

Microalbuminuria and Hyperinsulinemia as Predictors of Cardiovascular Disease in Metabolic Syndrome Patients

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Abstract: ***Introduction:** Metabolic syndrome is a cluster of metabolic factors which includes central obesity, insulin resistance, dyslipidemia, and hypertension. Microalbuminuria has also been considered to be a component of metabolic syndrome. It is associated with a two fold increase in cardiovascular diseases and 1.5 fold rises in all cause mortality. Microalbuminuria has an ability to predict cardiovascular disease mortality as it is a marker for endothelial injury. **Materials and Methods:** A cross sectional study was performed including 250 subjects aged between 18-60 years in a state of fasting for atleast 10 hours. Fasting insulin, fasting blood sugar, lipid profile and urinary microalbumin creatinine ratio (ACR) measurement were done in metabolic syndrome patients. Independent t test and chi square test were done to analyze the data. A p value <0.05 was considered statistically significant. **Results:** Hyperinsulinemia was found to be strongly and significantly associated with microalbuminuria and urinary microalbumin creatinine ratio (p value < 0.0001). There was a strong and highly significant correlation between insulin and urinary ACR. Microalbuminuria was also found to be significantly associated with diastolic blood pressure (p= 0.021) and systolic BP (p=0.016). **Conclusion:** Microalbuminuria has been reported to be a good cardiovascular marker by many research workers. In our cross sectional study, a strong and significant association has been observed between hyperinsulinemia and microalbuminuria. Hence hyperinsulinemia and microalbuminuria predict probability of developing cardiovascular disease and there is a need for developing guidelines for their management to decrease the global burden of cardiovascular diseases.*

Keywords: Metabolic Syndrome, Hyperinsulinemia, Microalbumin Creatinine Ratio, Microalbuminuria, Cardiovascular Disease

1. Introduction

Microalbuminuria is excretion of albumin in urine in the range of 20-200 microgram per minute. It is often expressed as Microalbumin Creatinine ratio and the range is 30-300 mg of albumin/gram of Creatinine in urine [1]. Microalbuminuria has been found to be associated with the metabolic syndrome, a syndrome of insulin resistance, obesity, hypertension, dyslipidemia and increased renal and cardiovascular morbidity [2]. According to Steno hypothesis [3] albuminuria reflects a widespread vascular dysfunction. Leakage of albumin and other plasma macromolecules may cause an inflammatory reaction that heralds the process of atherosclerosis hence increasing cardiovascular diseases. The predictive powers of microalbuminuria levels for cardiovascular risk are independent of other cardiovascular risk factors and not only present in individuals with diabetes and or hypertension but also in healthy individuals. Lowering albuminuria could decrease cardiovascular diseases [4].

Fasting serum insulin has been used as a surrogate index of insulin sensitivity in several epidemiological studies [5, 6] and hence Hyperinsulinemia indicates insulin resistance. A better approach for estimating insulin sensitivity or insulin resistance (IR) is the Homeostasis Model Assessment (HOMA), developed by Matthew et al. [7]. These authors stated that HOMA-IR scores strongly correlate with glucose clamp assessed insulin sensitivity.

Nearly 15-16 % of global mortality due to coronary heart disease (CHD) is contributed by India [8]. Insulin resistance and its metabolic consequences are increasingly being recognized as risk factors for CHD. Also there has been a relationship between the number of metabolic syndrome components and corresponding prevalence of microalbuminuria. Framingham Heart Study found that 6 year risk of cardiovascular disease was 3 fold higher in non hypertensive, non diabetic subjects with urinary albumin Creatinine ratio above the gender specific median than in those with urinary albumin Creatinine ratio below the median [9]. Causes of increased incidence of Microalbuminuria in insulin resistance patients is said to be due to increased permeability of vascular endothelial cell layer which is related to endothelial dysfunction leading to decreased bioavailability of nitric oxide [10]. Furthermore it has been found that Hyperinsulinemia may cause glomerular hypertension as well as hyperfiltration leading to increased albumin ultrafiltration and excretion [11]. A clear association has been found between more severe insulin resistance and Microalbuminuria [12]. In this study, an attempt has been made to find out an association between insulin resistance and Microalbuminuria as well as other markers of CVD in Indian patients.

2. Materials and Methods

A cross sectional study have been performed including the

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subjects coming for routine health check up or blood sugar check up to the Department of Biochemistry in a tertiary care centre, RIMS, Ranchi, India.

Subjects: A total of 250 subjects were selected for this study in between October 2012 to September 2013 out of which 160 subjects fulfilled the criteria of metabolic syndrome. Further 48 subjects were not considered for the study. Among 48 subjects, 12 were not willing to participate in the study, 10 had urinary tract infection, and 26 had acute or chronic illness due to which they were excluded. Finally 112 cases were enrolled for the study which was approved by the Institutional Ethics committee, RIMS, Ranchi.

Methods: Metabolic syndrome was diagnosed as per the criteria of modified NCEP ATP III definition [13]. Metabolic syndrome was considered to be present if three or more of the following definition criteria were present:-

- 1) Waist Circumference ≥ 90 cm in men and ≥ 80 cm in women.
- 2) Serum triglyceride ≥ 150 mg/dL
- 3) HDL cholesterol < 40 mg/dL in men and < 50 mg/dL in women or treatment for low HDL
- 4) Systolic blood pressure ≥ 130 mm Hg and or diastolic blood pressure ≥ 85 mm Hg
- 5) Serum fasting glucose ≥ 100 mg/dL
- 6) Body Mass Index ≥ 23 kg/m²

Inclusion Criteria:

Inclusion criteria were willingness to participate in the study, age between 18-60 years and a state of fasting for atleast 10 hours.

Exclusion Criteria:

Exclusion criteria included the patients suffering from any acute or chronic diseases like liver disease, renal disease, cardiac disease, respiratory disease or any other acute or chronic diseases. Patients suffering from AIDS, thyroid disorders or psychiatric illness or on insulin therapy were excluded. Patients having ≥ 5 pus cells in their urine were

also excluded from this study as this may cause albuminuria.

The baseline examination included fasting blood samples for glucose and lipid profile. Anthropometric measurements were done and a lifestyle questionnaire was filled up. The patients diagnosed to be having metabolic syndrome were selected and called for study participation in fasting state. They were told not to exercise or exert heavily on the day they had to come for sampling. Their blood samples were taken for biochemical examination. A spot urine collection was done for estimation of urinary microalbumin creatinine ratio.

Biochemical Examination: Fasting blood sugar, lipid profile and urinary ACR were analyzed in an automated analyzer (Beckman Coulter AU480). Insulin was measured by a chemiluminescent immunometric auto analyzer (Abbott i1000 SR). All the samples were kept at 2-8 °C and either analyzed same day or kept at -20 °C to be analyzed within next two days.

Statistical analysis: Statistical analysis was performed using SPSS software version 20.0 Data were expressed as mean \pm SD for continuous variables. Independent t test and chi square test were done to analyze the data. A p value < 0.05 was considered statistically significant. Associations between metabolic variables as well as anthropometric measurements were determined using Pearson Correlation analysis adjusted for age, sex and BMI. High and low HOMA IR were defined as > 2.3 and < 2.3 [14, 15] whereas hyperinsulinemia was defined as serum insulin level > 9.5 mIU/ml [16, 17].

3. Results

Hyperinsulinemia was present in 77.3 % of metabolic syndrome patients. Mean HDL level was 38.20 ± 7.17 , which is low and mean Triglyceride level was 190.89 ± 92.9 which is high in our study. However, no correlation was found between hyperinsulinemia and HDL or triglyceride level.

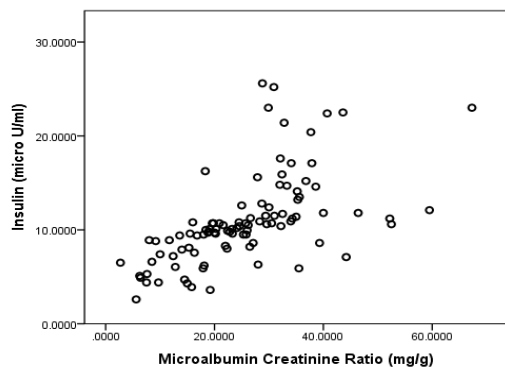
Table 1: Baseline demographic and biochemical characteristics of study participants on the basis of albuminuria

| | Overall (mean \pm SD) | Normoalbuminuria (mean \pm SD) | Microalbuminuria (mean \pm SD) | p value |
|---------------------|-------------------------|----------------------------------|----------------------------------|------------|
| N | 112 | 79 | 33 | |
| AGE | 37.13 \pm 8.11 | 36.99 \pm 8.43 | 37.48 \pm 7.42 | .769 |
| WEIGHT(Kg) | 62.52 \pm 8.23 | 61.96 \pm 7.23 | 63.85 \pm 10.24 | .271 |
| HEIGHT(Cm) | 156.47 \pm 7.11 | 155.96 \pm 6.76 | 157.7 \pm 7.87 | .241 |
| BMI | 25.55 \pm 3.05 | 25.51 \pm 2.89 | 25.65 \pm 3.47 | .834 |
| W/C (cm) | 88.16 \pm 7.89 | 88.11 \pm 7.42 | 88.27 \pm 9.03 | .923 |
| SBP | 133.57 \pm 18.44 | 130.89 \pm 16.86 | 140 \pm 20.65 | .016 |
| DBP | 86.62 \pm 9.57 | 85.28 \pm 9.64 | 89.82 \pm 8.71 | .021 |
| FPG(mg/dl) | 110.47 \pm 32.07 | 110.87 \pm 33.68 | 109.52 \pm 28.33 | .839 |
| T.Chol(mg/dl) | 186.6 \pm 55.49 | 187.14 \pm 53.34 | 185.3 \pm 61.19 | .874 |
| TG(mg/dl) | 190.89 \pm 92.94 | 196.47 \pm 102.84 | 177.55 \pm 62.62 | .328 |
| HDL (mg/dl) | 38.2 \pm 7.17 | 38.19 \pm 7.25 | 38.21 \pm 7.11 | .988 |
| Insulin(micro U/ml) | 10.81 \pm 4.67 | 9.36 \pm 3.82 | 14.28 \pm 4.75 | < 0.0001 |
| HOMA IR | 2.98 \pm 1.78 | 2.57 \pm 1.36 | 3.97 \pm 2.24 | < 0.0001 |

Table 1 displays the baseline demographic and biochemical characteristics of study participant based on ACR status. People who had Microalbuminuria were more likely to have high insulin levels. It has been observed that in

microalbuminuria, there is statistically significant difference between the insulin level which is high 14.28 ± 4.75 vs. 9.36 ± 3.82 , (p value < 0.0001), higher level of HOMA IR 3.97 ± 2.24 vs. 2.57 ± 1.36 , (p value < 0.0001), increased systolic

140 ± 20.65 vs. 130.89 ± 16.86, (p value 0.016) as well as diastolic blood pressure 89.82 ± 8.71 vs. 85.28 ± 9.64, (p value 0.021) compared to normoalbuminuria There was a positive correlation of ACR with diastolic blood pressure (p=0.015, r=0.228).



The graph shows positive correlation between insulin levels and urinary ACR levels in MS patients (p value <0.0001, r=0.389).

| | Normoinsulinemia (mean ± SD) | Hyperinsulinemia (mean ± SD) | p value |
|----------------|---------------------------------|---------------------------------|---------|
| N | 43 | 69 | |
| AGE | 38.28 ± 9.45 | 36.42 ± 7.14 | .240 |
| WEIGHT(Kg) | 60.12 ± 7.15 | 64.01 ± 8.54 | .014 |
| HEIGHT(Cm) | 154.86 ± 6.62 | 157.48 ± 7.27 | .058 |
| BMI | 25.18 ± 3.51 | 25.78 ± 2.73 | .311 |
| W/C(cm) | 87.56 ± 7.7 | 88.54 ± 8.03 | .526 |
| SES, N (%) | | | 0.021 |
| Low | 7 (6.2) | 3 (2.7) | |
| Middle | 29 (25.9) | 42 (37.5) | |
| High | 7 (6.2) | 24 (21.4) | |
| SBP | 134.7 ± 23.08 | 132.87 ± 15 | .612 |
| DBP | 86.26 ± 11.94 | 86.84 ± 7.82 | .755 |
| FPG(mg/dl) | 111.19 ± 22.5 | 110.03 ± 36.96 | .854 |
| T.Chol (mg/dl) | 188.07 ± 58.97 | 185.68 ± 53.64 | .826 |
| TG(mg/dl) | 175.77 ± 59.31 | 200.32 ± 108.13 | .175 |
| HDL (mg/dl) | 39.47 ± 7.92 | 37.41 ± 6.6 | .140 |
| HOMA IR | 1.94 ± 0.76 | 3.63 ± 1.92 | <0.0001 |
| U.Malb (mg/L) | 13.25 ± 9.82 | 21.49 ± 13.62 | .001 |
| U.Cr (g/L) | 0.85 ± 0.53 | 0.86 ± 0.49 | .939 |
| ACR | 16.87 ± 8.89 | 29.93 ± 9.88 | <0.0001 |

Table 2 displays the baseline demographic and biochemical characteristics of metabolic syndrome patients based on insulin status. Hyperinsulinemia was more prevalent in middle and high socio economic group patients as compared to low socio economic groups in our study group. Among higher socioeconomic group 77.4 % of patients were hyperinsulinemic and 22.6 % were normoinsulinemic. Among middle socioeconomic group 59.2 were hyperinsulinemic and 40.8 % were normoinsulinemic whereas 70 % of the low socioeconomic group were normal as compared to only 30 % being hyperinsulinemic.

The results from this study indicated that insulin resistance is very common among MS patients and it is strongly associated with Microalbuminuria. ACR has been considered to be a good cardiovascular marker and a marker for all-cause mortality in patients with MS [5, 21]. Steno hypothesis

suggested that albuminuria might reflect a general vascular dysfunction.

4. Discussion

Microalbuminuria has a strong association with increased carotid intimal medial thickness (IMT) and CAD in diabetic subjects [22]. The Heart Outcome Prevention Evaluation (HOPE) and Losartan Intervention For End point in hypertension trials (LIFE) found that albuminuria reduction from baseline predicted cardiovascular protection on follow up [23, 24]. Several studies highlight the importance of early intervention of Microalbuminuria to limit the excess cardiovascular morbidity and mortality [25, 26, 27]. In our study ACR was high in approximately 30 % patients of metabolic syndrome and it was found to be strongly and significantly associated with serum fasting insulin and HOMA IR values (p value <0.0001). This finding was consistent with the study of De Cosmo et al [28, 29]. Furthermore, simultaneous occurrence of hyperinsulinemia and microalbuminuria identifies a group of subjects with highly increased risk for CHD in elderly non diabetic subjects [30]. Insulin resistance causes endothelial dysfunction leading to decreased bioavailability of nitric oxide and acceleration of micro vascular disease. IR also adversely affects tubular albumin uptake leading to exertion of larger fraction of albumin. It also causes glomerular hyperfiltration [31] which in turn causes enhanced albumin ultrafiltration as well as excretion. In our study, no association could be found between fasting insulin or HOMA IR and waist circumference or BMI. This might be due to the fact that Asian Indians have high visceral fat often at BMI values in non obese range [32]. Indians have been found to have a mean BMI of 23.3 kg/m² with body fat approximately 35 % [33]. Intra abdominal fat is more in Asian Indians as compared to other ethnic groups and this may contribute to insulin resistance.

Our data demonstrated a significant association between ACR and SBP and DBP in metabolic syndrome patients and this is consistent with results from other studies [34, 35].

Low HDL and high triglyceride were present in 83 % and 76.8 % of people with metabolic syndrome respectively. However, in contrary to the fact that Hyperinsulinemia has been found to be associated with hypertriglyceridemia and low HDL cholesterol [34-36] no significant association was found between hyperinsulinemia and dyslipidemia in our study. This fact indicates that hyperinsulinemia correlates better with ACR [37] than with lipid profile in Indian MS patients. An important limitation of this study was the small sample size and that the ACR estimation was done only once. Nonetheless, the association that we observed between albuminuria and Hyperinsulinemia was statistically significant. Second, we did not measure abdominal adiposity by DEXA (Dual Energy X ray Absorptiometry) or CT (computed tomography).

ACR correlates with insulin status and is strongly associated with fasting insulin level as well as HOMA IR in Indian patients with MS. It may act as a good cardiovascular marker

in metabolic syndrome patients. ACR is significantly associated with systolic and diastolic blood pressure.

Hence, ACR and serum fasting insulin levels can be used as therapeutic target to reduce CV risk. Long term prospective trials are needed to establish the level of ACR and serum fasting insulin above which treatment should be instituted.

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