Original Article

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Correlation of Serum Calcium with Components of Metabolic Syndrome: A Cross-sectional Study

Biochemistry Section

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ABSTRACT

Introduction: Metabolic syndrome is a cluster of symptoms following impaired glucose tolerance, adiposity, abnormal lipid profiles and hypertension. Metabolic syndrome may serve as a precursor for type II diabetes mellitus and cardiovascular diseases. Therefore, it should be considered when interpreting calcium levels, as calcium is inexpensive, readily available and can also serve as a predictor for diabetic and cardiovascular risks.

Aim: To investigate the correlation of serum calcium with components of metabolic syndrome.

Materials and Methods: A cross-sectional study was conducted in the Department of Biochemistry, Government Medical College and General Hospital, Aurangabad, Maharashtra, India, from January 2016 to March 2016. A total of 80 patients were divided into two groups: subjects with metabolic syndrome (group I) and subjects without metabolic syndrome (group II). Data including age and components of metabolic syndrome such as Body Mass Index (BMI), Systolic Blood Pressure (SBP), Diastolic Blood Pressure (DBP), Waist Circumference (WC) and various biochemical parameters {plasma glucose, calcium, albumin, corrected calcium, total cholesterol, Triglycerides (TG), High-Density Lipoprotein (HDL) and Low-Density Lipoprotein (LDL)} were collected and compared between the two groups. The differences in the studied variables among the groups were analysed using an Unpaired t-test. A p-value less than 0.05 was considered statistically significant.

Results: In the present study, group I consisted of 23 males and 17 females with the mean±Standard Deviation (SD) age 49.88±8.7 years and group II had 19 males and 21 females with mean age 47.5±7.60 years. There were no significant differences in age, gender and blood pressure, while BMI and WC were significantly higher in group I. Serum calcium, fasting plasma glucose levels, and lipid profiles were significantly higher in subjects with metabolic syndrome compared to those without metabolic syndrome. Additionally, serum corrected calcium levels showed a positive correlation with serum TG and fasting plasma glucose (r-value=0.4, p-value=0.008), and a negative correlation with HDL-cholesterol (HDL-C) (r-value=-0.3, p-value=0.03).

Conclusion: In the present study, serum total calcium was found to be positively associated with metabolic syndrome. Estimation of serum calcium can help predict the risk of developing cardiovascular diseases or diabetes mellitus, which are associated with the metabolic syndrome.

Keywords: Cardiovascular disease, Diabetes mellitus, Dyslipidaemia, Hypocalcaemia

INTRODUCTION

Metabolic syndrome is a cluster of symptoms including impaired glucose tolerance, insulin resistance, central obesity, dyslipidaemia, high TG levels, LDL-cholesterol (LDL-C), HDL-C levels and hypertension [1]. The presence of metabolic syndrome was defined using the National Cholesterol Education Programme (NCEP) Adult Treatment Panel III (ATP III). Subjects with three or more of the following components were classified as having metabolic syndrome: i) Abdominal obesity WC ≥85 cm (for women) and WC ≥90 cm (for men), high serum TG ≥150 mg/dL, Low HDL <50 mg/dL (for women) and <40 mg/dL (for men), blood pressure ≥130/85 mm of Hg and Fasting Plasma Glucose (FPG) ≥100 mg/dL [2]. All of these are well-documented risk factors for cardiovascular diseases and type II diabetes [1,3,4]. A steady rise was found in the burden across the age groups from 13% (18-29 years group) to 50% (50-59 years) [5]. Subjects aged 40-60 years were selected in the present study, as the prevalence is common in the same age group for the study population.

A direct impact has been observed on cell membrane potentials by extracellular calcium concentration, which affects the function of all excitable tissues, particularly the nervous system and the heart. Calcium is a key messenger in the contraction of muscles, including the myocardium [6]. Few studies have suggested that diabetes and cardiovascular diseases are linked by a common defect of divalent cation metabolism, including calcium [6,7]. Calcium is a versatile intracellular messenger that is used throughout the lifecycle of an organism to control diverse physiological processes like neuronal transmission, muscle contraction, organelle communication, hormone secretion and cell growth [8,9]. Altered calcium homeostasis is associated with abnormalities of fasting plasma glucose, insulin resistance and B-cell function [10].

In diseases such as primary hyperparathyroidism with markedly elevated serum calcium levels, there is a two-four fold higher prevalence of type II diabetes and glucose intolerance compared with the general population [1,11]. A previous study found that increased dietary calcium intake and high serum calcium levels were associated with a decreased risk of metabolic syndrome among Turkish premenopausal women [3]. Some studies found that serum calcium is associated with cardiovascular disease in males. However, they have not corrected calcium for albumin in their study [12,13]. From total calcium, 40% of calcium is protein-bound. Among protein-bound calcium, 80% is bound to albumin. The recognition that serum albumin affects total calcium concentrations has resulted in the concept of albumin-corrected calcium, which can be calculated as corrected total calcium (mg/dL)=Total calcium (mg/dL)+0.8{4-albumin (g/dL)} [14].

Hence, the authors conducted a correlation between albumin-corrected calcium and other parameters as no study was found in the literature for this region of Maharashtra, India, where albumin-

corrected calcium was correlated. Therefore, the present study was conducted to investigate the correlation of serum calcium with components of metabolic syndrome such as BMI, SBP, DBP, WC, total cholesterol, TG, HDL and LDL.

MATERIALS AND METHODS

The present cross-sectional study was conducted in the Department of Biochemistry, University-affiliated Government Medical College and General Hospital, Aurangabad, Maharashtra, India, from January 2016 to March 2016. Ethical approval was granted by the Institutional Ethics Committee to conduct the study (Ref No. Pharma/IEC-GMCA/373/2015). Informed written consent was obtained from all subjects before their enrollment as study participants.

Inclusion criteria: Total of 80 ambulatory subjects aged 40-60 years, with or without metabolic syndrome according to National Centers for Environmental Prediction (NCEP criteria) [2] and who consented to participate in the study were included. Mainly, referral cases from different Outpatient Departments of the hospital presenting for routine check-ups were enrolled. Subjects aged 40-60 years were selected as the prevalence is common in the same age group for the study population.

Exclusion criteria: Patients with abnormal thyroid profiles, known cases of diabetes mellitus, pre-existing bone diseases, chronic diseases, renal diseases and subjects taking lipid-lowering agents were excluded from the study.

Study Procedure

Nurses specially trained for survey procedures measured the height, weight and WC of study subjects. Height was measured to the nearest 0.1 cm, and weight was measured to the nearest 0.1 kg in light clothing. BMI was calculated as weight (kg) divided by height squared (m^2). Blood Pressure (BP) was measured twice, and the latter reading was used in the analysis, in a sitting position after a minimum of 15 minutes of acclimatisation using a mercury sphygmomanometer.

Included 80 subjects of the present study were sub-classified into two groups:

- Group I (n=40): - subjects with metabolic syndrome and
- Group II (n=40): - subjects without metabolic syndrome

When patients in group I were included, care was taken to enroll patients fulfilling the three criteria for metabolic syndrome as per NCEP guidelines. Individuals with only one criterion were not considered for group I but was included in group II [2].

Sample collection: Under all aseptic precautions, approximately 2 mL of fasting venous blood samples were collected in fluoride and plain bulbs each for the estimation of plasma glucose and serum calcium, serum albumin and lipid profile parameters like serum total cholesterol, serum TG, HDL-C, LDL-C, respectively. Plasma and serum were separated by centrifugation at 2500 revolutions per minute for 10 minutes. The method of estimation and cut-off ranges for all the parameters are provided in [Table/Fig-1] [2,14-16].

Parameters	Method	Cut off reference range
Plasma glucose	Enzymatic end point by GOD-POD	74-100 mg/dL [14]
Serum calcium	oCPC method	8.8-10.4 mg/dL [15,16]
Albumin	BCG method	3.5-5.2 gm/dL [14]
Albumin corrected calcium	Serum calcium+0.8 (4-serum albumin)	Nil [14-16]
Cholesterol	Enzymatic end point	<200 mg/dL [2]
Triglycerides (TG)	Enzymatic end point	<150 mg/dL [2]
HDL direct	Enzymatic end point	40-60 mg/dL [2]
LDL	Friedwald's formula	<100 mg/dL [2]

[Table/Fig-1]: Biochemical parameters in study groups with reference ranges [2,14-16].
GOD-POD: Glucose oxidase-peroxidase; oCPC: o-cresolphthalein complexone; BCG: Bromocresol green

STATISTICAL ANALYSIS

Demographic and biochemical characteristics of all the participants were analysed as mean±SD. An Unpaired t-test was applied to analyse the differences in the studied characters in the study groups. In statistical analysis, a p-value <0.05 was considered statistically significant, and a p-value <0.01 was considered highly significant. Correlation coefficients (r) were calculated among various parameters in study subjects using Pearson's correlation test. Positive and negative r-values were interpreted as follows:

r=0 (no correlation)

r=0 to 0.3 (poor correlation)

r=0.3 to 0.7 (considerable correlation)

r=0.8 or more (strong correlation).

RESULTS

In the present study, WC and BMI were significantly higher in group I subjects compared to those in group II. However, no significant difference was found between group I and group II for age, SBP and DBP [Table/Fig-2].

Demographic parameters	Group I	Group II	p-value
Age (years)	49.88±8.7	47.5±7.60	0.2
BMI	27.1±3.24	23.04±2.53	<0.01
Systolic BP (SBP)	137±16.7	134.6±6.61	0.081
Waist Circumference (WC)	102.93±8.8	94.81±8.4	0.032
Diastolic BP (DBP)	86.23±5.73	83.98±5.23	0.074

[Table/Fig-2]: Demographic parameters expressed as (Mean±SD).
Values presented as mean±SD; Unpaired t-test; The p-value <0.05 was considered statistically significant

In the present study, calcium levels and albumin-corrected calcium levels were significantly higher in subjects of group I compared to group II. Fasting plasma glucose, serum total cholesterol, TG and LDL were significantly increased, while HDL was significantly decreased in subjects of group I compared to group II [Table/Fig-3].

Biochemical parameters	Group I	Group II	p-value
Fasting Plasma Glucose (FPG)	123.79±43.13	99.54±23.96	0.022
Calcium	10.57±1.3	9.52±0.83	<0.01
Albumin	4.07±0.46	3.98±0.33	0.47
Albumin corrected calcium	10.25±1.3	9.54±0.86	<0.01
Cholesterol	168.42±42.64	137.33±36.25	<0.01
Triglycerides (TG)	188.08±68.23	127.54±39.67	<0.01
HDL	39.89±5.84	44.87±4.72	0.041
LDL	91.80±38.13	69.81±36.83	0.038

[Table/Fig-3]: Comparison of biochemical parameters in study groups as (Mean±SD).
Values presented as mean±SD; Unpaired t-test

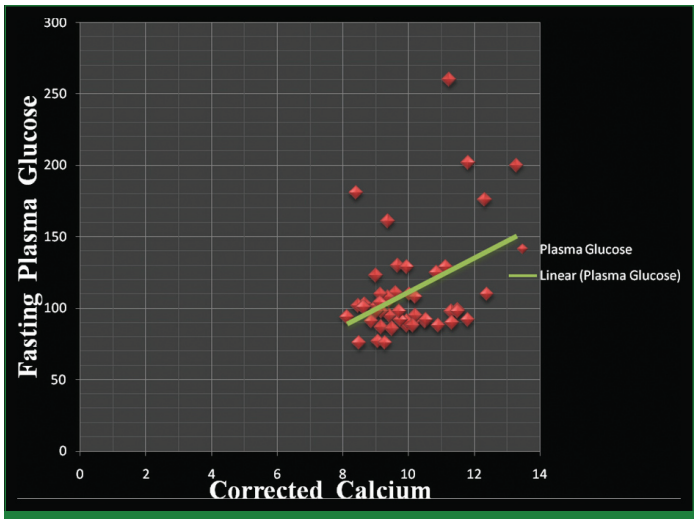
Corrected calcium levels were significantly positively correlated with serum TG and fasting plasma glucose. A significant negative correlation was found between serum calcium and HDL-C. No correlation was found between serum calcium and total cholesterol levels [Table/Fig-4-7]. SBP (r-value=0.1, p-value=0.4) and DBP (r-value=0.2, p-value=0.3). Albumin was estimated for calculating albumin-corrected calcium. The corrected calcium was not correlated with it.

DISCUSSION

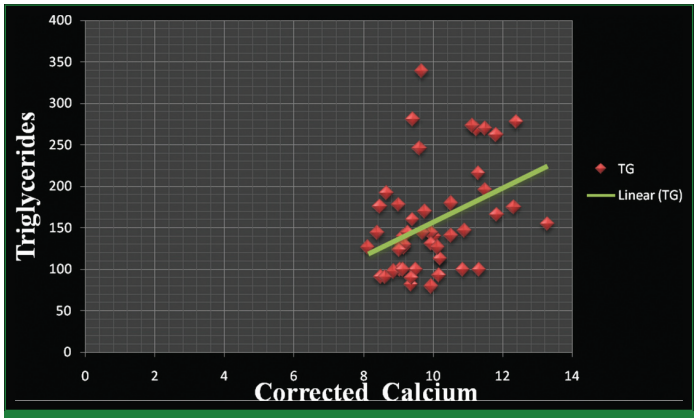
The present study evaluated the relationship between serum calcium and components of metabolic syndrome. When comparing demographic data between the two groups, authors found a statistically significant increase in BMI and WC in group I compared to group II. In terms of biochemical parameters, higher serum calcium levels in group I, consisting of subjects with metabolic syndrome, compared to group II, consisting of subjects without metabolic syndrome were observed. The increase in serum calcium levels was statistically highly significant (p-value <0.01) when comparing group I and group II.

Parameters	r-value	p-value
TG	0.4	0.009
Plasma glucose	0.4	0.008
HDL-C	-0.3	0.03
Total cholesterol	0.1	0.4
LDL-C	0.2	0.4
BMI	0.1	0.5
WC	0.3	0.07
Systolic Blood Pressure (SBP)	0.1	0.4
Diastolic Blood Pressure (DBP)	0.2	0.3

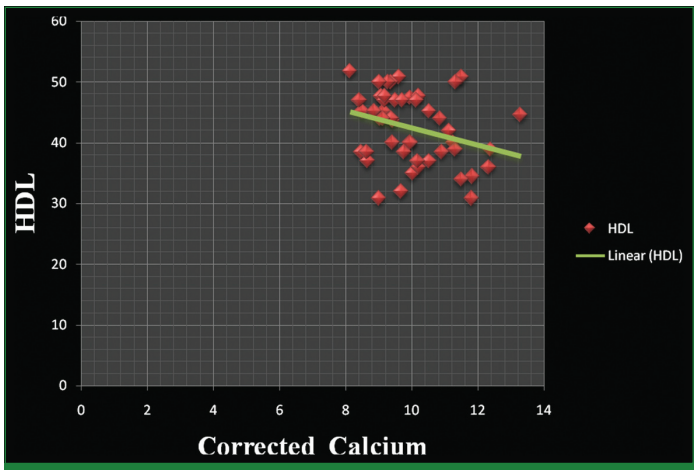
[Table/Fig-4]: Correlation of corrected calcium with other parameters.
Pearson's correlation test



[Table/Fig-5]: Correlation with Fasting Plasma Glucose (FPG); r-value=0.4, p-value=0.008.



[Table/Fig-6]: Correlation of corrected calcium with Triglyceride (TG); r-value=0.4, p-value=0.009.



[Table/Fig-7]: Correlation of corrected calcium with HDL; r-value=-0.3, p-value=0.03.

This increase may be related to an increase in intestinal and renal absorption, skeletal resorption, or a combination of these factors. Hormonal regulation of calcium homeostasis is maintained by calcitriol, Parathyroid Hormone (PTH) and calcitonin [15].

The normal reference interval for serum total calcium (Ca^{+2}) concentration is 8.8-10.4 mg/dL. The normal value for ionised Ca^{+2} is approximately half of the total serum Ca^{+2}, ranging from 4.4-5.2 mg/dL (2.2-2.6 mEq/L, or 1.10-1.30 mmol/L). Serum Ca^{+2} exists in three forms: ionised (free; 48%), protein-bound (mostly to albumin and less to globulins; 45%), and complexed (bound to citrate, oxalate, carbonate and phosphate; 7%). Both ionised and complexed Ca^{+2} are diffusible (ultrafilterable by the kidney), while protein-bound Ca^{+2} is not. Hypoalbuminaemia results in a decrease in protein-bound calcium, leading to hypocalcaemia. To correct for hypoalbuminaemia, the following formula is used: Corrected total serum Ca^{+2} (mg/dL)=measured serum Ca^{+2} (mg/dL)+0.8 (4.0-serum albumin g/dL) [15,16].

In the present study, serum calcium levels were positively correlated with fasting plasma glucose, and the correlation was statistically significant. The present study findings are consistent with Saltevo J et al., who concluded that serum calcium levels are associated with metabolic syndrome and its components, except HDL-C, when they studied the association of serum calcium with metabolic syndrome in the general population [1].

Additionally, Chou CW, in their study of the association between serum calcium and the risk of cardiometabolic disease among community-dwelling adults in Taiwan, found that higher serum calcium levels were associated with an increased risk of metabolic syndrome, diabetes and hypertension [17]. Baek JH et al., in their retrospective longitudinal study, found an association between higher serum calcium levels and decreased incident metabolic syndrome in individuals with central obesity or two components of metabolic syndrome at baseline. However, they did not find any positive correlation between the incident risk of metabolic syndrome and baseline serum calcium levels [18].

Insulin resistance is one of the most important manifestations of metabolic syndrome. Elevated calcium levels are mainly linked to impaired insulin sensitivity [19]. Insulin production by the islet cells of the pancreas requires calcium ions, and increased intracellular calcium concentrations may also cause insulin resistance and lipid abnormalities [19-21]. The effect of insulin in adipocytes has been shown to decrease with increasing intracellular calcium, resulting in a reduced number of glucose transporters GLUT4 and decreased insulin receptor activity [19,20]. Elevated cytosolic calcium is also responsible for disturbances in lipid metabolism and inducing hyperlipidaemia [21]. However, longitudinal intervention studies are needed to investigate and confirm these findings.

In our study, serum calcium is also positively correlated with TG levels and negatively correlated with serum HDL-C, which are important components in the definition of metabolic syndrome. Excessive calcium is accumulated in the cytosol due to increased PTH concentrations. High serum PTH levels suppress lipoprotein lipase activity [22]. This abnormality of the enzyme may result in increased LDL-C, TG and decreased HDL-C.

The association between serum calcium levels and risk factors for metabolic syndrome has been well-documented in cross-sectional study designs [1,4,17,18,23,24]. The association of serum calcium with components of metabolic syndrome has been proven in many previous studies and with increased metabolic syndrome risk scores [1,24]. The present study supports the existence of a positive correlation between serum corrected calcium and TGs, HDL-C and plasma glucose.

The association between increased baseline serum calcium levels and the risk of metabolic syndrome or type 2 diabetes mellitus can be explained by impaired insulin secretion and sensitivity or increased insulin resistance. Additionally, calcium influx into arterial

smooth muscle is shown to be caused by increased serum calcium levels, which induces muscle contraction, resulting in blood pressure elevation and increased peripheral vascular resistance, increasing the risk of cardiovascular diseases [18]. Sun G et al., in their study, found that serum albumin-corrected calcium is positively correlated with fasting plasma glucose and insulin resistance [25]. Kim MK et al., have shown the increased prevalence of metabolic syndrome with elevated albumin-corrected calcium levels [26].

The present study supports the findings of previous research studies regarding the positive correlation between baseline serum calcium and the development of metabolic syndrome. Estimation of serum calcium can help predict the risk of developing lifestyle-associated cardiovascular diseases or diabetes mellitus, which is associated with the increasing incidence of metabolic syndrome. Longitudinal intervention studies are needed to study the causal relationship between calcium levels and insulin sensitivity, through which insulin-resistant individuals and diabetics could benefit from interventions that lower serum calcium.

Limitation(s)

The sample size for the study is small. Further studies with a larger sample size should be conducted.

CONCLUSION(S)

Serum calcium is positively correlated with fasting plasma glucose and TG, and negatively correlated with HDL-C. Serum calcium levels can be taken into consideration for assessing the risk of developing metabolic syndrome. Metabolic syndrome is a precursor to the development of type II diabetes mellitus and cardiovascular diseases. Serum calcium, being an economical, affordable, and easily available laboratory investigation, can be used as a predictor and risk factor for diabetes mellitus and cardiovascular diseases. Further studies that consider PTH and vitamin D levels are required to confirm the association.

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- iThenticate Software: Apr 22, 2024 (16%)

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