ORIGINAL ARTICLE

# Association of Plasma Procalcitonin with Various Components of Metabolic Syndrome and Insulin Resistance in Urban Indian Population: A Novel Biomarker

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## Abstract

**Rationale**: Chronic low-grade inflammation is proposed as the keystone in pathogenesis of metabolic syndrome. The inflammatory biomarker Procalcitonin which is produced by adipose tissue, can serve as a biomarker for insulin resistant state present in metabolic syndrome.

**Objectives:** To evaluate the association of plasma Procalcitonin (PCT) with components of metabolic syndrome (abdominal obesity, dyslipidemia, hypertension, and hyperglycemia) and with insulin resistance as compared to healthy controls.

**Design:** In this case-control study Plasma Procalcitonin was measured in patients with metabolic syndrome and compared to healthy controls. Its association was investigated with insulin resistance, individual components of metabolic syndrome, cardiovascular complications and microalbuminuria.

**Result:** Plasma Procalcitonin was significantly higher (mean 0.55 ± 0.60 ng/ml, Median 0.156 ng/ml) in 53 patients with metabolic syndrome (n = 53) as compared to 26 healthy controls ($p < 0.001$). PCT significantly correlated with level of Insulin Resistance ($p<0.01$), Waist Circumference, S. Triglycerides, S. VLDL ($p <0.05$), fasting blood glucose ($p <0.01$) and inversely with S.HDL ($p<0.05$). PCT was significantly higher in patients with cardiovascular complication (n=16/53, z = -7.137) and in those with microalbuminuria (n=18/53, z = - 7.265) as compared to cases without complications.

**Conclusion:** Raised plasma procalcitonin levels in the normal range are associated with insulin resistance and components of the metabolic syndrome (abdominal obesity, hypertriglyceridemia, high VLDL, low HDL and hyperglycemia), suggesting its role as a promising biomarker.


## Introduction

Metabolic syndrome is a growing epidemic in India affecting more than one-third population in large cities[1]. Metabolic syndrome(MS) which is a clustering of metabolic risk factors (at least three out of five components) namely abdominal obesity, hypertension, hyperglycemia, high serum triglyceride levels and low serum HDL. MS harbingers the co-occurrence of risk factors for both type 2 diabetes and cardiovascular diseases (CVD) which have been attributed to the underlying insulin resistance (IR). MS being a constellation of conditions, there is lack of any one specific and sensitive laboratory parameter which can facilitate its prompt detection. Also, estimation of insulin resistance is a tedious process. Hence, a reliable biomarker for the diagnosis of MS and insulin-resistant state is the need of the hour.

Chronic low-grade inflammation is the key pathophysiological factor related to insulin resistance[2] and thus to all the components of MS, for which secretory role of adipose tissue has been implicated.[3] Procalcitonin is a polypeptide precursor of hormone calcitonin that is released in response to systemic inflammation not only by neuroendocrine cells of the lungs, intestine, and thyroid (C cells), but also by adipose tissue.[4,5] Thus plasma procalcitonin can serve as a potential biomarker for detection of obesity-related low-grade inflammation even in the very early stages. Available data in this regard is scarce and there is no data from India. Abbasi et al have described plasma procalcitonin to be associated with obesity, insulin resistance and all components of MS in a study from Netherland.[6] Indians with MS are phenotypically different from Caucasians, they tend to develop hypertension, hyperglycemia, and hypertriglyceridemia at lower levels of BMI and Waist Circumference.[7,8] Furthermore, Indians have an excess of truncal subcutaneous fat which positively correlates with insulin resistance. This makes the generalization of existing data to Indian population difficult.

The objective of this case-control study was to assess plasma procalcitonin levels in patients with metabolic syndrome as compared to healthy controls and to study its association with Insulin Resistance and components of the Metabolic syndrome; namely dyslipidemia, hypertension, hyperglycemia and abdominal obesity. We also aimed

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**Table 1: Demographic, anthropometric and laboratory parameters amongst cases and controls**

| Parameters | Cases (n = 53) | | Controls (n = 26) | |
|---|---|---|---|---|
| | Mean | SD | Mean | SD |
| Age (years) | 52.150 | 8.86 | 54.15 | 9.84 |
| Ht. (cm) | 160.020 | 7.45 | 160.15 | 7.17 |
| Wt. (kg) | 89.810 | 9.24 | 60.38 | 8.75 |
| BMI | 35.103 | 3.21 | 23.42 | 1.90 |
| Waist Circumference (cm) | 108.210 | 8.45 | 63.88 | 11.67 |
| SBP (mmHg) | 140.230 | 10.22 | 115.54 | 7.19 |
| DBP (mmHg) | 83.850 | 9.57 | 73.31 | 6.64 |
| TG (mg/dl) | 346.09 | 154.84 | 123.81 | 19.30 |
| Cholesterol (mg/dl) | 237.30 | 65.28 | 119.31 | 22.89 |
| HDL (mg/dl) | 36.08 | 8.85 | 61.98 | 12.86 |
| LDL (mg/dl) | 149.81 | 59.88 | 36.30 | 22.20 |
| VLDL (mg/dl) | 49.41 | 24.69 | 22.84 | 6.66 |
| RBS (mg/ml) | 206.13 | 69.92 | 87.60 | 14.02 |
| F. Insulin (µIU/ml) | 17.63 | 8.94 | 6.82 | 1.98 |
| HOMA IR | 2.96 | 1.60 | 0.88 | 0.27 |
| HOMA ß % | 45.18 | 25.29 | 97.65 | 34.12 |
| Pl. Procalcitonin (ng/ml) | 0.55 | 0.60 | 0.00 | 0.00 |
| S. Uric acid (mg/dl) | 5.86 | 1.36 | 3.53 | 0.94 |
| Ur. micro albumin (mg/dl) | 90.32 | 131.0 | 0.00 | 0.00 |

to gauge the association of plasma procalcitonin with complications of metabolic syndrome at presentation and during short-term follow-up.

## Participants and Methods

This prospective case control study was performed on patients presenting to a tertiary referral center in Mumbai from Sept 2011 to June 2015 after obtaining permission from the institutional ethics committee. Patients aged more than 18 years with Metabolic Syndrome were enrolled as cases (n=53) after voluntary informed consent. MS was defined as per International Diabetes Federation (IDF) consensus 2006 definition[9] as participants having increased waist circumference (South Asian cutoff ≥ 90cm for men and ≥80cms for women) plus any two of the following: Triglycerides ≥ 150 mg/dl or treatment for triglycerides; HDL cholesterol < 40 mg/dl in men and < 50 mg/dl in women or treatment for HDL; Systolic BP > 130 or diastolic BP >85 mm Hg or treatment for hypertension; Fasting plasma glucose ≥100 mg/dl , or treatment for type 2 diabetes.

Patients on lipid lowering drugs, with S. Creatinine >1.2 mg/dl and those

**Table 2: Clinical characteristics of cases**

| Parameter | Cases n=53 (%) |
|---|---|
| Obesity Class | |
| Overweight (BMI =25 -29.9) | 1 (1.9%) |
| Class I (BMI = 30 -34.9) | 22 (41.5%) |
| Class II (BMI =35 – 39.9) | 26 (49.1%) |
| Class III (BMI >40) | 4 (7.5%) |
| Presence of HTN | 38 (71.7%) |
| Presence of DM | 28 (52.8%) |
| ECG abnormality | |
| Normal | 34 (1.9%) |
| Left Ventricular Hypertrophy | 4 (7.5%) |
| Right bundle branch block | 1 (1.9%) |
| ST-T abnormalities | 13 (24.5%) |
| 2D Echocardiography | |
| Normal | 39 (73.6%) |
| Regional wall motion abnormality | 6 (11.3%) |
| Concentric LVH | 8 (15.2%) |
| Complications at presentation/ follow-up | |
| Myocardial infarction | 6(11.3%) |
| Unstable angina | 3 (5.7%) |
| Cerebrovascular accident | 7 (13.2%) |
| Microalbuminuria | 18 (34%) |

who had any evidence of infections were excluded. Age and sex matched healthy volunteers were recruited as controls (n=26).

For all the participants, complete medical history and physical examination including BMI and anthropometric measurements were recorded. Complete lipid profile, fasting plasma insulin, fasting blood glucose, microalbuminuria, electrocardiogram and echocardiography were performed for all the participants. Insulin resistance was calculated by the homeostasis model assessment for insulin resistance (HOMA-IR) using the formula: Fasting Glucose (mg/dl) X Fasting Insulin (mIU/ml)]/405.[10,11]

Plasma Procalcitonin (PCT) was analyzed using fully automated PCT sensitive KRYPTOR Random Access Analyzer.[12,13] (BRAHMS PCT sensitive LIA; Hennigsdorf, Germany). Blood sample volume needed was 50 µl, collected in EDTA aliquots with an incubation time of 19 minutes. Its measuring range is between 0.02 and 5000 ng/ml. The functional assay sensitivity (defined as the lowest analyte concentration that can be determined with an inter-assay CV <20) was 0.06 ng/ml with a probability of 95%. Its Analytical sensitivity (the detection limit calculated using the imprecision profile) is 0.019 ng/ml with a probability of 95 %. The intra-assay Coefficient of Variation (CV) and the inter-assay CV is 2-3% on the whole PCT concentration range. The antibodies used in this assay show no cross-reaction with human calcitonin (up to 2.5 ng/ml), human katacalcin (up to 10 ng/ml), human α-CGRP and ß-CGRP (up to 4 µg/ml). This assay technique has been described previously.[12]

All participants were screened for cardiovascular complications and microalbuminuria at the time of presentation and for next 3 months of follow-up.

Descriptive statistics were reported as frequency and percentage for categorical variables and mean and SD for continuous variables. Multivariate adjusted linear regression analysis was used to assess the independent predictor of IR. Correlation between plasma PCT, IR and various components of MS. IR was calculated using Pearson correlation coefficient (2 tailed tests). Mann-Whitney test was used to compare plasma PCT levels in cases versus controls; and also, amongst cases which had complications of metabolic syndrome. "p value" ≤0.05 from two-sided tests was considered statistically significant.

## Results

There were 30 (56.6%) males in the cases group (those with MS). Of 26 controls, 14 (53.8%) were males. Cases and controls were matched with respect to age and gender. Demographic, anthropometric, clinical and biochemical parameters of cases and controls are described (Tables 1, 2).

Plasma Procalcitonin (PCT) levels were higher in cases (Mean 0.55 ± 0.60 ng/ml; Median 0.156ng/ml; Range 0.002 – 1.990) as controls (Mean 0.001 ± 0.0 ng/ml; Median 0.00ng/ml; Range 0 – 0.01). This difference was statistically significant (Mann - Whitney "z": -7.02). PCT significantly correlated with level of Insulin Resistance as measured by HOMA-IR (Pearson correlation coefficient 0.771; p<0.01) (Figure 1). Amongst the various components of MS, PCT significantly correlated with Waist Circumference, S. Triglycerides, S. VLDL (P< 0.05) and with fasting blood glucose. (P< 0.01) and inverse significant correlation with S. HDL (Figure 2 and Table 3). However, there was no significant correlation between PCT and Systolic/ diastolic BP, S.

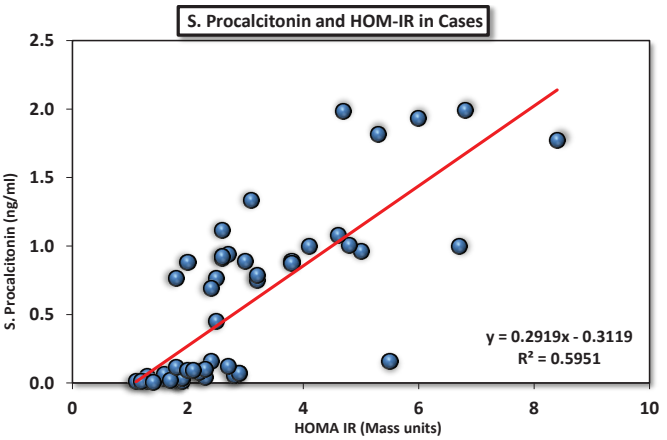


**Fig. 1: Correlation between S. Procalcitonin and HOMA-IR in cases**

**Table 3: Correlation of components of metabolic syndrome with HOMA- IR and procalcitonin**

| Components | Correlation with HOMA-IR (Mass units) | | Correlation with Procalcitonin (ng/ml) | |
|---|---|---|---|---|
| | Pearson coefficient | P value | Pearson coefficient | P value |
| Waist circumference | 0.337 | 0.014* | 0.290 | 0.0353* |
| SBP | 0.177 | 0.205 | 0.098 | 0.4832 |
| DBP | 0.103 | 0.464 | 0.198 | 0.1546 |
| Triglycerides | 0.305 | 0.026* | 0.288 | 0.0364* |
| Cholesterol | 0.069 | 0.623 | 0.144 | 0.3044 |
| HDL | -0.296 | 0.032* | -0.300 | 0.0292* |
| LDL | -0.112 | 0.424 | -0.014 | 0.9201 |
| VLDL | 0.351 | 0.01* | 0.297 | 0.0307* |
| Fasting blood sugar | 0.665 | 5.46E-08** | 0.578 | 5.93E-06** |

*Correlation is significant at the 0.05 level (2-tailed). **Correlation is significant at the 0.01 level

Cholesterol and S. LDL. Amongst all the components of MS, only fasting blood glucose was found to be independent predictor of IR on multivariate regression analysis ($p<0.001$).

PCT was significantly higher in patients with cardiovascular complication (n=16/53, z = -7.137) and in those with microalbuminuria (n=18/53, z = - 7.265) as compared to cases without complications.

## Discussion

Our results demonstrate association of raised levels of plasma Procalcitonin (in the normal range) with various components of metabolic syndrome and insulin resistance as compared to controls. We also found correlation of Procalcitonin with components of MS and with cardiovascular complications and microalbuminuria. To the best of our knowledge, this is the first study unveiling this association in Indian population. Our results are consistent with emerging data which suggests that Procalcitonin can be raised in the state of inflammation in absence of systemic infection.[14,15] MS is associated by infiltration of adipocytes by activated macrophages, phenomenon which leads to excess procalcitonin production by adipocytes *in vitro*,[4] thus similar secretory function may play a role in vivo too. This association is also studied in other diseases involving insulin resistance and abdominal obesity like polycystic ovarian syndrome.[15]

Amongst the components of metabolic syndrome, Procalcitonin was significantly associated with waist Circumference, S. Triglycerides, S. HDL and S. VLDL, hyperglycemia and with insulin resistance; but not with Blood pressure, S. Cholesterol and S. LDL. This partially conforms with findings of Abassi et al[6] where both procalcitonin and insulin resistance were associated with all the components of metabolic syndrome in Dutch population. This can be attributed to the ethnic differences and hence future studies are warranted to explore the role of procalcitonin and insulin resistance in Indian Population.

The fact that Procalcitonin is implicated in the pathophysiology of metabolic syndrome is further amplified by the finding that cases with metabolic syndrome with complications (cardiovascular and renal) had higher levels of Procalcitonin as compared to those without. This points towards the higher level of inflammation in this subset of population, which is at a higher risk for complications and thus will be maximally benefitted by aggressive therapeutic measures.

With the help of advanced PCT sensitive KRYPTOR Random Access Analyzer, it is now possible to measure plasma Procalcitonin within the normal range, with lowest detectable value of 0.06ng/ml. As there was no data addressing value of in plasma Procalcitonin in the general population, healthy age and sex matched controls were recruited only for the comparison of procalcitonin levels. We found that the level of plasma Procalcitonin was significantly lower in controls as compared to cases.

The importance of plasma procalcitonin as a biomarker for metabolic syndrome is highlighted by the fact that it is an easily available, one-time test which doesn't require fasting samples and the results are available within 25 minutes of centrifugation of the sample. Thus, it saves time and resources and is ideal for a developing country like ours. The scope of plasma procalcitonin can be extended to screening of relatively younger obese population who have not yet developed all the components of MS, but are at significantly higher risk as result of obesity related inflammation. This, if proved in larger prospective studies, may help detection of this younger population which will benefit maximally from rigorous life style modifications and timely pharmacological intervention. This may lead to prevention of further complications.

Smaller sample size and shorter duration of follow-up were notable limitations of our study. Also, as our participants belonged to urban India our results may be not be generalizable to whole population. This paves way for larger population-based study with longer follow-up for assessment of the role of procalcitonin as a biomarker for insulin resistance and metabolic syndrome.

In conclusion, our findings based on urban tertiary referral center data, suggest that higher plasma procalcitonin levels in the normal range are associated with insulin resistance and increased measures of abdominal obesity (waist circumference), other components of the metabolic syndrome (hypertriglyceridemia, low HDL, high VLDL and hyperglycemia) and higher rates of complications. Thus, plasma procalcitonin is a promising novel biomarker for chronic low-grade inflammation secondary to adipocyte

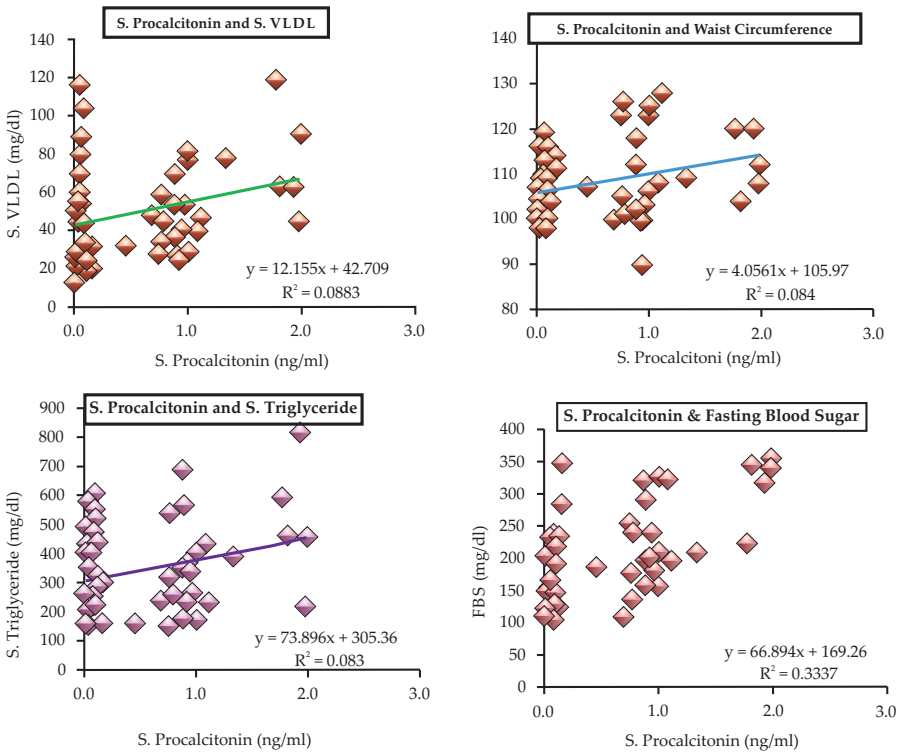


**Fig. 2: Correlation of S. Procalcitonin with components of metabolic syndrome**

dysfunction underlying metabolic syndrome; and can be used for early detection of this subset of population requiring timely therapeutic interventions.


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