia, electrical or haemodynamic instability or cardiac arrest. The pathological correlate at the myocardial level is cardiomyocyte necrosis [NSTE-myocardial infarction (NSTEMI)] or, less frequently, myocardial ischaemia without cell loss (unstable angina). A small proportion of patients may present with ongoing myocardial ischaemia, characterized by one or more of the following: recurrent or ongoing chest pain, marked ST depression on 12-lead ECG, heart failure and haemodynamic or electrical instability. Due to the amount of myocardium in jeopardy and the risk of malignant ventricular arrhythmias, immediate coronary angiography and, if appropriate, revascularization are indicated.

1. Patients with acute chest pain and persistent (>20 min) ST-segment elevation.

    This condition is termed ST-elevation ACS and generally reflects an acute total coronary occlusion. Most patients will ultimately develop an ST-elevation myocardial infarction (STEMI). The mainstay of treatment in these patients is immediate reperfusion by primary angioplasty or fibrinolytic therapy.[1]

2. Patients with acute chest pain but no persistent ST-segment elevation.

    ECG changes may include transient ST-segment elevation, persistent or transient ST-segment depression, T-wave inversion, flat T waves or pseudo-normalization of T waves or the ECG may be normal.

B. Diabetes:

(American Diabetes association 2017)[23]

History of diagnosis and /or on treatment of diabetes by a physician

The American Diabetes Association 2017 criteria include documentation of following:

1. Fasting plasma glucose > 126 mg/dl (7.0 mmol/l)

2. 2 hours plasma glucose > 200 mg/dl (11.1 mmol/l) during an oral glucose tolerance test (75g) or

3. Haemoglobin A1c > 6.5 % (48 mmol/l)

4. In a patient with classic symptoms of hyperglycemia or hyperglycemic crisis, a random plasma glucose >200 mg/dl (11.1 mmol/l)

C. Hypertension :

(The 7th reports of JNC 2003)[24]

Documented by,

1. History of hypertension diagnosed and treated with medication, diet and/or exercise.

2. Systolic blood pressure > 140 mm of Hg and/or diastolic blood pressure > 90 mm of Hg on at least two occasions.

3. The patient is on antihypertensive drug treatment.

D. *Coronary Artery disease:*[25]

Will be considered to be present if there is history of Chronic angina, a stress test positive for ischaemia, a prior myocardial infarction, coronary stenosis >50% by cardiac catheterization, or prior coronary angioplasty or coronary bypass surgery.

E. Dyslipidaemia:[26]

Indicate if the patient has a history of dyslipidaemia that was diagnosed and/or treated by a physician. National Cholesterol Education Program (NCEP) criteria include documentation of following: Total Cholesterol > 200 mg/dl (5.18 mmol/l)

Low density lipoprotein Cholesterol (LDL_C) > 130 mg/dl (3.37mmol/l)

High density lipoprotein Cholesterol (HDL_C) <40 mg/dl (1.04 mmol/l) in men and <50 mg/l (1.3mmol/l) in women

Currently receiving antilipidemic treatment

F. Smoking: [26]

Current: smoking cigarettes within 1 month of admission

Recent stopped smoking between 1 month and 1 year of admission

Past : Stopped smoking > 1 year ago

Never: Never smoked

G. Ejection Fraction: [27]

Left Ventricular Ejection fraction is a measurement of how much blood the left ventricular pumps out with each Cardiac cycle.

A normal heart's ejection fraction is > 55 %

It is calculated as the difference between LV end-diastolic volume (EDV) and end-systolic volume (ESV) divided by LV end-diastolic volume (EDV)

LVEF = Stroke volume (EDV-ESV)/EDV

It remains the most commonly used method for assessing systolic function.

Study Procedure:

This cross-sectional observational study has conducted in cardiology department of BSMMU from July 2018 to June 2019 after receiving approval of the protocol by Institutional Review Board (IRB) of Bangabandhu Sheikh Mujib Medical University (BSMMU). Patients with Acute coronary syndrome who had admitted in Cardiology department of BSMMU within 48 hours of the onset of chest pain enrolled into this study after fulfilling the inclusion and exclusion criterias. The purposes of the study have been explained in details to each subject and inform written consent was obtained. After getting consent, meticulous history was taken and relevant clinical examination was performed and recorded in predesigned structural proforma. Demographic data (Age, sex), risk factor profile (DM, HTN, BMI, Dyslipidaemia, Smoking, Family history of CAD) were recorded. 12 lead ECG had done to detect any ST change or new onset LBBB. During admission baseline investigations such as Troponin-I and CKMB 4 sample. If first sample showed increase titre then second sample was not taken. Blood for CBC, CRP, Blood sugar- FBS, 2 Hr ABF, HbA1c, (F) Lipid profile, Serum Urea, Serum creatinine, Serum electrolyte, S. Uric acid, S. Bilirubin, SGPT, SGOT, S.Alk. Phos, S.Total Protein, S. Albumin, A/G ratio, TSH, FT3, FT4 were done to detect risk factors and secondary causes. Xray chest P/A view was needed to see any cardiomegaly. Urine(R/E) was also done. If evidence of MI or UA then another blood sample was taken to do PTH level, Ca ++ level within the first 48 hours of the onset chest pain. 2D and M-mode Echocardiography was done to evaluate the regional wall motion abnormality, LV systolic and diastolic function and RV systolic function, to detect any mechanical complication of MI. USG of thyroid was done to detect any pathology in thyroid and Parathyroid scan was done to exclude any parathyroid adenoma. BMD was done to see bone mineral density.

Selection criteria of patient:

Inclusion Criteria:

1. Patients 18 years of age or above.

2. Patients present within 48 hours of the onset of chest pain.

3. Acute coronary syndrome patients (UA, NSTEMI, STEMI)

4. Give inform written consent.

Exclusion Criteria:

i) Chronic kidney disease patients

ii) Deformed bony disease

iii) Osteoporosis

iv) Patient in steroid.

Statistical Methods:

Data collection:

Data was collected according to the predesigned semi structured data collection sheet.

Data Analysis:

Statistical analyses was done and reviewed by the investigators. After editing data analysis was carried out by using the statistical package for Social Science (SPSS) version 20.0 windows software. Baseline characteristics have been compared using the independent sample student t-test test where appropriate. The student t-test was used to assess the correlation between PTH levels. p-value <0.05 was taken as significant.

Results:

Total 30 patients of acute coronary syndrome (ACS) were included in this study. ACS was confirmed by ECG change, cardiac bio markers (CKMB and Troponin- I). PTH level was high in 22(73%) patients, low in 3 (10%) and normal in 5 (16%) patients. Patients who have high PTH, 13(59%) patients had STEMI, 6 (27%) had NSTEMI and 3 (13%) had unstable angina. High serum PTH was seen more in acute STEMI cases than NSTEMI or UA. 5 patients have normal PTH and only 3 patients have low PTH.

Table-I
Distribution of parathyroid status (n=30)

Parathyroid status	Frequency	Percentage
High	22	73.0
Normal	5	16.0
Low	3	10.0

Table-II
Distribution of parathyroid status according to type of ACS

Type of ACS	High PTH (n=22)		Normal or Low PTH (n=8)		P value
	No	(%)	No	(%)	
STEMI	13	59.0	2	25	0.005
NSTEMI	6	27.0	4	50	0.763
Unstable angina	3	13.0	2	25	0.655

Discussion:

This study demonstrated that there is association between PTH levels and ACS. On the other hand, there was a statistically significant but weak correlation between PTH levels and Gensini score. It is well known that PTH regulates blood calcium and phosphorus concentrations. Elevated calcium is a risk factor for vascular disease, and it is associated with increased vascular stiffness and high pulse pressure.[28] Previous studies demonstrated that elevated PTH levels are related to impaired vascular function, increased vascular stiffness, carotid and brachial artery intima–media thickness, and increased systolic and diastolic blood pressure.[28-30] Previous studies showed that increased levels of PTH are associated with high risks for cardiovascular mortality and morbidity.[31] It has also been suggested that elevated PTH levels may be related to nonfatal atherosclerotic CVD and development of atherosclerosis in peripheral and central large arteries.[32] Moreover, elevated PTH levels have been associated with cardiac contractility, cardiomyocyte hypertrophy, and apoptosis, as well as structural and functional changes in the vascular system and low left-ventricular ejection fraction.[33-38] Additionally, elevated circulating levels of PTH are associated with significantly decreased functional capacity and advanced heart failure.[39]

According to recent data, PTH is suggested to affect the cardiovascular system through various mechanisms.[33-37] Many studies investigated the relationship between CAD and PTH, but conflicting results were obtained.[40-42] We found a similar result in our study population with ACS who has investigated. Shekarkhar et al. demonstrated an association between PTH levels and the number of stenotic coronary arteries. This study also showed that patients with high PTH levels were more hypertensive and had lower ejection fraction.[43] Our results were inconsistent with the findings of this study. We did not find significant differences between PTH levels and the number of stenotic coronary arteries or ejection fraction or a correlation between PTH level and Gensini score. We also could not demonstrate an association between PTH level and ACS or its subgroups. The strict exclusion criteria for our study population may have influenced the results. Moreover, we accept that our study population and groups were not homogeneous; but when we evaluated the relationship between the groups separately, the results did not change. However, more accurate results could be obtained by evaluating patients according to their glomerular filtration rate and PTH levels. The relationship between PTH and CVD was shown particularly in patients with chronic renal disease.[39] Also, higher PTH levels may be related with the risk of sudden cardiac death in elderly populations without CVD.[44] Our study was a cross-sectional study and has no long-term mortality or morbidity data; therefore, our results cannot provide additional data on this issue.

Conclusion:

It is difficult to draw a simple conclusion regarding the linear relationship between Acute Coronary Syndrome with raised Paratharmone level. However multicentre study with enrolment of different races are deemed to necessary before making a final comment.

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