Insulin Resistance is Associated with Increased Cardiovascular Risk in Asian Indians with Normal Glucose Tolerance - The Chennai Urban Rural Epidemiology Study (CURES-66)

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Abstract

Objective: The aim of the study was to assess the association of Insulin Resistance [IR] assessed by Homeostasis Assessment model (HOMA-IR) with cardiovascular risk factors in subjects with Normal Glucose Tolerance [NGT] in Asian Indians.

Methods: This cross-sectional study recruited subjects from the Chennai Urban Rural Epidemiology Study (CURES) an epidemiological study in a representative population of Chennai [formerly Madras], in South India. We included 1500 subjects with normal glucose tolerance, i.e., fasting plasma glucose <100 mg/dl [5.6 mmol/L] and 2 hour post load plasma glucose <140 mg/dl [7.8 mmol/L]. IR was calculated using the homeostasis assessment model (HOMA-IR) using the formula: fasting insulin (IU/mL) fasting glucose (mmol/L)/22.5. Metabolic syndrome (MS) was defined based on modified Adult Treatment Panel III (ATP III) guidelines.

Results: HOMA-IR was found to be positively associated with systolic blood pressure (β = 0.101, p<0.031), diastolic pressure (β = 0.104, p<0.017), total cholesterol (β = 0.188, p<0.003), triglycerides (β = 0.105, p<0.003), LDL cholesterol (β = 0.118, p<0.003), and HDL cholesterol (β = -0.090, p<0.003) even after adjusting age, gender and BMI. Subjects with family history of type 2 diabetes had significantly higher HOMA-IR (β = 0.041) compared to those without family history. In relation to physical activity, subjects with high grade activity had significantly lower HOMA-IR values compared to the light grade activity (p<0.001). Subjects with generalized obesity (p<0.001) and abdominal obesity (p<0.001) had significantly higher HOMA-IR which remained statistically significant even after adjusting for age and gender. There was a linear increase in the mean values of HOMA-IR with increase in number of components of MS (p for trend <0.001).

Conclusion: Among Asian Indians who are known to have high risk of premature coronary artery disease and diabetes, a significant association exists between insulin resistance with cardiovascular risk factors even among NGT subjects.

Introduction

Insulin Resistance [IR] is a condition characterized by decreased response of target tissues to insulin. IR develops first when tissues are unable to respond to normal circulating concentrations of insulin. This reduced sensitivity in body tissues to the action of insulin consequently limits glucose disposal in muscle and fat. In response, to maintain glucose homestasis, β cells in the pancreas secrete more insulin, which eventually results in pancreatic β cell exhaustion, decompensation, and eventual failure. Prospective studies have shown fasting insulin levels to be a surrogate marker of insulin resistance and a predictor of Coronary Artery Disease (CAD). IR has also been shown to be associated with most of the cardiovascular risk factors viz., dyslipidemia, hypertension, obesity, abdominal obesity and glucose intolerance, and a combination of these abnormalities could lead to CAD. IR clusters with many other metabolic abnormalities, and this is known as the insulin resistance syndrome or metabolic syndrome [MS]. IR is considered by many scientists to be the main link between diabetes and cardiovascular disease [CVD], even in the absence of glucose intolerance and indeed IR is a strong predictor of coronary artery disease.

Alarming trends have been reported in the prevalence of CAD worldwide. More recently, it is recognized that the major contribution to CAD is from developing countries. This has been confirmed by the Global Burden of Disease study, which predicts an increasing burden of CAD among the developing countries in the next decade. A recent analysis by Reddy et al. has also projected that the greatest impact of the global epidemic of CAD will fall in developing countries. While the decline in CAD mortality has been demonstrated among some developed countries, the reverse trend appears to be seen in developing countries particularly in India. Indeed, India seems to be particularly badly affected with nearly a 100% increase in the prevalence rates of CAD predicted between 1985 and 2025.

Asian Indians are known to have very high rates of premature coronary artery disease and diabetes. This is attributed to the so called "Asian Indian Phenotype" characterized by relatively lower prevalence rates of obesity but larger waist measurements indicating abdominal obesity and increased insulin resistance. In keeping with studies in the west, we have shown that in Asian Indians also, the risk for CAD and its risk factors start at the stage of impaired glucose tolerance [IGT].

However, to our knowledge, there is no data on the association of IR with cardiovascular risk factors in Asian Indians with normal glucose tolerance and this forms the basis of the present paper.

Research Design and Methods

The Chennai Urban Rural Epidemiology Study (CURES) is a large cross-sectional epidemiological study conducted in a
The representative population of Chennai (formerly Madras), the largest city in southern India with a population of approximately 5 million people. The methodology of CURES has been reported elsewhere. Briefly, the sampling for CURES was based on the model of systematic random sampling, wherein, of the 155 wards in Chennai, 46 were selected to provide a total sample size of 25,001 individuals ≥ 20 years of age. Phase 1 of CURES was conducted in the field, and involved a door-to-door survey in the selected wards. In Phase II, all the known diabetic subjects and age and sex matched non-diabetic subjects were brought to the centre for detailed anthropometric measurements and biochemical tests.

This study recruited subjects from Phase III in which every tenth subject recruited in Phase I was brought to the centre for detailed studies. Phase III had a 90% response rate [2350/2600]. Subjects with diabetes, impaired glucose tolerance (IGT) and impaired fasting glucose (IFG) were excluded from the present study, which deals only with subjects who had normal glucose tolerance (NGT) (0–1644) defined as fasting plasma glucose <100 mg/dl [5.6 mmol/L] and 2 hour post load plasma glucose <180 mg/dl [10 mmol/L]. Of the 1644 NGT subjects identified in Phase III, 1550 subjects [94.2%] in whom all biochemical parameters are available were mentioned in the present analysis study.

**Anthropometric Measurements**

Anthropometric measurements including weight, height and waist measurements were obtained using standardized techniques as detailed elsewhere. The body mass index (BMI) was calculated using the formula, weight (kg) / height (m)^2^. Blood pressure was recorded in the sitting position in the right arm to the nearest 2 mm Hg with a mercury sphygmomanometer (Diamond Deluxe BP apparatus, Pune, India). Two readings were taken 5 minutes apart and the mean of the two was taken as the blood pressure.

**Biochemical Parameters**

Fasting plasma glucose (glucose oxidase-peroxidase method), serum cholesterol (cholesterol oxidase-peroxidase- amidopropionate method) serum triglycerides (glycerol phosphate oxidase-peroxidase-amidopropionate method) and HDL cholesterol (direct method-polyethylene glycol-protein treated enzymes) were measured using Hitachi 912 Autoanalyzer (Hitachi, Mannheim, Germany). The intra and inter assay coefficients of variation (for the biochemical assays ranged between 3.1% to 7.6%. Low-density lipoprotein (LDL) cholesterol was calculated using the Friedewald formula. Glycated haemoglobin (HbA1C) was estimated by high-pressure liquid chromatography using the Variant machine (Bio-Rad, Hercules, Calif, USA). The intra and inter assay coefficients of variation of HbA1C was <10%.

**Measurement of Insulin**

Serum insulin concentration was estimated using enzyme-linked immunosorbent assay (Dako, Glostrup, Denmark). The intra-assay and the inter-assay coefficients of variation for insulin assay were 5.7% and 8.9% respectively and the lower detection limit was 0.5 μU/ml.

**Definitions and Diagnostic Criteria**

Metabolic abnormalities: Hypercholesterolaemia [serum cholesterol ≥200 mg/dl] or subjects who self reported hypercholesterolaemia and were on statins], hypertriglyceridaemia [serum triglycerides ≥150 mg/dl] or subjects who self reported hypertriglyceridaemia and were on drugs for hypertriglyceridaemia] and low HDL cholesterol [males: HDL cholesterol ≤40 mg/dl, females: HDL cholesterol ≤50 mg/dl] were diagnosed based on ATP III guidelines. Metabolic syndrome was diagnosed based on modified ATP III guidelines, if any three of the following abnormalities were present: abdominal obesity (defined as waist circumference ≥90 cm for males and ≥80 cm for females according to modified Asia Pacific WHO guidelines), high blood pressure [systolic blood pressure (SBP) ≥130 mmHg or diastolic blood pressure (DBP) ≥85 mmHg] or subjects who self reported hypertension and were on antihypertensives], hypertriglyceridaemia or low HDL cholesterol. Insulin resistance was calculated using the homeostasis assessment model (HOMA-IR) using the formula: fasting insulin (IU/mL) x fasting glucose (mmol/L)/22.5.

**Physical Activity**

Study individuals were categorized based on a Physical Activity (PA) questionnaire. The questionnaire had 4 questions on job related and leisure time activities and exercise. The physical activity was then graded as light, moderate and heavy, using a scoring system. The following questions were asked: 1. How do you get to work? 2. Overall is your work very demanding / fairly demanding / not demanding? 3. How many days per week do you take exercise and what type of exercise? 4. How much do you walk during the whole day? The physical activity was then graded as light, moderate and heavy, using a scoring system. For example individuals were categorized as heavy grade if occupation was very demanding, mode of transport was walking or bicycling, and did some kind of exercise or walked for more than 2 km a day. Light grade if occupation was not demanding, mode of transport was vehicles and did not exercise.

**Statistical Analysis**

Student's t test or one-way ANOVA was used to compare groups for continuous variables and Chi-square test or Fisher's Exact test as appropriate was used to compare proportions. Pearson correlation analysis was done to examine the association of HOMA-IR with age, gender and BMI. Linear regression analysis was done to look at the association of HOMA-IR with cardiovascular risk factors. Multiple logistic regression was used to determine the association of HOMA-IR with hypertension, dyslipidaemia and metabolic syndrome.

**Results**

The clinical and biochemical characteristics of the study subjects stratified according to tertiles of HOMA IR are shown in Table 1. Body mass index, waist circumference, systolic and diastolic blood pressure, fasting plasma glucose, HbA1C, serum cholesterol, LDL cholesterol increased significantly with increasing tertiles of HOMA IR for trend <0.001].

Table 2 shows linear regression analysis of HOMA-IR with cardiovascular risk factors. HOMA-IR was found to be significantly associated with systolic blood pressure (β = 0.100, p < 0.001), diastolic pressure (β = 0.094, p < 0.001), total cholesterol (β = 0.068, p < 0.005), serum triglycerides (β = 0.105, p < 0.001), LDL cholesterol (β = 0.118, p < 0.005), and HbA1C (β = 0.06, p < 0.001) even after adjusting age, gender and BMI.

Subjects with family history of type 2 diabetes had significantly higher HOMA-IR [1.80 ± 1.14, p < 0.001] compared those without family history [1.63 ± 1.12, p = 0.004]. The difference was significant even after adjusting for age and gender [p < 0.004]. In relation to physical activity, subjects with heavy grade activity had significantly lower HOMA-IR values compared to the light grade activity [1.33 ± 1.04 vs. 1.72 ± 1.16, p < 0.03] (Fig. 1). There was a negative linear association of HOMA-IR with grades of physical activity [p for trend <0.001] which remained significant after adjustment of age, gender and BMI [p < 0.001].

Subjects with generalized obesity (Fig. 2A) and abdominal...
obesity (Fig. 2B) had significantly higher HOMA-IR (without generalized obesity: 1.83 ± 1.4 vs. with generalized obesity: 2.5 ± 1.7, p=0.001; without abdominal obesity: 1.4 ± 1.0 vs. with abdominal obesity 2.0 ± 1.5, p=0.001) which remained statistically significant even after adjusting for age and gender [p=0.001].

Table 3 shows multiple logistic regression analysis which included hypertension, dyslipidemia and MS as the dependent variables. HOMA-IR was significantly associated with hypertension (Odds Ratio (OR): 1.132, 95% Confidence interval (CI): 1.018 - 1.258; p=0.021) after adjusting for age, gender and BMI. HOMA-IR showed a significant association with dyslipidemia (OR: 1.269, CI: 1.132 - 1.423; p=0.001) after adjusting for age, gender and BMI. HOMA-IR was also found to be associated with MS (OR: 1.325, CI: 1.183 - 1.484; p=0.001) after adjustment for age, gender and BMI.

There was a linear increase in the mean values of HOMA IR with increase in number of components of MS (no metabolic abnormality: 1.2 ± 0.8, one metabolic abnormality: 1.5 ± 1.0, two metabolic abnormalities: 1.8 ± 1.2, ≥3 metabolic abnormalities: 2.2 ± 1.4 [p for trend <0.001] (Fig. 3).

Discussion

Studies on migrant Asian Indians have suggested that Asian Indians have a strong ethnic susceptibility to insulin resistance compared to ethnic groups.8 The results of the present study show that individuals with family history of type 2 diabetes had significantly higher insulin resistance compared to those without a family history of type 2 diabetes independent of age and gender. This supports the findings of several studies done on migrant Indians and confirms the fact that Asian Indians have a strong familial predisposition to insulin resistance.20 However whether this is due to genetic or environmental factors clustering with families would need genetic testing.

Obesity is invariably associated with insulin resistance. In this

Table 1: Clinical characteristics of study subjects in tertiles of HOMA IR

<table>
<thead>
<tr>
<th>Parameters</th>
<th>1st Tertile [n=512]</th>
<th>2nd Tertile [n=513]</th>
<th>3rd Tertile [n=523]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>36 ± 13</td>
<td>37 ± 19</td>
<td>40 ± 21**</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>21 ± 3.6</td>
<td>22 ± 3.7**</td>
<td>24 ± 4.2**</td>
</tr>
<tr>
<td>Waist circumference (cm)</td>
<td>77 ± 10</td>
<td>81 ± 11**</td>
<td>86 ± 12**</td>
</tr>
<tr>
<td>Systolic blood pressure (mm Hg)</td>
<td>113 ± 14</td>
<td>115 ± 16</td>
<td>120 ± 17**</td>
</tr>
<tr>
<td>Diastolic blood pressure (mm Hg)</td>
<td>70 ± 10</td>
<td>72 ± 11</td>
<td>75 ± 11**</td>
</tr>
<tr>
<td>Fasting plasma glucose (mg/dl)</td>
<td>81 ± 6</td>
<td>83 ± 7**</td>
<td>85 ± 7**</td>
</tr>
<tr>
<td>HbA1c [%]</td>
<td>5.4 ± 0.4</td>
<td>5.5 ± 0.4</td>
<td>5.6 ± 0.5**</td>
</tr>
<tr>
<td>HOMA IR</td>
<td>0.7 ± 0.19</td>
<td>1.3 ± 0.21**</td>
<td>2.9 ± 1.0**</td>
</tr>
<tr>
<td>Total cholesterol (mg/dl)</td>
<td>166 ± 32</td>
<td>173 ± 37</td>
<td>182 ± 39**</td>
</tr>
<tr>
<td>Serum triglycerides (mg/dl)</td>
<td>94 ± 46</td>
<td>112 ± 68**</td>
<td>126 ± 72**</td>
</tr>
<tr>
<td>LDL cholesterol (mg/dl)</td>
<td>104 ± 28</td>
<td>108 ± 32</td>
<td>115 ± 33**</td>
</tr>
<tr>
<td>HDL cholesterol (mg/dl)</td>
<td>45 ± 12</td>
<td>43 ± 9</td>
<td>42 ± 9</td>
</tr>
</tbody>
</table>

*p=0.01, **p<0.001 compared to 1st tertile of HOMA IR; p=0.01, **p<0.001 compared to 2nd tertile of HOMA IR

Table 2: Linear regression analysis of HOMA-IR with cardiovascular risk factors

<table>
<thead>
<tr>
<th>Parameter</th>
<th>β0, p value</th>
<th>β1, p value</th>
<th>β2, p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systolic blood pressure</td>
<td>0.160, &lt;0.001</td>
<td>0.144, &lt;0.001</td>
<td>0.160, &lt;0.001</td>
</tr>
<tr>
<td>Diastolic blood pressure</td>
<td>0.165, &lt;0.001</td>
<td>0.154, &lt;0.001</td>
<td>0.094, &lt;0.001</td>
</tr>
<tr>
<td>Total cholesterol</td>
<td>0.136, &lt;0.001</td>
<td>0.118, &lt;0.001</td>
<td>0.068, 0.005</td>
</tr>
<tr>
<td>Serum triglycerides</td>
<td>0.176, &lt;0.001</td>
<td>0.177, &lt;0.001</td>
<td>0.105, &lt;0.001</td>
</tr>
<tr>
<td>HDL cholesterol</td>
<td>-0.106, &lt;0.001</td>
<td>-0.130, &lt;0.001</td>
<td>-0.060, &lt;0.001</td>
</tr>
<tr>
<td>LDL cholesterol</td>
<td>0.118, &lt;0.001</td>
<td>0.118, &lt;0.001</td>
<td>0.318, &lt;0.001</td>
</tr>
</tbody>
</table>

Model 1: Unadjusted; Model 2: Adjusted for age and gender; Model 3: Adjusted for age, gender and BMI

Fig. 1: Insulin resistance in relation to physical activity grade in the study groups

Fig. 2A: Insulin resistance in relation to generalized obesity

Fig. 2B: Insulin resistance in relation to generalized and abdominal obesity
Table 3: Multiple Logistic Regression Analysis using Hypertension, Dyslipidemia and Metabolic Syndrome as Dependent Variables

<table>
<thead>
<tr>
<th></th>
<th>Odds Ratio (95% CI)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hypertension</strong></td>
<td></td>
<td></td>
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<tr>
<td>Unadjusted</td>
<td>1.17 (1.04 - 1.31)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Adjusted for age, gender</td>
<td>1.24 (1.07 - 1.44)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Adjusted for age, gender, BMI</td>
<td>1.13 (1.01 - 1.27)</td>
<td>0.021</td>
</tr>
<tr>
<td><strong>Dyslipidemia</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unadjusted</td>
<td>1.14 (1.03 - 1.26)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Adjusted for age, gender</td>
<td>1.23 (1.11 - 1.38)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Adjusted for age, gender, BMI</td>
<td>1.21 (1.09 - 1.36)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Metabolic Syndrome</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unadjusted</td>
<td>1.56 (1.41 - 1.73)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Adjusted for age, gender</td>
<td>1.38 (1.24 - 1.53)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Adjusted for age, gender, BMI</td>
<td>1.32 (1.18 - 1.48)</td>
<td>&lt;0.001</td>
</tr>
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</table>

In our study we found that mean HOMA-IR levels were significantly higher in the obese individuals compared to non-obese independent of age and gender. Although the exact molecular mechanisms by which adipose tissue affects insulin sensitivity is still unclear, it is believed that the bioactive peptides secreted by the adipose tissue collectively called as adipokines could modulate insulin action and affect glucose disposal. In an earlier study we had showed that adiponectin was associated with insulin resistance in Asian Indians. Abdominal obesity is considered to be the main link between inflammation and metabolic disorders, which results in insulin resistance in various tissues. In our earlier study, we have reported that the inflammatory markers like IL-6 and CRP showed a strong association with higher insulin resistance even in non-diabetic subjects.

We observed in the present study that insulin resistance was associated with abdominal obesity independent of generalized obesity. This supports our recent report showing that visceral fat was independently associated with insulin resistance in non-diabetic Asian Indians.

Physical inactivity is also an important determinant of insulin resistance. Regular physical activity, fitness and exercise are critically important for the health and well being of people of all ages. The LookAHEAD Diabetes Prevention trial revealed the importance of both physical activity and weight loss in preventing type 2 diabetes. A graded inverse association between physical activity and the risk of coronary events have been demonstrated in a prospective study on 7,446 male nurses by Manson et al. Similarly a prospective study from Finland had suggested that the risk of hypertension was reduced by regular physical activity and weight control. The Whitehall study showed an inverse relation between mortality and physical activity. We found that there was a negative association of HOMA-IR with increased grades of physical activity which was independent of age, gender and obesity.

Physical inactivity precedes diabetes and increasing physical activity at this stage offers a ray of hope for prevention of diabetes. This finding could partly explain the fact that increased insulin resistance in Asian Indians despite having lower BMI compared to other ethnic groups. We had earlier reported that increased physical activity was associated with the components of metabolic syndrome and coronary artery disease in Asian Indians. Rapid urbanization and changes in lifestyle has led to drastic decline in physical activity in Asian Indians which has in turn led to the epidemic of type 2 diabetes in Asian Indians.

Fig. 3: Mean HOMA-IR with increasing components of metabolic syndrome.

Indians. Insulin resistance thus could be one of the mechanisms by which physical inactivity leads to increased diabetes, metabolic syndrome and CAD in Asian Indians.

Another important finding of this study is the association of insulin resistance with cardiovascular risk factors. HOMA IR was found to be independently associated with systolic blood pressure, diastolic pressure, total cholesterol, serum triglycerides and HDL cholesterol. Although the exact molecular mechanisms behind the role of insulin resistance in the development of dyslipidemia is still not clearly elucidated, it is believed that insulin resistance at the adipocytes level results in increased release of fatty acids into circulation which in turn stimulates the secretion of very low density lipoproteins (VLDL) from the liver resulting in hypertriglyceridemia. Support for this hypothesis comes from a study on migrant Asian Indians which showed that Asian Indians who were more insulin resistant compared to Caucasians had higher levels of adipose tissue metabolites and free fatty acids.

Early identification of individuals with insulin resistance and appropriate intervention in the form of weight loss and exercise could help in prevention of cardiovascular risk factors like hypertension, dyslipidemia and metabolic syndrome. One of the limitations of this study is that being of a cross sectional nature, it can show statistical associations and not a cause and effect relationship. We also have not looked at the effects of diet on insulin resistance. Although HOMA-IR is not considered to be a gold standard measurement of insulin resistance, it is considered to be a good surrogate marker for large epidemiological studies.

In conclusion, the results of the present study suggest that in non diabetic Asian Indians, insulin resistance defined by HOMA-IR is determined by family history of type 2 diabetes, obesity, abdominal obesity and physical inactivity. Insulin resistance is independently and significantly associated with cardiovascular risk factors like hypertension, dyslipidemia and metabolic syndrome. Further, with increasing components of metabolic syndrome, the severity of insulin resistance was also found to be higher. Early identification of individuals with insulin resistance would help in the prevention of metabolic disorders.
syndrome, type 2 diabetes and CAD in Asian Indians.

Acknowledgement

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References


Consultants Needed for Dr. Niphadiar’s Polyclinic

We are seeking MD/MS doctors/physicians with around 5 years of experience to join our polyclinic situated at Hindu Colony, Dadar, Mumbai. For more details please contact 74454646 or 9833877923. Ref: http://www.asthmaallergymic.com