RELATION OF INSULIN RESISTANCE AND BMI WITH SEVERITY OF CORONARY ARTERY DISEASE IN PATIENTS WITH AND WITHOUT DIABETES MELLITUS

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ABSTRACT: Currently, coronary artery disease is reported as the major cause of mortality and morbidity and is expected to be the reason for 40% death in 2020. Since its rate is high in type 2 diabetes mellitus patients, a study has been designed to analyze the correlation of insulin resistance and obesity with incidence and severity of disease. Study was done on 109 individuals with established CAD in the age group of 40 - 70 years who had undergone coronary angiography and diagnosed with coronary artery disease including single vessel, double vessel and triple vessel and seventy one healthy individuals matched for age, and sex. The estimation of fasting FBG, post prandial blood glucose (PPBG), fasting insulin and insulin resistance by gold standard methods. In our study BMI and insulin resistance was found to be significantly high in CAD with diabetes mellitus subjects compared to CAD without DM and control (with p<0.001). Also in our study significantly high percentage of incidence of CAD and significantly high level of severity in CAD WDM patients with BMI >30 kg/m² was observed. Insulin resistance which is the major etiological factor of T2DM influence (affect) HDL, LDL and TG level which can increase the risk of CAD. The increase in IR leads to increased BMI as a part of dyslipidemia events.

INTRODUCTION: Coronary artery disease is the leading cause of mortality and morbidity in the world and had become a global problem with the increasing prevalence of obesity, metabolic syndrome and diabetes ¹. In India, coronary artery disease (CAD) has increased more than 6 fold in the last 5 decades to reach a prevalence of 10% among persons in the 35 to 65 years age group. It is the most frequent cause of cardiovascular disease, and is expected to account for 40% of all deaths by 2020 ². An early assessment of CAD using valuable predictors can delay the onset of disease and improve the quality of life.

Obesity can predispose the development of other risk factors, and the greater the degree of overweight, the greater the likelihood of developing other antecedents of atherosclerosis (such as high blood pressure and diabetes) that increase the probability of heart disease. People who are obese (more than 30 percent over their ideal body weight) are the most likely to develop heart disease, even in the absence of other risk factors.
One recent study that examined more than 100,000 women aged between 30 to 55 showed that the risk for heart disease was more than three times higher among the most obese group than among the leanest group. Diabetes mellitus is considered as an important risk factor for the development of CAD. Currently 246 million people Worldwide are affected by diabetes and the number is expected to rise to 380 million by 2025. A substantial 80% increase will be seen in middle to low income countries and the highest rise will be seen in Indian sub-continent. It has been estimated that 80% of the deaths in diabetic patients may be attributed to CAD. When compared to non-diabetic counterparts, cardiovascular mortality rate in diabetic patients is found to be more than double in men and quadruple in women. A post-MI prognosis is also found to be worse in these patients.

Since the risk of CAD-related events in patients with diabetes mellitus is as high as that of individuals with known CAD, diabetes is currently considered a CAD equivalent. The basis for the increase in CVD risk in patients with T2DM is multifactorial and may include the metabolic consequences of insulin resistance that happens in type 2 DM like disturbances in glucose metabolism and dyslipidemia.

As insulin resistance an etiology of diabetes mellitus is interrelated to obesity, a study has been designed to correlate IR and BMI with incidence and severity of CAD in patients with or without diabetes mellitus.

**MATERIALS AND METHODS:**

**Study Design:** This study was conducted at the department of biochemistry and cardiology of Vinayaka Missions Hospital, Salem. Study was done on 180 subjects who were selected by simple random technique from the group of patients referred to the department of cardiology for coronary angiography and who met the inclusion criteria. Among the study subjects 32% were coronary artery disease patients with type 2 DM (CAD WDM, n = 57), 29% were coronary artery disease patients without type 2 DM (CAD WNDM, n = 52) and 39% control subjects (n = 71). The study protocol was approved by the Ethics Committee of Vinayaka Missions Medical College and Hospitals (VMKVMC/IEC/3-08/9). From each subject, their medical history was obtained through a structured questionnaire and an informed consent was obtained.

**Inclusion Criteria:** Patients with established coronary artery disease including single vessel, double vessel and triple vessel, those who had undergone a treadmill test positive for inducible ischemia, patients with history of essential hypertension, coronary artery disease patients with essential hypertension who had border line rise in fasting blood glucose, and patients with recent onset of diabetes Type II diabetic mellitus was diagnosed according to the WHO criteria.

**Exclusion Criteria:** Patients excluded were those diagnosed to have coronary artery disease with atrial fibrillation or pacemaker, history of congestive heart failure, history of stroke, transient ischemia or carotid surgery, history of coronary artery bypass graft surgery or percutaneous, transluminal coronary angioplasty, history of intermittent claudication or peripheral vascular surgery.

**Collection of Sample:** Venous blood sample was collected after an overnight fast of 12 h and the serum was used for the estimation of fasting blood glucose (FBG) and post prandial blood glucose (PPBS) by enzymatic GOD-POD method. The height of the study subjects was measured to the nearest centimeter and weight to the nearest pound with participants in scrub suits and without shoes. BMI was computed as weight divided by height squared (kg/m²). Homeostasis model assessment for insulin resistance (HOMA index) [fasting glucose (mmol/l) x fasting insulin (UI/l)/22.5] was used as the evaluation of insulin resistance.

**Statistical Analysis:** The data were expressed as means ± SD. Statistical comparisons were performed by one way analysis of variance (ANOVA). The results were considered statistically significant if the p values were ≤ 0.05.

**RESULT AND DISCUSSION:** The present study was undertaken to correlate the influence of insulin resistance and BMI on the severity of coronary artery disease subjects with and without T2DM.
Among the control subjects 65% were males and 35% were female. Among the CAD WNDM patients 88% were males and 12% were female and in CAD WDM 82% were male and 18% were female. The base line characteristics of study subjects are shown in Table 1.

Age of the study subjects were from 40 to 75 years. The mean age of onset of CAD in the group with type 2 DM was 52 ± 9.5 years when compared to 55.4 ± 5.657 years in CAD WNDM. 79% of CAD WDM subjects and 48% of CAD WNDM subjects were of the age group 51 - 60 years. The mean duration of diabetes in CAD WDM was 6.2 ± 2.5 years. Statistically no significant difference in SBP and DBP was observed in CAD WDM when compared to CAD WNDM Table 2. Significant difference in BMI was observed in the CAD WDM subjects when compared to CAD WNDM and control (with p<0.001).

TABLE 1: DEMOGRAPHIC DETAILS OF STUDY SUBJECTS

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Control (n=71)</th>
<th>CAD WNDM (%)</th>
<th>CAD WDM (%)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (Years)</td>
<td>40-50</td>
<td>15(29%)</td>
<td>1(2%)</td>
<td>0.0001</td>
</tr>
<tr>
<td></td>
<td>51-60</td>
<td>25(48%)</td>
<td>45(79%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>61-70</td>
<td>12(23%)</td>
<td>11(19%)</td>
<td></td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>18.5-24.9</td>
<td>1(2%)</td>
<td>6(11%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>25-30</td>
<td>28(54%)</td>
<td>12(21%)</td>
<td>0.0004</td>
</tr>
<tr>
<td></td>
<td>&gt;30</td>
<td>23(44%)</td>
<td>39(68%)</td>
<td></td>
</tr>
<tr>
<td>SBP</td>
<td>&lt;140 mm of Hg</td>
<td>2(4%)</td>
<td>4(7%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>&gt;140 mm of Hg</td>
<td>50(96%)</td>
<td>53(93%)</td>
<td>0.6807</td>
</tr>
</tbody>
</table>

BMI: Body mass index, SBP: Systolic blood pressure, DBP: diastolic blood pressure. Data are expressed as (mean ± S.D). All comparisons by t- test. Statistical analysis was done by Anova (post hoc test: Bonferroni. a: Statistically significant from control group at p<0.05; b: Statistically significant from CAD patients without type 2 DM at p<0.05.

CAD is a complex, multifactorial disorder. Type 2DM is associated with an increased risk of CAD and is considered to be a model of premature atherosclerosis. Grundy et al., has reported that 40-50% of individuals with CAD has type 2 DM. The occurrence of CAD was computed in relation to age, BMI, and hypertension.

Table 1 Age has not been considered to be a modifiable risk factor but, it out ranks all other factors like lipids, blood pressure, and smoking-as a predictor of clinical events 11. Biological changes within the arteries - the non-modifiable effects of disintegration of tissues over time and those produced by the chronic exposure to risk factors such as hyperglycemia and its complications such as dyslipidemia might be the reason for observed high positive correlation in the incidence of CAD with age 11. The incidence of CAD was high among the patients of the age group 51 - 60 (79%) in CAD with type 2 DM patients when compared to CAD without DM (48%).

According to the percentage of stenosis and involvement of coronary vessels, severity of CAD was assessed and classified as Grade I (mild), Grade II (Moderate) and Grade III (Severe). Analysis on frequency of distribution has revealed that severity was significantly high in CAD WDM Table 3. A significantly high percentage of multivessel atherosclerosis was observed in CAD WDM when compared to CAD WNDM.

TABLE 3: SEVERITY OF CAD AMONG THE STUDY SUBJECTS

<table>
<thead>
<tr>
<th>CAD subject</th>
<th>Severity of CAD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade I</td>
<td>Grade II</td>
</tr>
<tr>
<td>CAD WNDM</td>
<td>24(46%)</td>
</tr>
<tr>
<td>CAD WDM</td>
<td>91(16%)</td>
</tr>
</tbody>
</table>

CAD WMD: Coronary artery disease with diabetes. CAD WNDM coronary artery disease without diabetes. Statistical analysis was done by Chi square test.

The severity of CAD and significantly high percentage of multi-vessel atherosclerosis was observed in CAD WDM.
These findings showed a delayed recognition of CAD in type 2 DM. The typical symptoms of cardiac ischemia are often masked in diabetic patients. Hence the pathological events are not identified at the preliminary stages. This might be the reason for the observed high frequency of grade III severity in CAD WDM and high percentage of CAD related mortality in diabetic patients as observed in various epidemiological studies.

**TABLE 4: BIOCHEMICAL PARAMETERS OF STUDY SUBJECT**

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Control (n=71)</th>
<th>CAD WNDM (n=52)</th>
<th>CAD WDM (n=57)</th>
</tr>
</thead>
<tbody>
<tr>
<td>FBS (mg/dL)</td>
<td>85.04±6.2</td>
<td>85.65±5.657</td>
<td>147.05±30.4 (a,b)</td>
</tr>
<tr>
<td>PPBS (mg/dL)</td>
<td>101.81±5.1</td>
<td>109.4±7.071</td>
<td>403±53 (a,b)</td>
</tr>
<tr>
<td>Insulin (µIU/ml)</td>
<td>8.41±0.533</td>
<td>8.76±5.37</td>
<td>22.93±3.25 (a,b)</td>
</tr>
<tr>
<td>HOMA-IR</td>
<td>1.77±0.33</td>
<td>1.8±0.445</td>
<td>9.7±1.1 (a,b)</td>
</tr>
</tbody>
</table>

Data are expressed as (mean ± S.D). Statistical analysis was done by Anova (post hoc test: Bonferroni) \(a, b\): Statistically significant from control group at \(p<0.05\); \(b\): Statistically significant from CAD patients without type 2 DM \((p<0.05)\)

Analysis on frequency of distribution has revealed that severity was significantly high in CAD subjects with IR >1.6 Table 4. Our results have shown that severity was significantly high in patients with an elevated IR level \((p<0.0001)\) Table 5.

**TABLE 5: IR AND SEVERITY OF CAD AMONG THE CAD SUBJECTS**

<table>
<thead>
<tr>
<th>Insulin resistance</th>
<th>Grade I</th>
<th>Grade II</th>
<th>Grade III</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;1.6</td>
<td>30(58%)</td>
<td>18(35%)</td>
<td>4(8%)</td>
</tr>
<tr>
<td>&gt;1.6</td>
<td>9(16%)</td>
<td>12(21%)</td>
<td>36(69%)</td>
</tr>
</tbody>
</table>

Cut off values: 1.6 was considered as median value in our study. IR: Insulin resistance. Statistical analysis was done by Chi square test. \(\text{Gary et al., 1997}\)

One of the basic factor which was found to be significantly elevated in CAD WDM group when compared to other two groups was insulin resistance - which is the underlying defect in >90% of patients with type 2 diabetes mellitus. Insulin resistance has been defined as a condition of low insulin sensitivity, in which the ability of insulin to lower circulating glucose levels is impaired. The gold standard for assessing insulin resistance and insulin sensitivity is the hyperinsulinemic euglycemic clamp technique; however, this test was found to be too labor intensive, time consuming, and costly for routine clinical practice. The homeostasis model assessment (HOMA) is used alternatively as it is minimally invasive, easy to apply in a standard office setting and provide reasonable indices of insulin action in pre diabetes and diseases of recent onset. The biochemical defects that provoke insulin resistance involve impaired insulin signaling as well as reductions in glucose transport within insulin sensitive tissues.

Insulin resistance not only contributes to the pathogenesis of type 2 diabetes but also linked to cardiovascular risk factors and premature cardiovascular disease. It has been reported that insulin resistance predisposes individuals to the development of obesity and dyslipidemia which are considered as the traditional risk factors. As insulin stimulates the production of NO which has both anti atherogenic and anti inflammatory effects, IR is considered as an endothelial dysfunction risk equivalent. IR results in the down regulation of the antiatherogenic phosphatidylinositol-3-kinase-mediated insulin receptor signaling pathway, and maintained activity of the pro atherogenic mitogenic activated protein kinase pathway. It also results in a state of low-grade, chronic, systemic inflammation, which in turn links the metabolic and the vascular pathologies. All these might have lead to accelerated atherogenesis and increased severity of CAD in patients with type 2 DM.

In our study significantly high level of BMI was observed in the CAD WDM subjects when compared to CAD WNDM and control \((p<0.001)\). Analysis on frequency of distribution has revealed that severity was significantly high in CAD subjects with BMI >30 kg/m² Fig. 1.
Body mass index (BMI) is a simple index of weight-for-height that is commonly used to classify overweight and obesity in adults. The WHO defines a BMI greater than or equal to 25 as overweight and a BMI greater than or equal to 30 is obesity [19, 20]. BMI provides the most useful population-level measure of overweight and obesity as it is the same for both sexes and for all ages of adults. Raised BMI is a major risk factor for non-communicable diseases such as CAD [21]. The increase in BMI in the CAD WDM subjects might be due to the Insulin resistance, the major causative factor for type 2 DM [22]. IR greatly reduces the sensitivity of cell to insulin. So the vital process such as transport of glucose across the cell membrane and its catabolism to produce energy gets greatly impaired. As a result, excess glucose that remains in the blood are sent to the liver [23]. Once it reaches there, the sugar gets converted into fat and carried via the blood stream throughout the body. This process can lead to weight gain and obesity.

Evidences have revealed that normal function of Adipose issue is disturbed during obesity and adipose tissue dysfunction plays a prominent role in the development and/or progression of insulin resistance [21]. Boden and Chen et al., had identified that Insulin-resistant fat cells of obesity can confer insulin resistance to muscle through the excessive release of free fatty acids into the general circulation and/or through the accumulation of intra myocellular triglyceride. Thus obesity is not only a contributor to insulin resistance, but also to other risk factors of CAD like dyslipidemia, hypertension and endothelial dysfunction [24]. This might be the reason for the observed significantly high percentage of incidence of CAD and significantly high level of severity in CAD patients with BMI >30 kg/m².

**CONCLUSION:** Diabetes mellitus forms a major non-communicable disease carrying the greatest risk for CAD. The present study conducted on newly diagnosed CAD patients with and without diabetes mellitus showed that people with type 2 DM develop CVD at a younger age and have a high rate of multivessel disease. Since typical symptoms of cardiac ischemia are often masked in diabetic patients, pathological events are not identified at the preliminary stages. This study reveals the positive correlation of BMI and IR with incidence and severity of CAD. Further studies in a large population will be able to elucidate the molecular basis for macro and micro vascular changes with IR and BMI.

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**CONFLICT OF INTEREST:** There are no conflicts of interest.

**REFERENCES:**