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Factors Correlating with Severity of Coronary Artery Disease in Type 2 Diabetic Patients on Treatment for More Than 5 Years

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Authors' contributions

This work was carried out in collaboration between all authors. Authors PKK, NDP, PAM were responsible for study design, critical revision of manuscript for important intellectual content. Author CM was responsible for study design, concept, critical revision of the manuscript, data interpretation, reviewed the draft and study supervision. Author MPS initiated the project, acquisition of data, data analysis, and interpretation of the data, wrote the manuscript and had full access to all the data in the study and takes responsibility for integrity of data and the accuracy of the data. All authors read and approved the final manuscript.

Original Research Article

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ABSTRACT

Aims: To evaluate the correlation between insulin resistance and other conventional risk factors with respect to severity of coronary artery disease (CAD) in patients with more than 5 years of treatment for type 2 diabetes mellitus.
Study Design: Cross-sectional study.
Place and Duration of Study: Department of Medicine and Department of Cardiology, Kasturba Medical College, Hospital Mangalore, between February 2013 and December 2013.
Methodology: 61 people with more than 5 years of type 2 diabetes who underwent

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coronary angiogram for the evaluation of CAD were recruited in this study. Insulin resistance (HOMA-IR), anthropometric and biochemical parameters were determined, and was correlated with severity of CAD which was assessed by syntax score.
Results: There was significant positive linear correlation between log HOMA-IR and syntax score in people with more than 5 years of type 2 diabetes [r=0.605 (95%CI 0.417–0.744), *P<0.001*]. The correlation of syntax score with other known risk factors of CAD was not significant. Further multivariate analysis after adjusting for conventional risk factors showed a significant association of Log-IR with severity of CAD in people with type 2 diabetes mellitus of more than 5 years of duration (β=0.667, *P<0.001*)
Conclusion: In type 2 diabetes mellitus with treatment more than 5 years of duration, high HOMA-IR appears to be a good indicator of severity of CAD in Type 2 diabetes mellitus and might be a marker of severity of disease, thus helping us in identifying high risk type 2 diabetes mellitus subjects.

Keywords: Insulin Resistance; type 2 diabetes mellitus; coronary artery disease; syntax score.

1. INTRODUCTION

Coronary artery disease (CAD) accounts for as much as about 80% deaths in people with type 2 diabetes mellitus [1]. Development of CAD is multi factorial and known risk factors account for only about 25% of the disease [2]. Despite the treatment of conventional risk factors in type 2 diabetes mellitus, the individuals still remain at a substantial residual risk of coronary artery disease when compared to non-diabetics [2-3].

Diabetes itself is a considerably more heterogeneous disease [4], the profile, complications and severity of CAD could be different across type 2 diabetes mellitus. A meta-analysis of four studies has shown that the spectra of CAD are different in less than 5 years of diabetes and more than 5 years of diabetes [5]. Even in the UKPDS risk engine the events less than 4 years were not included in its analysis [6]. Thus it is quite likely that the full impact of risk factors for CAD become apparent only after 5 years of type 2 diabetes mellitus.

Earlier Reaven had proposed that, the CAD complications could be predicted by measurement of insulin resistance [7] and the observations from subsequent longitudinal studies showed association between insulin resistance and CAD, but not for the severity of CAD. Long term outcome not only depends on association but also depends on the severity of the disease. There is a need to look at insulin resistance and CAD in terms of severity, since strong correlation between the two would establish insulin resistance as a major risk factors in pathogenesis of CAD in type 2 diabetes mellitus.

In our previous study we had established a moderate linear correlation between insulin resistance and severity of CAD [8], but correlation with respect to specific time frames of diabetes was not considered. Since full effects of diabetic risk factors likely to come into play only after specific period of time needed for its biological alterations, we wanted to look for the impact insulin resistance and other known risk factors of CAD in patients on treatment for more than 5 years of type 2 diabetes mellitus.

2. MATERIALS AND METHODS

61 people with type 2 diabetes full filling the diagnostic criteria as recommended by the American Diabetes Association [9] and who underwent a coronary angiogram for evaluation of coronary artery disease at a tertiary care hospital were recruited in this cross sectional study between February 2013 to December 2013, after obtaining informed consent. In order to minimize the effect of confounders the age of the study participants were set between 45 to 65 years. 50 people with less than 5 years of type 2 diabetes were compared. Patients on steroids, chronic kidney disease, and valvular heart disease were excluded from the study. The study was conducted after obtaining the approval by the Institutional human Ethics Committee.

Systolic blood pressure was recorded. Height, weight, waist circumference and hip circumference were noted, Body Mass Index (BMI) and waist hip ratio were calculated as per world health organization (WHO) norms [10]. Biochemical parameters was analyzed as described earlier by Srinivasan et al. [8]. Homeostasis model assessment HOMA 2 computerized method was preferred for the measurement of insulin resistance which has been shown to correlate well with the euglycemic clamp for use in epidemiological studies [11-12]. In order to achieve the steady state and avoid changes in insulin resistance caused due to the acute stress of the disease and angiography procedure, blood tests were done two weeks after coronary angiogram [13]. Severity of coronary artery disease was assessed and calculated by syntax score [14]. Syntax scoring was done by a cardiologist, who was blind to other parameters.

2.1 Statistical Analysis

Karl Pearson's correlation coefficient was applied to find out the between these parameters. $P<0.05$ was considered statistically significant. Logarithmic transformation of HOMA-IR values were done for its analysis [11]. Further Multivariate analysis was done after adjusting for conventional risk factors to find out whether there is a significant association between HOMA-IR and syntax score. Data were analyzed using SPSS Version 16 (SPSS, Chicago, IL, USA).

3. RESULTS AND DISCUSSION

Mean age of the subjects was 57.41±5.26 years. The overall syntax score ranged from 0 to 48.50 among diabetes. The mean Syntax score was 13.27±8.93 in less than 5 years of type diabetes and 17.50±11.79 in more than 5 years of type 2 diabetes (*P=0.03*). Mean HOMA-IR was 2.77±0.91 in less than 5 years of type 2 diabetes and 3.40±1.62 in more than 5 years of type 2 diabetes (*P=0.01*) respectively.

Scatter plot depicting the relation between syntax score and insulin resistance more than 5 years of type 2 diabetes is shown in the (Fig. 1). There was a moderate positive linear correlation between log HOMA-IR and severity of CAD in less than 5 years of type 2 diabetes ($r=0.327$, *P=0.02*). There was a significant strong positive linear correlation between log HOMA-IR and severity of CAD in more than 5 years of type 2 diabetes ($r=0.605$, *P<0.001*).

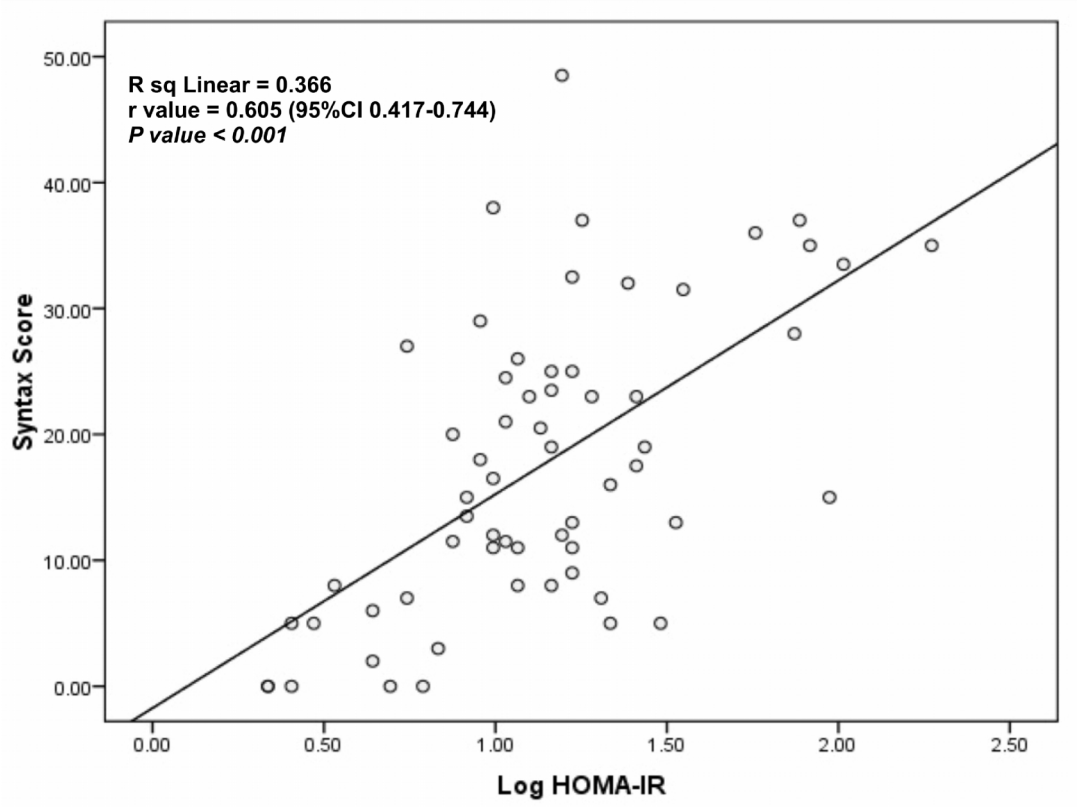

Fig. 1. Scatter plot showing positive linear correlation between severity of coronary artery disease (syntax score) and log of insulin resistance (HOMA-IR) in more than 5 years type 2 diabetes mellitus

Further there was no significant correlation between severity of CAD and other known risk factor of CAD in both less than and more than 5 years of type 2 diabetes (Table 1).

The multi regression analysis after adjusting for sex and other conventional risk factors of CAD showed that insulin resistance was significantly associated with severity of CAD in more than 5 years of type 2 diabetes (β=0.667, *P<0.001*) (Table 2).

3.1 Discussion

In this present study we have examined the impact of insulin resistance along with other conventional risk factors of CAD in more than 5 years of type 2 diabetes mellitus. The correlation of IR with severity of CAD remained moderate in less than 5 years of type 2 diabetes and a strong correlation was seen in more than 5 years of type 2 diabetes. The other conventional risk factors of CAD were not correlated well with severity of CAD.

Numerous studies have shown that insulin resistance has key role in every phase atherosclerosis and is closely linked to increased cardiovascular risk [15-17]. But the strength of association between the two with respect to duration of diabetes mellitus has not been studied so far.

Table 1. Correlation of syntax score versus other parameters in less than 5 years and more than 5 years of type 2 diabetic patients

	Diabetes less than 5 years syntax score	Diabetes more than 5 years syntax score
	r value (*P value*)	r value (*P value*)
Log HOMA-IR	0.327(0.020)	0.605(<0.001)
Systolic blood pressure	0.010(0.921)	0.115(0.376)
Fasting blood sugar	0.107(0.459)	0.157(0.228)
Total cholesterol/ HDL cholesterol ratio	-0.126(0.383)	0.150(0.247)
LDL cholesterol	-0.163(0.257)	0.038(0.771)
VLDL cholesterol	-.063(0.675)	0.073(0.591)
Triglycerides	-0.090(0.536)	0.042(0.748)
HbA_{1c}	-0.055(0.704)	-0.006(0.964)
Urine Microalbumin	-0.004(0.978)	0.079(0.545)
Body mass index	-0.120(0.405)	0.109(0.404)
Waist/Hip ratio	0.112(0.440)	0.077(0.555)

** HOMA-IR-Homeostasis model assessment–insulin resistance; HDL-High Density Lipoprotein; LDL–Low Density Lipoprotein; VLDL–Very Low Density Lipoprotein; HbA_{1c}–Hemoglobin A1C*

Table 2. Multiple regression analysis of Insulin resistance and other known risk factors CAD in less than 5 years and more than 5 years of type 2 diabetes

	Diabetes less than 5 years syntax score	Diabetes more than 5 years syntax score
	β *(P value)*	β *(P value)*
Insulin resistance	0.320(0.055)	0.667(<0.001)
Hypertension	-0.050(0.765)	0.083(0.491)
Smoking	0.044(0.786)	0.053(0.691)
Sex	-0.142(0.440)	0.014(0.926)
Total cholesterol/ HDL cholesterol ratio	0.284(0.348)	0.456(0.025)
LDL cholesterol	-0.189(0.395)	-0.159(0.328)
VLDL cholesterol	-0.451(0.625)	0.846(0.519)
Triglycerides	0.213(0.807)	-1.083(0.405)
HbA_{1c}	-0.113(0.492)	-0.126(0.346)
Urine microalbumin	-0.043(0.794)	-0.049(0.696)
Body mass index	-0.580(0.059)	-0.086(0.483)
Waist/hip ratio	0.480(0.080)	0.047(0.698)

HDL- High Density Lipoprotein; LDL–Low Density Lipoprotein; VLDL–Very Low Density Lipoprotein; HbA_{1c}–Hemoglobin A1C

This strong temporal association along with dose effect response as manifested by very strong correlation co-efficient suggests, IR is not just a mere association but important independent risk factor for diabetic macrovascular disease.

Initial studies focused on the presence and absence of CAD based on IR as a risk factor, however the enthusiasm faded away because focus being shifted towards other risk factors of CAD. In view of our observation of strong correlation between insulin resistance and severity of CAD there is need for reappraisal of insulin resistance as a most important risk factor for CAD. Since reduction of insulin resistance is not significant in most of the diabetic patients it could explain the residual risk even after controlling for conventional risk factors of type 2 diabetes mellitus.

The Insulin resistance is the only component of the metabolic syndrome that is shown to be relatively constant in type 2 diabetes mellitus whereas all the other risk factors change over a period of time [18-20]. Even the United Kingdom Prospective Diabetes study over six years of conventional treatment for type 2 diabetes has shown that insulin sensitivity, the reciprocal of insulin resistance being constant with 62, 60 and 62% at 0, 1 and 6 years [21]. This unique evolution of insulin resistance and its significant correlation with subsequent CAD time might help us in identifying this high risk individual from the beginning itself.

Type 2 diabetes mellitus with more than 5 years of duration have quantitative and qualitative, severe vascular disease compared to less than 5 years of diabetes. The peak effect of hyper insulinemia and insulin resistance probably appears at 4 to 5 years of diabetes mellitus and thus possibility of developing a significant vascular changes might occur after 5 years of diabetes. In our study we observed that subjects with more than 5 years of type 2 diabetes mellitus were characterized by severe, long segment, multi-vessel CAD when compared to less than 5 years of type 2 diabetes mellitus. The mean syntax score was 13.27 ± 8.93 in less than 5 years of diabetes and 17.50±11.79 in more than 5 years of diabetes. A previous study showed that higher syntax score do better with coronary artery bypass graft (CABG) than percutaneous coronary interventions (PCI). A 4 year follow-up study showed that syntax score of 15 or more had a better outcome in CABG than PCI [22]. Since in our study, the subjects with more than 5 years are presented with complex CAD, it is likely that patients with more than 5 years of diabetes might be candidates for CABG for revascularization.

Aggressive glycemic control for type 2 diabetes mellitus of longer duration has not resulted in macrovascular benefit. Hyper insulinemia brings about both functional and structural changes in the blood vessels. Functional changes are mediated through nitric oxide by receptor mediated resistance. But the structural changes occur by proatherogenic response mediated by MAP kinase pathway which is not affected by IR. The continuous action of hyper insulin through the MAP kinase pathway results in a significant structural change over a period of time [23]. From our observation changes are evolved over 5 years of diabetes mellitus and aggressive glycemic therapy later not be able to reverse this structural change. Since there is strong association and possible biological explanation targeting IR as a therapeutic modality might be crucial. Thus the window of opportunity for targeting the cardiovascular complications in type 2 diabetes mellitus is restricted to 0 to 5 years of diabetes, beyond 5 years complications are severe. From our observations it is possible to conclude that patients with high insulin resistance are likely to develop higher amount of CAD after 5 years of diabetes. Since Insulin resistance remains fairly constant from the beginning, patients who are likely to develop severe CAD can be easily identified in the beginning itself. For the clinicians this will allow proper risk stratification and identification of

high risk diabetics, to initiate very aggressive risk reduction strategies from the beginning itself. Patients with high IR should be managed aggressively.

Multiple regression analysis shows that correlation between insulin resistance and other risk factors appears to be showing highest value for insulin resistance and other conventional risk factors did not have such positive correlation. While control of other risk factors like hypertension, dyslipidemia, body mass index, waist hip ratio and urine microalbumin are important for risk reduction. Our study highlights that there is a need to focus on insulin resistance also.

Although the cross sectional study design might be a limitation, since the burden of insulin resistance remains relatively constant from the beginning, the strong association seen in more than 5 years of type 2 diabetes mellitus makes it possible to extrapolate this association to the beginning of the disease itself. Those with high IR in the beginning are likely to get severe disease.

4. CONCLUSION

The result of our study indicates that IR appears to be the important factor that accounts for most of the cardiovascular burden in more than 5 years of type 2 diabetes mellitus. Since IR remains relatively constant, it allow us to identify the patients well in advance and manage the patient's aggressively in first 5 years of type 2 diabetes mellitus which would allow us to minimize the cardiovascular burden in this high risk population, as the clock for cardiovascular complications as already started ticking in terms of insulin resistance.

CONSENT

All authors declare that 'written informed consent was obtained from the patient (or other approved parties) for participating in this study.

ETHICAL APPROVAL

All authors hereby declare that all experiments have been examined and approved by the appropriate ethics committee and have therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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