Role of adipocytokines in insulin resistance: Studies from Urban Western Indian Population

Sujata R Mahadik 1, Sudha S Deo 2, Suresh D Mehtalia 3

Sir Hurkisondas Narrotumdas Medical Research Society, Mumbai, India

Abstract

We determine the relative contribution of adipocytokines to insulin resistance (IR) in urban Western Indian population. The serum adipocytokine [leptin, adiponectin, resistin, tumor necrosis factor (TNF), and interleukin-6 (IL-6)] levels and their association with IR in different metabolic disorders state like obesity and type 2 diabetes mellitus (T2DM) was determined. A total of 215 subjects including 41 control, 41 obese, 89 T2DM and 44 diabetic patients with hypertension were recruited in this cross sectional study. Fasting adipocytokines and high sensitivity C Reactive Protein (hsCRP) levels were measured by ELISA method. Insulin Resistance index of Homeostasis Model Assessment (HOMA-IR) was calculated. The relation between these variables was studied by Univariate and multiple logistic regression analysis. Adipocytokine profile was altered in insulin resistance state like obesity and T2DM compared to controls. Stepwise multiple linear regression analysis with insulin resistance as a dependent variable shows that adiponectin as a significant predictor of insulin resistance in urban Western Indian population. Multiple logistic regression analysis using diabetes and obesity as the dependent variable revealed that adipocytokines had a strong association with insulin resistance. This study provides a strong association between adipocytokine and IR. With the increasing epidemic of obesity and T2DM in India, these adipocytokine markers that integrate metabolic and inflammatory signals may play important roles in the early detection of diabetes and planning of therapeutic strategies.

Keywords: Adipocytokines, insulin resistance, Urban Indian Population

Introduction

Asian Indians suffer from increased susceptibility to type 2 diabetes mellitus (T2DM), insulin resistance (IR) and cardiovascular disease (CVD) compared to Western population due to increased prevalence of central obesity and high body fat (%) even at low BMI 1-2. Central obesity is a well recognized risk factor for the development of IR, although the mechanism remains unclear. Central obesity is also associated with increased local adipose tissue inflammation. With the recent progress in adipocyte biology it is clear that adipose tissue is not just an energy storage organ but it is an active endocrine organ, secreting number of bioactive mediators (namely, leptin, adiponectin, resistin, TNFα, IL-6 collectively termed as adipocytokines 3,4. Excess adipose tissue and adipocytokines secreted by them may play an important role in IR 5,6,7.

The adipocytokine, leptin is a peptide hormone secreted principally but not exclusively by adipocytes. It plays an important role in the central regulation of food intake and energy expenditure 8. Although a strong correlation between serum leptin and insulin levels has been demonstrated in human studies 9, its role in type 2 diabetes is not yet clear.

Another adipocyte-derived hormone is resistin, a member of newly discovered cysteine rich secretory protein family. Initial studies in rodents suggest that it may be involved in the development of insulin resistance. 10 However, later studies failed to confirm this hypothesis. 11, 12, 13 Thus, the role of resistin in relation to obesity and insulin resistance is questionable.

Tumor necrosis factor α (TNFα) is a multi-potential cytokine with diverse immunologic function. TNFα has a variety of metabolic effect including increased lipolysis and decreased lipogenesis and also reduced insulin stimulated glucose transport thus contributing to insulin resistance by modulation of genes involved in glucose and lipid metabolism. 14 Thus, the role of TNFα in obesity induced insulin resistance in human is not so clear. 15 Interleukin 6 (IL-6) is a proinflammatory cytokine produced by many cell types including immune cell, fibroblast, endothelial cell, skeletal muscle and adipose tissue. The association between IL6 and insulin resistance is supported by many studies. 15, 16 IL6 may exert its adverse effect by increasing circulating free fatty acid (FFA) and decreasing adiponectin concentration. 17 Although much evidence implicates IL6 in insulin resistance there is some conflicting evidence that IL6 deficient mice were not protected from development of obesity and glucose intolerance. 18

Adiponectin is exclusively expressed in white adipose tissue and is located on chromosome 3q27 that have mapped a susceptibility locus for T2DM and metabolic syndrome. 3,4

Received on: 18/6/2009
Accepted on: 3/3/2010
Correspondence to: Ms. Sujata R Mahadik, Sir Hurkisondas Narrotumdas Medical Research Society, Raja Ram Mohan Roy Road, Girgaum, Mumbai: 400 004, India. E-mail: sujatais1@rediffmail.com
Low plasma adiponectin levels in insulin resistant states suggest that adiponectin might have several therapeutic advantages, although its physiological role in relation to disease associated with the metabolic syndrome remains to be determined. Anti-inflammatory and anti-atherogenic properties of adiponectin and the ability to stimulate insulin sensitivity have made adiponectin an important object for physiological and pathophysiological studies with the aim of potential therapeutic applications.1, 17

Thus till date several studies have been carried out to elucidate the role of different adipocytokines in insulin resistance but results obtained from different studies were very controversial and the mechanism by which they modulates insulin sensitivity are complex and our understanding is incomplete.18-20 There is virtually no study available where adipocytokine profile in the different insulin resistance states like obesity and T2DM were assessed. The present study was carried out to evaluate the circulating serum concentrations of adipocytokines and their interaction with each other and with IR in Asian Indian population.

Methods

Subjects
A total of 215 subjects aged 30-70 years were taken up for study after an overnight fast. Past medical history and clinical data were collected and anthropometrics measurements including height, weight, and waist circumference were taken. Waist circumference was measured around the abdomen just above the hip bone. Body Mass Index was calculated from the ratio of body weight in kg to height in square meters and expressed as kg/m² units. Blood pressure was measured using random mercury sphygmomanometer. Based on physical examination, history and treatment if any taken by them, study subjects were categorized into following groups (i) control (ii) obese (iii) Type 2 diabetes (iv) hypertension and (v) diabetes with hypertension. These groups were further divided into 2 groups based on BMI ≤ 25 kg/m² and BMI ≥ 25 kg/m² (Table 1).

Table 1: Study Groups

<table>
<thead>
<tr>
<th>Total Subjects</th>
<th>Control (n = 82)</th>
<th>Type 2 DM (n = 89)</th>
<th>Type 2 DM + HT (n = 44)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMI &lt; 25 Kg/m²</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BMI ≥ 25 Kg/m²</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

All the subjects gave their informed consent after the procedure was explained to them. The ethics committee of Sir Hurkisondas Narrotundas Hospital and Medical Research Society approved the project.

Study Design
Each subject’s venous blood was collected after 12 to 14 hours fast for estimation of fasting glucose, lipid profile, insulin, hsCRP and adipocytokines including leptin, adiponectin, resistin, TNFα, IL-6. Glucose concentration was also estimated 2 hours after a 75g oral glucose load (OGTT) for control and obese subjects and post-prandial glucose levels were detected for T2DM patients.

Inclusion and Exclusion Criteria for selection of subjects

Diabetic Patients
1. Diabetes was defined based on history (for patients taking oral hypoglycemic drugs) or according to WHO criteria of fasting glucose ≥ 7.0 mmol/l or 2 hr glucose ≥ 11.1 mmol/l for subjects without a clinical history of diabetes.
2. Most of the diabetic patients were receiving anti-diabetic agent sulphonylurea, metformin or combination of both.
3. Diabetic patients were not receiving treatment for hypertension or any other illness at the time of study.
4. None of the diabetic patients had significant renal, hepatic or cardiovascular disease.
5. The duration of Diabetes was 4.36±0.47 years (Mean ± SE).
6. 3.4 % (3 out of 89) of Diabetic patients were smokers.

Diabetes with Hypertension
Diabetes with hypertension was defined based on history and medication taken by them.

Obese subjects
Obesity was defined if their BMI ≥ 25 kg/m² according to cut-off suggested for Asian Indians.22

Control subjects
Controls were classified as having normal glucose tolerance (Fasting plasma glucose < 6.1 mmol/l and 2 hrs glucose < 7.8 mmol/l).
2. They were non hypertensive and non obese.
3. And were confirmed to have no known disease including cardiac, thyroid disease or any other acute and chronic disease condition or any current infection condition.

Biochemical analysis
Fasting and 2 hrs plasma glucose was measured by the glucose peroxidase method (Randox USA). Serum cholesterol, HDL cholesterol and triglyceride levels were measured by the enzymatic method (Randox USA). Fasting serum insulin was assayed by radioimmunoassay using RIA kit from BRIT Mumbai, India incorporating 125 I-labelled porcine insulin as a tracer and guinea-pig antiserum. Serum hsCRP levels were measured by a highly sensitive ELISA assay from (DSL, Webster, TX, USA), which has a lower detection limit of 1.6ng/ml with intra-assay coefficient of variation 4.25% and inter-assay coefficient of variation 5.95%. Serum leptin, adiponectin and resistin, TNFα, IL-6 levels were measured by an ELISA assay from (Linco Res, St. Charles, Missouri, USA). Intra-assay and inter-assay coefficient of variation are as follows for leptin (1.4%, 4.6%), for adiponectin (4.4%, 6.6%), for resistin (2.75%, 6.7%), for TNFα (4.3%, 4.2%), for IL-6 (3.5%, 7.4%).

Calculation & Data analysis
Insulin resistance measured as Homeostasis Model Assessment-Insulin Resistance (HOMA-IR) using following formula.23
Insulin resistance (HOMA-IR) =
Fasting insulin (uU/ml) X Fasting glucose mmol/l

22.5

Statistical Analysis
Data are presented as Mean ± SD or median and interquartile range. Group means were compared using unpaired t test or the Mann Whitney Rank Sum Test when applicable. Univariate and linear regression analysis were performed for determining relationship between serum hsCRP and other variables like different adipocytokines and Insulin Resistance. Pearson’s correlation coefficient was obtained and a p value of less than 0.05 was considered as statistically significant. Logistic regression analysis was carried out using either diabetes or obesity as dependent variable and biomarkers as independent variables. All analysis was performed using SPSS (version 15).

Results
Clinical Characteristics:
Table 2 presents the anthropometrical and biochemical characteristics of study subjects with BMI < 25 kg/m^2 including 41 non-obese control, 38 T2DM and 19 diabetic patients with hypertension. Mean levels of waist size, plasma glucose, triglycerides, WBC count were significantly increased and HDL-Cholesterol levels were significantly reduced in T2DM patients compared to control subjects. In case of diabetic patients with hypertension exhibited increased, waist size, plasma glucose, blood pressure and significantly reduced HDL-Cholesterol compared to control subjects.

Table 3 presents characteristics of study subjects with BMI ≥ 25 where diabetic patients exhibited increased waist size abdominal obesity, plasma glucose and WBC count compared to control. Diabetic patients with hypertension exhibited increased BMI, waist circumference, blood pressure and plasma glucose levels compared to controls.

Metabolic Characteristics:
Table 4 presents the HOMA-IR levels in different metabolic disorder state compared to control subjects. HOMA-IR levels were significantly increased in different metabolic disorder state like obesity, diabetes and diabetes with hypertension compared to control subjects indicating that all these state represent the insulin resistance state. In obese, obese diabetic and diabetic patients with hypertension serum CRP levels were significantly increased compared to control subjects thus also represents a pro-inflammatory state.

Study of Adipokytokines
Adiponectin
Pearson correlation analysis in control subjects shows that adiponectin is negatively associated only with HOMA-IR (0.395, p<0.02) while no association was found with obesity parameter and other adipokytokines. In diabetic patients adiponectin is negatively associated HOMA-IR (-0.459, p<0.02) and waist circumference (-0.437, p<0.02) after adjustment age and sex. In obese and diabetic patients with hypertension and obesity adiponectin is not associated with any of other parameter. The findings from the above bivariate correlation analysis were further explored using stepwise multiple linear regression analysis with HOMA-IR as a dependent variable where we found that among the adipokytokines only adiponectin is a important predictor of insulin resistance in our population (Table 4).

Adiponectin levels were significantly reduced in obese, diabetic patients compared to control subjects. Gender based analysis shows that there is no sex specific difference in adiponectin levels in our control subjects (Male: 9.29 ± 0.8 vs Female: 10.1 ± 0.78, NS).

To see the effect of treatment and obesity on adiponectin levels in diabetic patients we divided them into following groups (1): Treated and Un-treated non obese T2DM (2): Treated and Un-treated obese T2DM. We observed that in untreated patients levels were significantly reduced but in treated patients no significant difference was found compared to control (Table 5).

Leptin
Serum leptin levels were significantly associated with BMI (0.541, p<0.001), in addition also associated with resistin (0.651, p< 0.001) and inflammatory factor like WBC (0.575, p< 0.001) and hsCRP (0.355, p< 0.02) in control subjects. In obese subjects significantly associated with BMI (0.784, p < 0.001) as expected. Interestingly diabetic patients show significant association with insulin (0.249, p< 0.01), obesity parameter BMI (0.55, p < 0.001) and among adipocytokine with resistin (0.228, p< 0.05) and with inflammatory factor like WBC (0.264, p< 0.01) and hsCRP (0.412, p< 0.01). In diabetic patients with hypertension and obesity leptin is significantly associated only with obesity parameter like BMI (0.685, p < 0.001) and waist (0.452, p< 0.01).

We found that serum leptin levels were significantly increased in obesity and reduced in T2DM. Gender based difference was found, where in female 3-4 fold increase in the serum leptin levels were observed compared to male.(Male: 6.99 ± 0.79 vs Female: 24.04 ± 2.99 *** p< 0.001). Table 5 presents the effect of treatment and obesity on serum leptin levels. We observed that both treated non obese and obese T2DM exhibits reduced leptin levels compared to their BMI matched control subjects.

Resistin
In our studies we found that serum resistin levels were associated with obesity parameter BMI (0.333, p< 0.05), and with inflammatory factor like WBC (0.632, p< 0.001) and hsCRP (0.495, p< 0.001) and among adipocytokines with leptin (0.651, p<0.001) and IL6 (0.307, p < 0.05) in control subjects. In obese subjects only associated with waist (0.379, p< 0.02) and WBC (0.605, p < 0.001). In diabetic patients it is significantly associated with obesity parameter like BMI (0.289, p < 0.05) and with WBC (0.445, p< 0.001) and hsCRP (0.379, p< 0.01) In diabetic patients with hypertension and obesity resistin is significantly associated only with waist (0.485, p< 0.001).
Table 2: Anthropometrics and biochemical characteristics of study subjects, all values are given as (Mean ± SD)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Control (n=41)</th>
<th>T2DM (n=51)</th>
<th>DM+HT (n=25)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yrs)</td>
<td>47.2 ± 4.4</td>
<td>49.7 ± 8.09</td>
<td>56.3 ± 8.9***</td>
</tr>
<tr>
<td>BMI (Kg/m²)</td>
<td>22.0 ± 1.93</td>
<td>22.3 ± 2.08</td>
<td>22.7 ± 2.0</td>
</tr>
<tr>
<td>Waist (cm)</td>
<td>77.7 ± 7.65</td>
<td>83.6 ± 6.65***</td>
<td>83.8 ± 5.4***</td>
</tr>
<tr>
<td>SBP (mmHg)</td>
<td>115.6 ± 15.72</td>
<td>117.0 ± 13.9</td>
<td>127.9 ± 20.4*</td>
</tr>
<tr>
<td>DBP (mmHg)</td>
<td>75.8 ± 7.74</td>
<td>74.8 ± 9.59</td>
<td>83.7 ± 11.6**</td>
</tr>
<tr>
<td>Glucose F (mmol/l)</td>
<td>4.53 ± 0.51</td>
<td>9.29 ± 3.8***</td>
<td>8.87 ± 4.37***</td>
</tr>
<tr>
<td>Glucose 2hrs (mmol/l)</td>
<td>5.05 ± 1.23</td>
<td>12.5 ± 6.2***</td>
<td>13.1 ± 4.4***</td>
</tr>
<tr>
<td>Cholesterol (mmol/l)</td>
<td>5.06 ± 1.10</td>
<td>5.11 ± 1.02</td>
<td>4.59 ± 0.75</td>
</tr>
<tr>
<td>Triglyceride (mmol/l)</td>
<td>1.23 ± 0.36</td>
<td>1.99 ± 1.23***</td>
<td>1.47 ± 0.78</td>
</tr>
<tr>
<td>HDL-Cholesterol (mmol/l)</td>
<td>1.32 ± 0.23</td>
<td>1.07 ± 0.22***</td>
<td>1.10 ± 0.21***</td>
</tr>
<tr>
<td>WBC count</td>
<td>7.20 ± 1.55</td>
<td>8.07 ± 1.6* #</td>
<td>8.14 ± 2.31</td>
</tr>
</tbody>
</table>

*** p < 0.001, ** p < 0.01, * p < 0.05, *# p < 0.02

Table 3: Characteristics of study subjects with BMI ≥ 25 (Mean ± SE)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Control (n=41)</th>
<th>T2DM (n=51)</th>
<th>DM+HT (n=25)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yrs)</td>
<td>47.2 ± 1.09</td>
<td>50.8 ± 0.99** #</td>
<td>54.3 ± 8.2***</td>
</tr>
<tr>
<td>BMI (Kg/m²)</td>
<td>29.1 ± 0.46</td>
<td>28.6 ± 0.39</td>
<td>31.6 ± 4.8*</td>
</tr>
<tr>
<td>Waist (cm)</td>
<td>91.5 ± 1.27</td>
<td>96.1 ± 1.27***</td>
<td>99.3 ± 13.8#</td>
</tr>
<tr>
<td>SBP (mmHg)</td>
<td>120.2 ± 2.33</td>
<td>125.5 ± 2.21</td>
<td>136.4 ± 25.3**</td>
</tr>
<tr>
<td>DBP (mmHg)</td>
<td>79.0 ± 1.39</td>
<td>81.1 ± 1.46</td>
<td>83.4 ± 16.1</td>
</tr>
<tr>
<td>Glucose (mmol/l)</td>
<td>4.57 ± 0.09</td>
<td>9.0 ± 0.44****</td>
<td>7.71 ± 2.6***</td>
</tr>
<tr>
<td>Glucose 2hrs (mmol/l)</td>
<td>5.01 ± 0.19</td>
<td>13.49 ± 5.2***</td>
<td>12.0 ± 4.7***</td>
</tr>
<tr>
<td>Cholesterol (mmol/l)</td>
<td>5.07 ± 0.14</td>
<td>5.01 ± 0.17</td>
<td>5.09 ± 1.16</td>
</tr>
<tr>
<td>Triglyceride (mmol/l)</td>
<td>1.52 ± 0.09</td>
<td>1.8 ± 0.12</td>
<td>1.58 ± 0.75</td>
</tr>
<tr>
<td>HDL-Cholesterol (mmol/l)</td>
<td>1.15 ± 0.02</td>
<td>1.12 ± 0.03</td>
<td>1.22 ± 0.26</td>
</tr>
<tr>
<td>WBC Count</td>
<td>7.27 ± 0.32</td>
<td>8.23 ± 0.31*</td>
<td>8.06 ± 1.56</td>
</tr>
</tbody>
</table>

*** p < 0.001, ** p < 0.01, * p < 0.05, *# p < 0.02

Table 4: Stepwise Multiple Regression analysis using HOMA-IR as dependent variable.

<table>
<thead>
<tr>
<th>Significant Variable</th>
<th>β</th>
<th>S.E.(β)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALL (215)</td>
<td>-0.297</td>
<td>0.133</td>
<td>0.027</td>
</tr>
<tr>
<td>Adiponectin</td>
<td>-0.177</td>
<td>0.066</td>
<td>0.011</td>
</tr>
</tbody>
</table>

Table 5: Effect of Treatment on Adipocytokines levels in non-obese & Obese T2DM patients. All values are given as Median & Interquartile range.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Control (n=41)</th>
<th>Treated (n=29)</th>
<th>Untreated (n=25)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adiponectin levels (mg/l)</td>
<td>9.0 (7-11.5)</td>
<td>7.5 (5.25-9.75)</td>
<td>5.75 (2.8-6.62)***</td>
</tr>
<tr>
<td>Leptin levels (ng/ml)</td>
<td>11.5 (6.35-20)</td>
<td>11 (6.8-15.5)</td>
<td>4.2 (0.82-7.6)** (All Males)</td>
</tr>
<tr>
<td>Resistin levels (ng/ml)</td>
<td>10.5 (7.2-13.0)</td>
<td>6.2 (4.3-8.3)***</td>
<td>9.0 (7.05-12.1)</td>
</tr>
<tr>
<td>TNFα levels (pg/ml)</td>
<td>23 (12.5-39)</td>
<td>38 (16.75-83) *</td>
<td>62.5 (31.5-174)***</td>
</tr>
<tr>
<td>IL-6 levels (pg/ml)</td>
<td>120 (53-225)</td>
<td>140 (58.5-310)</td>
<td>360 (83-1375) *</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Control (n=41)</th>
<th>Treated (n=37)</th>
<th>Untreated (n=14)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adiponectin levels (mg/l)</td>
<td>6.5 (5.25-9.5)</td>
<td>7 (5.0-8.75)</td>
<td>7.12 (6.19-8.12)</td>
</tr>
<tr>
<td>Leptin levels (ng/ml)</td>
<td>22 (13.5-44)</td>
<td>13.5 (8.6-23.2)***</td>
<td>25.2 (14.9-36.4)</td>
</tr>
<tr>
<td>Resistin levels (ng/ml)</td>
<td>10.5 (6.13-13)</td>
<td>7.6 (5.9-10.9)</td>
<td>10.7 (7.2-14.4)</td>
</tr>
<tr>
<td>TNFα levels (pg/ml)</td>
<td>42 (13.8-97.5)</td>
<td>29 (14.5-81.5)</td>
<td>41.5 (2.5-80.6)</td>
</tr>
<tr>
<td>IL-6 levels (pg/ml)</td>
<td>160 (62.5-429.5)</td>
<td>57.5 (26.95-237.5)</td>
<td>226 (42.2-537.5)</td>
</tr>
</tbody>
</table>

* p < 0.05, ** p < 0.01, *** p < 0.001.
It was observed that serum resistin levels were significantly reduced in non obese T2DM and in diabetic patients with hypertension. No difference was found in the resistin levels in obese subjects compared to controls. Gender based difference was found, with significantly increased serum resistin levels in female compared to male (Male: 9.13 ± 0.69 vs Female: 12.06 ± 0.99, * p < 0.05). Table 5 presents the effect of treatment and obesity on serum resistin levels. We found that treated non obese T2DM exhibits reduced resistin levels compared to their BMI matched control subjects.

**TNFα**

Serum TNFα levels were neither associated with insulin, HOMA-IR nor with Obesity parameter in our population. Among the adipocytokines serum TNFα levels shows strong association with IL-6 in all subjects including control (0.424, p < 0.001, obese (0.868, p < 0.001) and diabetic patients (0.762, p < 0.001).

Serum TNFα levels were significantly high in obese and T2DM compared to control subjects. No gender based difference was found in TNFα levels in our population (Male: 35.14 ± 11.02 vs Female: 33.4 ± 6.19, NS).

Table 4 presents the effect of treatment and obesity on serum TNFα levels in T2DM patients. We found that untreated non obese T2DM exhibits significantly increased TNFα levels compared to control subjects. But in the treated patients these levels were reduced and no significant difference was found compared to controls.

**IL-6**

Serum IL-6 levels are not associated with HOMA-IR and obesity parameter in our population. Among the adipocytokines serum IL-6 levels were significantly associated with TNFα in all subjects including control (0.424, p < 0.001, obese (0.868, p < 0.001) and diabetic patients (0.762, p < 0.001) and with resistin (0.307, p < 0.05) in controls subjects. Serum IL-6 levels were significantly high in obese, T2DM but statistically significant only in obesity compared to control subjects. No gender based difference was found in TNFα levels in our population (Male: 175.48 ± 45.09 vs Female: 195.67 ± 41.9, NS). Table 5 presents the effect of treatment and obesity on serum IL-6 levels in T2DM patients. We found that untreated non obese T2DM exhibits significantly increased IL-6 levels compared to control subjects. But in the treated patients these levels were reduced and no significant difference was found compared to controls.

In multiple logistic regression analysis using diabetes as the dependent variable revealed that adipocytokines, like leptin, adiponectin, resistin and TNFα had strong association with diabetes (Table 5a) and using obesity as the dependent variable only leptin and adiponectin shows significant association with obesity (Table 5b).

**Discussion**

Obesity and obesity related diseases (T2DM and CVD) are major public health problems. Recent studies have shown that fat tissue is not a simple energy storage organ but exerts important endocrine and immune functions. These are achieved predominantly through release of adipocytokines like leptin, adiponectin, resistin, TNFα and IL6. All of these molecules may act on immune cell leading to local and generalized inflammation and results in obesity related disorder includes insulin resistance, diabetes, hypertension and atherosclerosis. Though these adipocytokines are proposed to link obesity and diabetes their relationship with each other and their interplay are still poorly understood. Hence in the present study, we evaluated the circulating serum concentration of adipocytokine and the interaction with each other and with insulin resistance in Asian Indian population.

Interesting findings reported in our study are as follows:

1. HOMA-IR levels were significantly increased in diabetes and obesity confirmed that both are insulin resistance states and significantly increased CRP levels states that both these are pro-inflammatory state also. 
2. Adipocytokine levels were altered in both of these states when compared to controls. 
3. Among these adipocytokines only adiponectin is significantly associated with insulin resistance in our population. 
4. We also found significant association of adipocytokines (leptin, resistin and IL-6) with each other as well as with inflammatory factor like WBC and CRP. 
5. Treatment based analysis shows that anti-diabetic treatment plays considerable role in bringing favorable changes in adipocytokine profile.

Adiponectin is an adipocyte specific secretory protein of about 30 KD that appears to be involved in the regulation of energy balance and insulin action and also seems to have anti-inflammatory and anti-atherogenic properties. Adiponectin is the product of the adipose tissue most abundant gene transcript –r(apMr), on chromosome 3q27 3.4.

In the present study, serum adiponectin levels decreased in obese and T2DM patients. In addition it is negatively associated with obesity parameter and IR measure HOMA-IR and thus supports the findings from the previous study. 3, 4, 17, 24. Though many studies have proven that insulin sensitizing thiazolidenediones (TZD) strongly increased plasma adiponectin 25, 26., there are very few reports where the effects of anti-diabetic agent like sulphphonylurea and metformin on adiponectin levels were assessed 27. Interestingly in present study we found that anti-diabetic treatment has a favorable effect on adiponectin levels in our diabetic patients. Low plasma adiponectin levels and negative association with insulin resistance in obesity and T2DM suggest that adiponectin might have several therapeutic advantages. Insulin sensitizing, anti-inflammatory and anti-atherogenic properties of adiponectin have made this adipocytokine a promising tool in the future for the treatment of T2DM and related CVD.

Leptin is a 16 KDa, adipocyte secreted protein that is not only involved in food intake and energy metabolism but clearly also has a role in glucose metabolism and regulation
of insulin secretion. Leptin is a master regulator of human hormone system. Obesity is frequently associated with high plasma leptin levels. Most of the studies reported that serum leptin levels is correlated with obesity parameter and insulin resistance in obese subjects. In the present study, we found significantly increased leptin in obesity, also significantly associated with obesity parameter like BMI but not associated with IR. On the contrary literature regarding the role of leptin in diabetes is conflicting. In light of alarming rise in diabetes among Indians, reduced serum leptin levels in diabetic patients in our population is of interest. The reason for decreasing leptin levels could be due to effect of anti-diabetic agent or could be due to altered insulin secretion or due to difference in body fat distribution.

The mechanistic link between insulin resistance and hyperleptinism is not completely elucidated though in our study we found no association with IR, but significantly associated with obesity parameter like BMI as expected. Interestingly leptin was significantly associated with resistin in our population suggest that there could be existence of metabolic regulation in which both these factors are involved, consistent with the previous findings from other population. In addition its significant association with inflammatory marker CRP and WBC confirms the role of leptin as an inflammatory cytokine.

Resistin has been proposed as an adipocyte secreted factor that is thought to link obesity and T2DM. Though few Indian studies have indicated some adipocytokines to be associated with diabetes and obesity, there are virtually no studies available on serum resistin levels in our population. In our study we found that N-OB treated T2DM but not obese T2DM patients exhibited reduced resistin, the reason could be low BMI and effect of treatment since untreated patients unable to show these changes. Interestingly similar to leptin, serum resistin levels were also significantly associated with inflammatory marker CRP and WBC and also with leptin supporting the findings from previous studies. Association of serum resistin with obesity parameter and adipocytokines like leptin and IL-6 suggest there might be indirect role in the pathogenesis of T2DM in our population.

TNFα is a multi-potential cytokine that has been implicated in the pathogenesis of IR in rodents, but the in vivo data in humans has not been as conclusive. Some studies have documented increased TNFα levels in subjects with obesity and diabetes. Findings of the present study support this previous report. Interestingly we also found the favorable effect of anti-diabetic agent on serum TNFα levels in the treated diabetic patients compared to untreated diabetic patients. Though no association was found with insulin resistance, obesity parameter and with other adipocytokines except IL-6, in multiple logistic regression analysis TNFα one of the predictor of T2DM, suggesting its role in Indian diabetic patients.

Another adipocytokine is IL-6, is a proinflammatory cytokine produced by many cell types. The association between IL-6 and IR is supported by many studies. In the present study, though we do not found association with IR, but IL-6 levels were significantly increased in obesity and T2DM supporting the findings from other studies and shows significant association with resistin in control subjects suggesting its role in inflammatory pathway. Favorable changes were observed in serum IL-6 levels of treated diabetic patients. Till date no studies were available where they have found the effect of anti-diabetic agent on TNFα and IL-6 levels in diabetic patients. In this study we have selected diabetic patients randomly from the clinic hence we could not focus clearly on the effect of anti-diabetic agent. In addition the groups we examined are relatively small, it is likely that with a large number of subjects, the statistical analysis could show better significance; this was the limitation of our study. Hence more detailed study including large number of study subjects need to be undertaken to further confirm the effect of anti-diabetic treatment for the favorable changes in adipocytokines profile.

In conclusion, this study demonstrates that altered adipocytokine profile in obesity and T2DM patients as well as their association with each other and with Insulin resistance in our population. The findings of present study thus confirm the role of adipocytokines in the development of insulin resistance in Asian Indians. The evolving role of adipocytokine production in insulin resistance state opens a new avenue for therapeutic interventions.

Acknowledgement
The Sir H.N. Medical Research Society supported this work. The author wishes to thank research staff, R. Mokal, S.Mithbawkar, K. Mistry and P. Thakur for the technical and social help received by them in carrying out the study.

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