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RESEARCH ARTICLE

SERUM CALCIUM AND PHOSPHATE LEVEL ALTERATIONS IN METABOLIC SYNDROME

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TGs(triglycerides)].

ABSTRACT

Introduction: Metabolic syndrome by itself is a constellation of multiple risk factors causing cardiovascular diseases. Serum calcium and phosphate has been shown to be associated with metabolic syndrome, coronary artery disease, and also correlated with individual components of metabolic syndrome. Disturbances in calcium and phosphate metabolism can cause CVD and may be a predisposing factor for metabolic syndrome. This study is designed to find out the correlation of serum calcium and phosphate with individual components of metabolic syndrome.

Aim:

- To measure serum calcium and serum phosphate levels in diagnosed metabolic syndrome patients.
- To assess the correlation between serum calcium and individual components of metabolic syndrome in the above patients.
- To assess the correlation between serum phosphate and individual components of metabolic syndrome in the above patients.

Method: Data of 30 out-patients with diagnosed metabolic syndrome (cases) and 30 age and sex matched healthy individuals from general population(controls)were collected and their blood drawn for serum calcium, serum phosphate, Fasting blood glucose(FBG) and lipid profile analysis in Beckman coulter Biochemistry auto analyser.

Results: Serum calcium was higher in cases compared to controls. Serum calcium in cases was 11.2 ± 0.8 and in controls was 9.5 ± 0.4with t score of 7.3291 with P value of 0.0001 which is statistically very significant. Serum calcium showed positive correlation with components of metabolic syndrome namely FBG (r score: 0.1482 p: 0.001), triglycerides (r score: 0.116 p: 0.001) and TC (r score:0.181 p:0.001), Serum phosphate was lower in cases compared to controls. Serum phosphate in cases was 2.5 ± 0.7 and in controls was 3.3 ± 0.5 with t score of 7.1458 with P value of 0.0001 which is statistically very significant. Serum phosphate showed negative correlation with components of metabolic syndrome namely FBG (r score:-0.748 p: 0.001), triglycerides (r score:-0.716 p: 0.001) and WC (r score:-0.620 p: 0.001), SBP (r score:-0.804 p:0.001) and positive correlation with HDL-C (r score:0.690 p:0.001) in patients of metabolic syndrome.

Conclusion: The results of this study indicate that serum calcium and serum phosphate may serve as a potential risk assessment marker of cardiovascular disease in metabolic syndrome.

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INTRODUCTION

Metabolic syndrome is caused byinsulin resistance accompanying abnormal adipose deposition and function (Olufadi and Byrne, 2008). It is a risk factor for coronary heart disease, as well as for diabetes, fatty liver, and several cancers. The clinical manifestations of this syndrome may include hypertension, hyperglycemia, hypertriglyceridemia, reduced high-density lipoprotein cholesterol, and abdominal obesity (Grundy *et al.*, 2005; Malik and Razig, 2008).

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Patients meeting these diagnostic criteria have a greater risk of developing diabetes mellitusand coronary heart disease. Pooled data from 37 studies involving more than 170,000 patients have shown that metabolic syndrome doubles the risk of coronary artery disease (Haglin, 2001). Calcium is a versatile intracellular messenger that is used throughout the life cycle of an organism to control diverse biological processes. It has been suggested that metabolic syndrome and cardiovascular disease are linked by a common defect of divalent cation metabolism, namely calcium (Kjeldsen *et al.*, 1998). Lind *et al*. suggested that serum calcium was highly associated with individual components of metabolic syndrome and alterations of serum calcium could play an important role in the development of

this syndrome (Bucher *et al.*, 1996). Parathyroid hormone increases intracellular calcium by stimulating calcium channels and thus influence insulin sensitivity and blood pressure. Increased serum calcium concentration has been found to be associated with high blood pressure, impaired glucose tolerance, and dyslipidemia. Also increased serum calcium concentration has been described as a feature of the metabolic syndrome. Haglin presented a hypothesis in 2001 suggesting that low serum phosphate is the cause of the disturbed metabolism in the metabolic syndrome (Haglin, 2001). This was based on the fact that serum phosphate is an important component of energy metabolism (Grundy *et al.*, 2005; Malik and Razig, 2008). Reduction of serum phosphate levels could therefore theoretically contribute to the pathogenesis of the syndrome by leading to disturbances in energy metabolism resulting in insulin resistance, hyperglycemia, disturbed lipid metabolism, increased weight, and hypertension. It was suggested for the first time in 1926 that hypophosphatemia might contribute to impaired glucose tolerance (Lind *et al.*, 1988). More recently, hypophosphatemia has been linked to impaired glucose utilization, insulin resistance, and hyperinsulinemia (Bucher *et al.*, 1996; Lind *et al.*, 1988; Fardella and Rodriguez-Portales, 1995) in patients with the metabolic syndrome; a negative correlation between serum phosphate and body mass index (BMI) has been observed (Kim *et al.*, 2008; Wang *et al.* 2008). Recent studies shows that the phosphate is involved directly in carbohydrate metabolism: hypophosphatemia can result in impaired utilization of glucose, insulin resistance, and hyperinsulinemia (Dobnig *et al.*, 2008). So, reduced phosphate levels may contribute directly to the development of the obesity, hypertension, and dyslipidemia that characterize metabolic syndrome. The aim of the present study is to investigate the relation of calcium, phosphate levels with the characteristics of metabolic syndrome, as well as the mechanism that may be responsible for alterations in serum calcium and phosphate level in patients with this syndrome.

Objectives

- õ To determine serum calcium levels in patients with metabolic syndrome.
- õ To determine serum phosphorus levels in patients with metabolic syndrome.
- õ To assess the correlation of serum calcium with components of metabolic syndrome.
- õ To assess the correlation of serum phosphorus with components of metabolic syndrome.

MATERIALS AND METHODS

Source of data

Study comprised of 30 patients with metabolic syndrome of age group 30-65 years and 30 healthy individuals of same age group, attending the outpatient & in patient departments of Medicine of Victoria hospital and Bowring and Lady Curzon Hospitals attached to Bangalore Medical College and Research Institute, Bangalore.

Study design: Case control study.

Sample size: 60, with 30 cases and 30 age and sex matched controls.

Inclusion criteria

All patients were diagnosed according to International Diabetes Federation criteria and it requires the presence of waist circumference : ≥ 90cm(males) and ≥80cm(females) along with 2 or more of the following:

- Fasting triglyceride level: >150mg/dl or on specific medications.
- HDL cholesterol <40mg/dl(men) and <50mg/dl(females) or on specific medications,
- Blood pressure :systolic>130mm Hg or diastolic>85mmHg or on specific medications
- Fasting blood glucose ≥100mg/dl or previously diagnosed type 2 Diabetes mellitus

Exclusion criteria

- patients with known preexisting liver or kidney diseases or with thyroid dysfunction,
- individuals consuming more than 30g/wk of alcohol and drugs that may interfere with glucose or lipid metabolism (corticoids, beta blockers)

Methodology

Following selection of subjects & after obtaining informed consent about the proposed study, about 3 ml of fasting venous blood was obtained by venepuncture under aseptic precautions. After centrifugation, serum was used for estimation of parameters required for the study. Serum parameters measured were: concentration of glucose, total cholesterol, HDL - cholesterol , LDL cholesterol, triglycerides, calcium and phosphate .All above parameters were measured by automated clinical chemistry analyser BECKMAN COULTER AU480.

RESULTS

Data is expressed as mean ± SD. Unpaired t-test was used for comparison between study groups, whereas differences in proportions were assessed by using chi-square test; $p<0.05$ is considered significant.

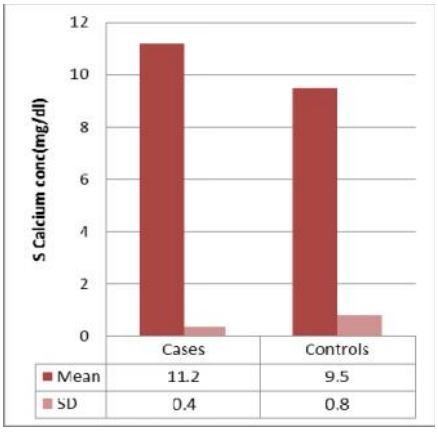


Figure 1. Serum calcium in cases and controls

There were no differences in age, sex distribution between cases and controls, however, patients with metabolic syndrome had significantly greater body mass index (BMI) and waist circumference values compared to controls. Patients with metabolic syndrome had greater fasting glucose values ($p<0.001$). In addition, these patients showed significantly greater blood pressure values (both systolic and diastolic). Finally, patients in the metabolic-syndrome group had an adverse lipid profile, characterized by elevated concentrations of total cholesterol, LDL cholesterol, and triglycerides, as well as lower concentrations of HDL cholesterol.

Biochemical Characteristics of the Study Population

Biochemical Parameter	Cases	Controls	P
FBS (mg/dl)	107±17	92 ± 9	≤ 0.001
SBP (mm Hg)	158±16	134±22	0.08
DBP (mm Hg)	95 ± 10	82 ± 14	≤0.001
TC (mg/dl)	242 ± 45	226 ± 41	≤0.001
TAG (mg/dl)	177 ± 77	107 ± 52	≤0.001
HDL (mg/dl)	38 ± 8	51 ± 12	≤0.001
LDL (mg/dl)	169 ± 42	154 ± 36	0.02
Calcium(mg/dl)	11.2±0.8	9.5 ± 0.4	≤0.001
Phosphate(mg/dl)	2.5±0.7	3.3 ± 0.5	≤0.001

Serum calcium levels were higher than normal range in cases compared to controls with mean ± SD of 11.2 ±0.8 and 9.5±0.4 respectively. Serum phosphate levels were lower than the normal range in cases compared to controls with mean ± SD of 2.5± 0.7 and 3.3± 0.5 respectively.

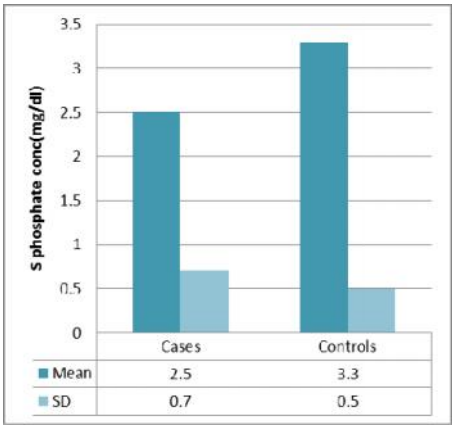
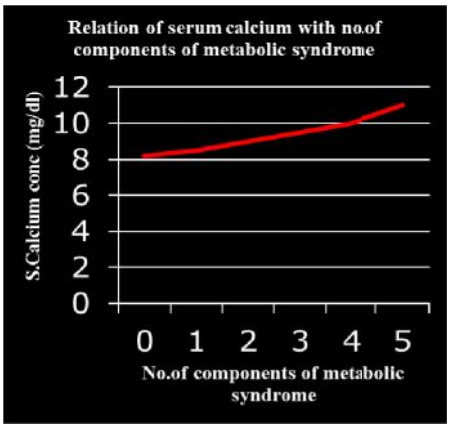


Figure 2. Serum phosphate in cases and controls

Serum calcium concentration increases linearly with increase in number of components of metabolic syndrome.



Serum phosphate concentration decreases with increase in number of components of metabolic syndrome.

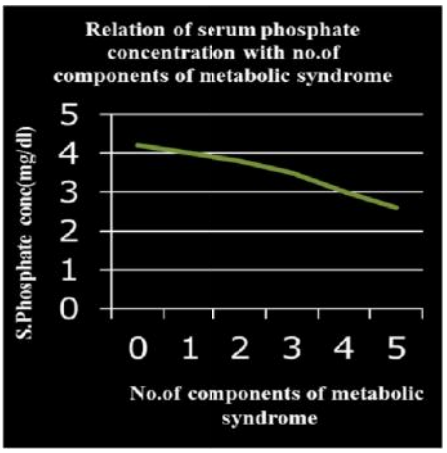


Table 2. Pearson correlation of serum calcium levels with individual components of metabolic syndrome in cases

Components of Metabolic syndrome	Correlation coefficient 'r'	p value
BMI(Kg/m^2)	0.033	0.354
WC(cm)	0.018	0.536
SBP(mmHg)	0.004	0.74
DBP(mmHg)	0.027	0.021
FBs(mg/dl)	0.148	<0.001
TC(mg/dl)	0.181	<0.001
S HDL(mg/dl)	0.090	<0.001
S TGs(mg/dl)	0.116	<0.001

Table 2, shows that serum calcium concentration has weak positive correlation with FBS, TC, serum HDL and serum triglycerides. There is no significant correlation with BMI, WC and systolic BP.

Table 3. Pearson correlation of serum phosphate levels with individual components of metabolic syndrome in cases

Components of Metabolic syndrome	Correlation coefficient 'r'	p value
BMI(Kg/m^2)	0.022	0.313
WC(cm)	-0.620	<0.001
SBP(mmHg)	-0.804	<0.001
DBP(mmHg)	-0.727	<0.001
FBs(mg/dl)	-0.748	<0.001
TC(mg/dl)	0.181	0.531
HDL(mg/dl)	0.690	<0.001
TGs(mg/dl)	-0.716	<0.001

Table 3, shows that serum phosphate concentration has negative correlation with FBS, TG, blood pressure and WC. There is a weak positive correlation with HDL-Cholesterol.

DISCUSSION

Patients with metabolic syndrome has increased BMI, WC, FBS, systolic BP, diastolic blood pressure and altered lipid profile (decreased serum HDL and increased serum triglycerides) Patients showed significantly lower phosphate concentrations and elevated calcium concentrations compared with controls. Serum calcium concentration has weak positive correlation with FBS, TC, serum HDL and serum triglycerides.

There is no significant correlation of serum calcium with BMI, WC and systolic BP. Serum phosphate concentration has negative correlation with FBS, TG, blood pressure, WC and a weak positive correlation with HDL-Cholesterol. The reduction in phosphate concentration and increase in calcium concentration were proportional to the number of components of metabolic syndrome. Present study findings are in agreement with the studies done by Haglin, Rigas Kalaltzidis and Geum Joon Cho (Haglin, 2001; Kalaitzidis *et al.,* 2005; Geum Joon *et al.,* 2001). Phosphate depletion may result from decreased dietary intake or reduced intestinal absorption, increased urinary excretion, and internal redistribution (Paula *et al.,* 1998). In 2001, Haglin proposed that an unbalanced diet, characterized by low phosphate and high carbohydrate consumption, may lead to reduced serum phosphate levels in patients at risk for the development of metabolic syndrome. Reduced phosphate levels in the metabolic-syndrome group may represent the consequence of increased transfer of phosphate from the extracellular to the intracellular compartment (Kjeldsen *et al.,* 1998). The activation of sympathetic nervous system observed in patients with metabolic syndrome and the resulting increment in serum catecholamine levels also contribute to the intracellular shift of phosphate (Resnick, 1989; Kim *et al.,* 2010). Both insulin and catecholamine stimulate glycolysis, thus increasing the intracellular formation of phosphorylated carbohydrate compounds in the liver and skeletal muscles. The source of this phosphate is the inorganic phosphate of the extracellular fluid; serum phosphate concentrations may decrease rapidly (Kim *et al.,* 2010).

Because phosphate is vital to carbohydrate metabolism, it is possible that the reduced levels of this ion in patients with metabolic syndrome may decrease the peripheral utilization of glucose, thus leading to the development or exacerbation of insulin resistance. In this case, the resulting compensatory hyperinsulinemia can further decrease phosphate concentrations; there is a vicious circle that may contribute to the pathogenesis of metabolic syndrome. Besides the classical functions of PTH and vitamin D, these hormones play important roles in the development of metabolic syndrome, insulin resistance and synthesis, obesity, diabetes, and hypertension (Sowers *et al.,* 1998). Increase in serum calcium was shown to activate lipogenesis and to inhibit lipolysis. Increased levels of calcium leads to accumulation of triglyceride in adipocytes and activation of lipogenesis and obesity (Berridge *et al.,* 2000). Studies reported that elevated serum calcium levels may increase vascular smooth muscle intracellular calcium causing an increase in vascular smooth muscle tone, peripheral vascular resistance, and BP (Ahlström *et al.,* 2009). Studies suggest that secondary hyperparathyroidism may contribute to the development of metabolic syndrome. Thus, a dietary pattern characterized by a high intake of calcium may down regulate PTH release, resulting in a reduced risk of metabolic syndrome (George *et al.,* 2013).

Conclusion

Altered calcium and phosphate metabolism in metabolic syndrome is evident from the present study. Secondary hyperparthyroidism is found to be associated with metabolic syndrome which may be responsible for altered calcium and phosphorus metabolism. Causal association of these metabolic alterations with metabolic syndrome is not established .These metabolic alterations increase the risk of CVD in metabolic syndrome patients who are already prone for CVD. Hypercalcemia and hypophosphotemia, if detected and corrected early in patients of metabolic syndrome, the components of this syndrome can be reversed and these patients can be protected from the risk of CVD.

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