

Risk Factors for Complex and Severe Coronary Artery Disease in Type 2 Diabetes Mellitus

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ABSTRACT

Background: Type 2 diabetes mellitus is often associated with severe Coronary artery disease (CAD). Since patients with higher risk of severe disease are likely to get better benefit from aggressive management, it is essential to identify factors which are associated with severe macrovascular disease. We looked at the possibility of hyperinsulinemia being a marker for severe and complex coronary artery disease in type 2 diabetes mellitus, to select patients who would benefit from aggressive treatment. **Methods:** A cross sectional study of 290 type 2 diabetic patients, who underwent coronary angiogram for the evaluation of clinically suspected CAD at a tertiary care hospital were recruited. Biochemical and anthropometric parameters were analysed. Insulin resistance was measured by homeostasis model assessment method. Angiographically measured syntax score of more than 22 is considered to be severe and complex CAD. Receiver operating curve characteristic was performed to find out the optimal cut-off value for insulin resistance and fasting insulin. Predictors of syntax score greater than 22 were identified by multiple logistic regression analysis. **Results:** An insulin level > 20 µIU/ml (OR: 6.86, 95% CI: 2.25-20.88) emerged as an independent predictor of severe and complex CAD. The optimal cut-off of insulin for predicting severe CAD was 20 with sensitivity and specificity of 80% (95% CI: 0.68 - 0.88) and 79% (95% CI: 0.73 - 0.83) respectively. **Conclusion:** Hyperinsulinemia could serve as a marker to identify severe and complex CAD in type 2 diabetes at an earlier stage of diabetes.

Key words: Coronary Artery Disease, Hyperinsulinemia, Insulin resistance, Syntax score, Type 2 diabetes mellitus.

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INTRODUCTION

Type 2 diabetes mellitus is an important predisposing factor for coronary artery disease (CAD) leading to, increased morbidity and mortality among people with diabetes.¹ Although type 2 diabetes itself is considered as CAD equivalent, development of this complication is not uniform across the entire spectrum of diabetes.^{2,3} The risk of progression to severe CAD remains unpredictable.³ The known conventional risk factors do not explain such extensive coronary artery disease in type 2 diabetes, and they account for only about 25% of these changes.⁴

The majority of long term studies, have focused on occurrence and pathogenesis of CAD without referring to its severity. It is the severe disease that entirely alters cardiovascular outcomes in diabetic population. In a computer model evaluation, the patients with high cardiovascular risk derived significant benefit from aggressive treatment whereas those with lower risk levels had net negative effect on their Quality Adjusted Life Years suggesting overall harm in low risk patients.⁵

The syntax score is one such anatomical based risk score used to identify the severe and complex CAD.⁶ The angiographically measured syntax score of more than 22 is considered to be severe and complex CAD,^{6,7} and most of these patients are not suitable candidates for angioplasty.⁸ Since patients at higher risk of severe disease are likely to derive a greater benefit from aggressive management,⁵ it is essential to identify factors, which are associated with severe and complex macrovascular disease.

Several studies have reported the association between insulin and other conventional risk factors and development of atherosclerosis.⁹⁻¹² Nitric oxide is a key molecule responsible for maintaining endothelial function in vasculature. A decreased bioavailability of nitric oxide plays an important role in the development of cardiovascular diseases. A recent study has shown that, hyperglycemia results in increased levels of nitric oxide in type 2 diabetic subject with and without CAD. However, the

levels of nitric oxide depends on duration of type 2 diabetes and is not affected by insulin, C-peptide and uric acid.^{13,14}

Higher levels of baseline insulin have been associated with incident CAD and also predicted new cardio-vascular events on longitudinal follow up.¹⁵⁻¹⁷ A significant positive linear correlation has been established between insulin resistance and severity of CAD in type 2 diabetes mellitus.¹⁸ However a threshold level beyond which insulin/insulin resistance is associated with severe and complex CAD has not been determined.

The objective of this study was to identify the risk factors for severe and complex CAD among patients with type 2 diabetes mellitus. Thus, the study was designed to identify clinical and biochemical parameters of angiographically determined severe CAD in type 2 diabetes mellitus.

MATERIAL AND METHODS

Two hundred and ninety consecutive patients with type 2 diabetes mellitus who underwent a coronary angiogram for evaluation of CAD (Positive treadmill test) were included in this cross sectional study. Patients were recruited for the study from February 2012 to December 2014 after obtaining the written informed consent. The age of the study population was restricted to 45 to 65 years, as studies show that beyond 65 years of age, the extent and degree of CAD remained same in all the population.¹⁹ Diabetes was defined according to the American Diabetes Association (ADA) definition,²⁰ and those satisfying the ADA criteria were included in the study. Patients with known cases of chronic kidney disease, valvular heart disease, thyroid disorders, and exogenous insulin administration and on steroids were excluded from the study. The study was approved by the Institutional ethics committee.

Individuals with syntax score greater than 22 was considered to be severe and complex CAD (Group I) and those with score < 22 were considered to be in group II.^{6,7} Based on severity criteria, 61 subjects were found to

have a syntax score > 22 and remaining 229 had a syntax score less than 22. The assessment and calculation of severity of CAD was done by using the syntax score, a web-based algorithm consisting of sequential and interactive self-guided questions.²¹ The syntax scoring was performed by a cardiologist, who was blinded to metabolic parameters.

All the clinical findings were noted. Anthropometric measurements such as height, weight, waist and hip circumference were noted prior to / on the day of the angiogram as per WHO norms.²² Body Mass Index (BMI) and waist-hip ratio were calculated. Biochemical parameters such as fasting blood sugar, fasting insulin, fasting lipid profile, Glycated hemoglobin and urine microalbumin were analyzed as previously described by Srinivasan *et al.*¹⁸ The degree of insulin resistance was measured by Homeostasis model assessment HOMA 2 computerized method.²³ In large epidemiological studies, the use of HOMA-IR has been shown to correlate well with the gold standard hyper-insulinemia euglycemic glucose clamp technique for the measurement of insulin resistance.²⁴ In order to achieve steady state and to avoid changes in insulin resistance that may occur due to acute stress of the disease and due to an angiographic procedure, the blood test was done two weeks after coronary angiogram.²⁵

Statistical Analysis

Data were presented as mean \pm SD. The normality assumption for continuous variables was evaluated by the Kolmogorov-Smirnov test. Independent sample t-test was done to compare the mean difference between those with the syntax score greater than 22 and syntax score less than 22. Receiver operating curve (ROC) was plotted to find out the optimal cut-off value for HOMA-IR and fasting insulin to predict severe CAD. Multivariate logistic regression analysis was done to identify the variables that were independently associated with a syntax score of above 22. The adjusted odds ratios for Insulin resistance, fasting insulin and other biochemical markers were estimated, and the results were given as adjusted odds ratio (OR) and 95% CI. The $p < 0.05$ was considered to be

statistically significant. Analysis was done using Statistical Package for Social Sciences (SPSS Version 15, Chicago IL).

RESULTS

Two hundred and ninety patients with type 2 diabetes mellitus who underwent a coronary angiogram for the evaluation of clinically suspected CAD were analyzed in this cross sectional study. The mean age of the study population was 56.98 ± 5.35 . The clinical and demographic characteristics of diabetic patients with the syntax score more than 22 (GII) and less than 22 (GI) are shown in Table 1. We observed a significant difference in HOMA-IR ($p < 0.001$), microalbumin ($p = 0.046$), fasting blood sugar ($p < 0.001$) and insulin ($p < 0.001$) among patients with severe CAD when compared to patients with mild CAD [Table 1]. There was no difference in the fasting lipid profile, waist circumference and body mass index between the two groups [Table 1].

The area under the receiver operating curve for HOMA-IR and insulin was found to be statistically significant [Figure 1]. In our model, an HOMA-IR value of 3-4 had sensitivity and specificity of 78% (95% CI: 0.66 - 0.87) and 80% (95% CI: 0.74 - 0.84) respectively for predicting the syntax score of above 22. In our study, an insulin value of 20 μ IU/ml had a sensitivity of 80% (95% CI: 0.68 - 0.88) and specificity of 79% (95% CI: 0.73 - 0.83) for severe CAD.

In addition of ROC curve, the adjusted odds ratio for severe and complex CAD by insulin deciles is shown in figure 2. The adjusted odds ratio for predicting severe and complex CAD was heightened beyond an insulin level of 20 μ IU/ml. Using this contemporary threshold value of 20 μ IU/ml for insulin, 54 (89%) subjects were found have severe and complex CAD.

Multiple logistic regression analysis was performed with syntax less than and more than 22 as the dependent variable and the following as predictive variables: HOMA-IR, insulin, duration of diabetes, age, gender, hypertension, smoking, microalbumin, BMI, Low density lipoprotein-cholesterol (LDL), total cholesterol to HDL ratio and waist circumfer-

Table 1: Clinical and demographic characteristics of type 2 diabetic patients with syntax score less than and more than 22.

Variable	Syntax score > 22 (G 1) (N = 61)	Syntax score < 22 (G 11) (N = 229)	p value
Duration of Diabetes (Years)	9.55 \pm 6.23	6.59 \pm 5.73	< 0.001
Fasting blood sugar (mg/dl)	217.93 \pm 57.25	175.07 \pm 48.59	<0.001
Fasting Insulin (μ IU/ml)	26.44 \pm 7.28	18.34 \pm 5.59	<0.001
HOMA-IR	4.29 \pm 1.44	2.73 \pm 0.83	<0.001
HbA1c	8.88 \pm 1.39	8.95 \pm 2.00	0.801
Total cholesterol (mg/dl)	163.63 \pm 44.69	167.26 \pm 49.51	0.605
TC/HDL	4.35 \pm 1.32	4.23 \pm 1.46	0.573
LDL-C (mg/dl)	106.01 \pm 36.22	104.58 \pm 42.66	0.812
Microalbumin (mg/l)	52.70 \pm 16.48	31.30 \pm 19.73	0.046
Body mass index (kg/m ²)	22.74 \pm 2.11	23.06 \pm 2.82	0.412
Waist circumference (cm)	88.64 \pm 9.26	86.63 \pm 8.25	0.127
Males (%)	46 (75.4%)	158 (69%)	0.330
Females (%)	15 (24.6%)	71 (31%)	0.330
Presence of Hypertension (%)	28 (45.9%)	107 (46.7%)	0.909
Smoking (%)	5 (8.2%)	32 (14%)	0.229

*HOMA-IR- Homeostasis model assessment-insulin resistance; | TC/HDL- Total cholesterol/ High density lipoprotein ratio; # LDL - Low Density Lipoprotein; ** HbA1c - Hemoglobin.

ence. After adjusting for age and gender, an insulin level > 20 µIU/ml [OR: 6.86 (95% CI: 2.25-20.88), *p* < 0.001], HOMA-IR > 3.4 [OR: 5.21 (95% CI: 2.03-13.36), *p* < 0.001] and duration of diabetes > 5 years [OR: 3.19, (95% CI: 1.46-7.01), *p* = 0.004] were independently associated with severe CAD. The adjusted odds ratio for lipid profile, BMI, hypertension, smoking status and waist circumference were not statistically significant [Table 2].

DISCUSSION

So far the link between atherosclerosis and hyperinsulinemia/insulin resistance has been studied extensively.^{4,15} Although hyperinsulinemia is identified as a possible risk factor for cardiovascular mortality and morbidity,^{26,27} at what level or threshold of insulin / insulin resistance it is serious is not known. In this study, a clear risk of hyperinsulinemia / insulin resistance appears to be at a threshold level of 20 µIU/ml and HOMA-IR 3-4, beyond which it has a very high odds ratio towards a severe and complex CAD. The high odds ratio for the severe disease was observed after adjusting for microalbumin, glycated hemoglobin, BMI and other conventional risk factors of CAD.

This finding has important clinical implications. In clinical practice this threshold value is a practical tool. It helps to identify high risk groups and intensify management efforts. Treatment strategies for managing CAD, which include drugs which inhibit vascular remodeling, dual anti-platelet therapy etc. may be more useful in this subset.

Most of the longitudinal studies have given importance to the occurrence and pathogenesis of the disease without referring to its severity. It is the severity of the disease that entirely alters the cardiovascular outcomes in diabetic population. In this regard, our study identifies hyperinsulinemia, HOMA-IR and duration of diabetes which are independently associated with angiographically determined severe and complex CAD.

It has been shown that, the development of insulin resistance is found to be distinct in type 2 diabetes mellitus. Insulin resistance is shown to be relatively constant from the onset of type 2 diabetes mellitus. Other conventional risk factors do not remain constant and tend to change over a period of time. The insulin resistance as measured by HOMA-IR method has been indicated to be generally steady in type 2 diabetes mellitus, even after many years of conventional treatment for type 2 diabetes mellitus which is very well demonstrated in U.K Prospective Diabetes Study (UK-PDS).²⁸⁻³⁰ Since the exposure is constant, this allowed us to calculate the odds ratio based on case-control study design and thereby enabling us to assess the impact of risk factors on severe coronary artery disease.

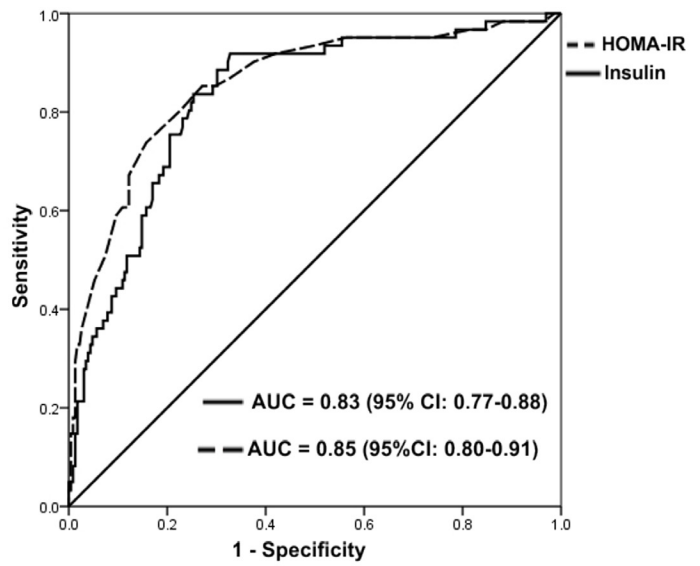


Figure 1: Receiver operating characteristic curves showing the performance of insulin and insulin resistance in predicting severe and complex CAD (Syntax Score > 22).

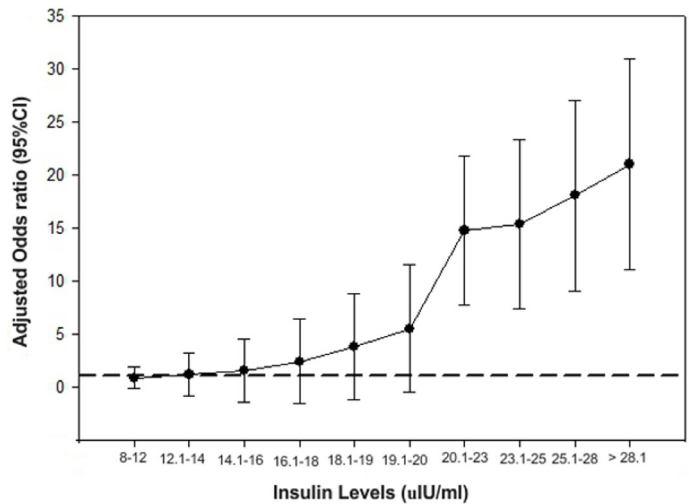


Figure 2: Adjusted Odds ratio for severe and complex CAD by insulin deciles in type 2 diabetes mellitus.

Table 2: Logistic regression analysis for predicting severe CAD in type 2 diabetic patients

Variable	Wald	B	Adjusted odds ratio	p value	95% CI
Fasting Insulin > 20 µIU/ml	11.50	1.92	6.86	0.001	2.25-20.88
HOMA-IR > 3.4	11.86	1.65	5.21	0.001	2.03-13.36
Duration of Diabetes > 5 Years	8.43	1.16	3.19	0.004	1.46-7.01
Microalbumin	0.003	0.02	1.02	0.955	0.47-2.18
TC/HDL	0.030	0.08	1.08	0.862	0.43-2.68
Hypertension	0.252	-0.18	0.82	0.616	0.39-1.72
Age	1.21	0.04	1.04	0.270	0.96-1.12
Body Mass Index	2.73	-0.71	0.48	0.098	0.20-1.14
Waist Circumference	3.35	0.79	2.21	0.067	0.94-5.19
Gender	3.42	0.80	2.23	0.064	0.95-5.22
Smoking	2.02	-0.90	0.40	0.154	0.11-1.40

*HOMA-IR- Homeostasis model assessment – insulin resistance; † TC/HDL- Total cholesterol/ High density lipoprotein ratio.

The severity of CAD seems to be threshold related for insulin levels. The threshold level for insulin has been very well demonstrated in our study. Hyperinsulinemia is a part of type 2 diabetes mellitus, anything above normal range for insulin is commonly seen in type 2 diabetes mellitus, and until it reaches certain high levels they do not seem to have risk for developing complex CAD. In our study, it is observed that the risk for predicting severe and complex CAD was heightened beyond an insulin level of 20 μ IU/ml, and those below this threshold are at lower risk for developing severe and complex CAD. The findings of our study highlights that not all patients with type 2 diabetes are at risk for developing severe and complex CAD, only those who are having insulin levels beyond 20 μ IU/ml are the one who are susceptible to develop malignant CAD.

A molecular basis by which hyperinsulinemia and insulin resistance leads to severe CAD has been elucidated. The complications encountered in type 2 diabetes mellitus seems to be associated with the threshold level of basal insulin. At normal physiological level of insulin, the metabolic functions are mediated through phosphatidylinositol (PI) 3-kinase pathway, on the contrary the mitogenic action of insulin is mediated through mitogen-activated protein kinases (MAPK) pathway. In the case of insulin resistance, the phosphatidylinositol (PI) 3-kinase pathway is inhibited, while the MAPK pathway continues to function.³¹ We speculate that the MAPK pathway might be activated beyond threshold level of insulin, which leads to fibrotic and proliferative changes in the vasculature, and that threshold levels for insulin may be beyond 20 μ IU/ml.

It is important to realize that even with aggressive risk factor modification certain diabetics did not get sufficient cardiovascular benefit as per the ACCORD study.³² The intensive treatment which aimed to bring down HbA1c levels below 6% in type 2 diabetic patients, resulted in increased weight, mortality and risk of hypoglycemia in the subjects, without any significant reduction in macro-vascular events.³² It is possible that these are the individuals who have got a complex and severe disease because of the burden of severe hyperinsulinemia over a period of time.

It is known that risk factor reduction to target levels after optimized therapies does not reduce the risk of developing severe CAD in all diabetic patients. The presence of hyperinsulinemia despite optimized therapies to reduce the atherosclerotic risk factor may be a residual risk factor. It is evident from our study that individuals with insulin levels > 20 μ IU/ml are likely to be associated with severe CAD, thus making it possible to identify these high-risk individuals at the beginning itself.

Maintaining a normal blood glucose level in type 2 diabetics by use of either oral medications or insulin will only fulfil the guideline requirements and may not achieve any long term benefits. It might not decrease insulin resistance or hyperinsulinemia that is present in these patients. The treatment should focus on improving the sensitivity of insulin receptors. Using the insulin properly and enhancing insulin sensitivity have significant implications for stabilizing blood glucose level, relieving hyperinsulinemia, and decreasing the occurrence and progress of complications from cardiovascular diseases.

Since IR/hyperinsulinemia is likely to be a major contributor for the cardiovascular complications, Insulin provisioning treatment strategy is less likely to be effective compared to insulin restricting strategies in especially those who are having relatively high insulin levels. This was very well demonstrated in UKPDS, wherein metformin resulted in substantial reduction of more than 30% cardiovascular risk.³³ Sulfonylurea and insulin were associated with around 15% risk reduction which was statistically not significant.³⁴

It is better to compare insulin levels than the HOMA-IR because HOMA-IR is basically ethnic specific, and it would not be possible to compare HOMA-IR across different population and genetic backgrounds.³⁵ In

this context, our observations suggest the possibility of using insulin > 20 μ IU/ml as an indicator of high risk CAD across the population.

Limitations

The present study has a few limitations. Firstly, it is the study design. Ideally prospective studies need to carry out to find out the role of hyperinsulinemia/insulin resistance leading to severe CAD in type 2 diabetic patients. Long term follow up with hyperinsulinemia measured at the beginning of the disease and compared with angiographic findings after a few years along with other known risk factors might allow us to evaluate the role of each factor associated with the severe CAD. The hyperinsulinemia euglycemic glucose clamp technique is said to be the gold standard for the measurement of insulin resistance/hyperinsulinemia but due its practical inconvenience, HOMA-IR index was used which has shown a good correlation with hyper-insulinemic euglycemic clamp test.

CONCLUSIONS

We observed an insulin level > 20 μ IU/ml was predicting severe and complex CAD in type 2 diabetes mellitus. Hyperinsulinemia could serve as a marker for identifying severe CAD in type 2 diabetic patients. This parameter may help physicians to identify patients with DM who are likely to develop severe CAD. Hence target them for close monitoring and intensify therapy early in the course of the disease management. Periodic measurement of serum insulin levels may be useful for risk stratification of type 2 diabetic patients. Monitoring serum insulin levels might become an important risk marker and also therapeutic tool in the future.

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CONFLICT OF INTEREST

None

ABBREVIATIONS USED

ACCORD: Action to Control Cardiovascular Risk in Diabetes; CAD: Coronary Artery Disease; HOMA: Homeostasis model assessment; UK-PDS: United Kingdom Prospective Diabetes Study.

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