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Original Article

Biochemistry Section

Glycaemic Control and Inflammatory Mediators in Diabetic Patients with Coronary Artery Disease

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ABSTRACT

Introduction: Glycaemic control in diabetic patients is directly related to the severity of Coronary Artery Disease (CAD) and increased morbidity and mortality rates. Inflammation plays an important role in the pathogenesis of disease and inflammatory markers such as High sensitive C-Reactive Protein (hsCRP), and inflammatory cytokines such as Interleukin-6 (IL-6), and Tumour Necrosis Factor-alpha (TNF-α) have been found to be implicated in the initiation and progression of CAD. Literature suggests that inflammation is a key feature for atherogenesis in Type 2 Diabetes Mellitus (T2DM).

Aim: To compare the severity of CAD and assess the level of glycaemic control and inflammatory mediators in CAD patients with and without T2DM.

Materials and Methods: The present prospective study was conducted on 80 angiographically diagnosed CAD patients (aged >30 years) with (40) and without (40) T2DM. The metabolic risk factors including levels of blood sugar fasting and post-prandial were assessed by Glucose Oxidase Peroxidase (GOD-POD) method, and glycated haemoglobin (HbA1c) level by "Nycocard" reader. Serum Total Cholesterol (TC) was estimated by CHOD-POD method, Triglyceride (TG) by GPO-PAP method, and High density lipoprotein-cholesterol (HDL-C) by Immuno-inhibition method. Low-density lipoprotein cholesterol (LDL-C) and Very low-density lipoprotein (VLDL-C) was calculated by Friedewald formula. Serum insulin, hsCRP, IL-6, TNF-α levels was assessed by sandwich Enzyme linked Immunosorbent Assay (ELISA), and Homeostasis Model was used for assessment of insulin Resistance (HOMA-IR). Chi-square test, Independent t-test and ANOVA were used for statistical analysis, and p-value <0.05 considered as significant.

Results: The level of hsCRP, IL-6, TNF-α, and HbA1c was significantly increased due to cytokines released by monocytes/macrophages mediated β-cell damaging process. Diabetic patients with poor glycaemic control, i.e., HbA1c >8.5%, had higher incidence of triple/multivessel disease suggesting involvement of higher number of coronary vessels with higher severity of the stenosis. Among lipid profile, significantly raised TG and LDL-C levels (p<0.005) and significantly decreased HDL-C in CAD patients with T2DM and its severity (p<0.005) was observed. Significantly elevated inflammatory markers, hsCRP, IL-6 and TNF-α were found to be associated with severity of CAD.

Conclusion: Combinatorial analysis of glycaemic control (HbA1c) and serum cytokines (IL-6, TNF-α, and hsCRP) with clinical risk factors (Triglyceride and LDL-C) may contribute to the assessment of the severity of CAD, and thereby help in the risk stratification of T2DM and CAD.

Keywords: Atherogenesis, β cell-damaging, Inflammatory cytokines, Severity of stenosis

INTRODUCTION

Type 2 Diabetes Mellitus is a risk factor for development of CAD [1]. CAD alone accounts for 40% of deaths of diabetic individuals in their 40s, and the death percentage rises to 50-70% in diabetic individuals above the age of 65 years [2]. Although traditional cardiovascular and metabolic risk factors like hyperglycaemia, hypertension, dyslipidemia are more prevalent in diabetic patients, factors affecting activated innate immunity such as age, inactive lifestyle, improper dietary habits, smoking, psychological stress and low birth weight also holds high potential for development and progression of T2DM. The changes in innate immunity often lead to endothelial cells, and vascular smooth muscle dysfunction, impaired platelet function, abnormal coagulation, obesity and insulin resistance. Therefore, it was postulated that activated immunity is the common antecedent of developing T2DM and activation of the inflammatory mechanism leads to secretion of inflammatory and pro-inflammatory cytokines from adipose tissues. This cytokine mediated acute-phase reaction was reported to be involved in the pathogenesis of T2DM [3].

Based on these findings, the present study was conducted to assess the glycaemic control (HbA1c) and inflammatory mediators like hsCRP, TNF-α, and IL-6 in the angiographically proven coronary artery disease patients with and without T2DM.

MATERIALS AND METHODS

The present prospective study carried out from August 2017 to December 2018 at Mahatma Gandhi Mission Hospital, Navi Mumbai, Maharashtra, India. Ethical approval was obtained from the Institutional Ethics Committee (IEC registration number- MGMIHS/RS/2015-16). Angiographically proven 80 CAD patients, 40 with T2DM (HbA1c >6.5%) and 40 without T2DM were selected by convenient sampling. Drug history of patients, metformin and gliptin were recorded and patients of on statin or insulin or with chronic renal disease, liver diseases & other inflammatory disorders were excluded from the study. After obtaining written informed consent, 5-8 mL of overnight fasting blood samples were collected while maintaining aseptic conditions. The serum samples vacutainers were stored at -70°C until further analysis of biochemical parameters.

Blood glucose and lipid profile were measured on the same day of collection by using commercially available kits and Beckman Coulter Au480 autoanalyser (Beckman Coulter, catalogue number: glucose-OSR6621, cholesterol-OSR6516, triglyceride-OSR 66118, and HDL-C-OSR6295). Low-density lipoprotein (LDL) cholesterol and VLDL-C were calculated using the Friedewald formula: LDL=TC-(TG/5)-HDL and VLDL-C=TG/5 [4]. Serum insulin, hsCRP TNF-α, and IL-6 were determined within 10 days of sample collection using ELISA kits according to the manufacturer's instructions and read spectrophotometrically (Chemux Bioscience, Cal-biotech, & Krishgen

BioSystems resp.). HOMA-IR calculated by the homeostatic model to assess the index of insulin resistance [5].

STATISTICAL ANALYSIS

The evaluation of inflammatory mediators and metabolic risk factors with severity of CAD (based on number of vessels involved) was analysed by using Statistical Package Social Sciences (SPSS version 20). Chi-square test, Independent t-test, and ANOVA were used to assess the association among parameters. The p-value <0.05 was considered as statistically significant with 95% CI.

RESULTS

Significantly high levels of diabetic profile with poor glycaemic control HbA1c >7.5% and insulin resistance, assessed by HOMA-IR was observed in CAD patients with T2DM as compared to CAD patients without T2DM [Table/Fig-1].

Parameters		CAD with DM (n=40)	CAD without DM (n=40)	p-value
Age (year)		56.7±10.8	55.05±5.8	0.126
Sex	Male	28	26	0.134
	Female	12	14	
BMI (kg/m^2)		27.4±3.08*	25.9±2.06	0.045
BSL-F (mg/dL)		176±49.7**	90.3±6.7	0.001
BSL-PP (mg/dL)		253.7±62.5**	105.3±8.2	0.0001
HbA1c (%)		9.7±2.23**	4.7±0.48	0.0001
Insulin (µU/mL)		15.1±3.5**	9.84±2.8	0.001
HOMA-IR		6.0±2.5**	2.2±0.6	0.001

[Table/Fig-1]: Biochemical and glycaemic control parameters of CAD patients with and without diabetes.
BMI: Body mass index; BSL-f/PP: Blood sugar fasting/post prandial; HbA1c: glycosylated haemoglobin; HOMA-IR: Homeostasis model assessment of insulin resistance. Chi-square test; independent t-test; and ANOVA; p*<0.05 significant; p**<0.001 highly significant with 95% CI

The maximum numbers of males with around 60 years of age were diabetics and hypertensive, and had triple/multi-vessels CAD [Table/Fig-2].

Factors		SVD (n=25, 31.25%)	DVD (n=23, 28.75%)	TVD/MVD (n=32, 40%)
Age (Year)		55.68±10.39	57.3±7.8	59.34±5.71
Sex	Male	13	19	22
	Female	12	04	10
T2DM (n %)		07 (28%)	10 (43.47%)	27 (71.87%)
HTN (n %)		16 (64%)	19 (82.6%)	28 (87.5%)

[Table/Fig-2]: Age and sex wise distribution: Percentage of diabetic and hypertensive subjects with varying severity of CAD (based on number of coronary vessel involved).
SVD: Single vessel disease; DVD: Double vessel disease; TVD/MVD: Triple/Multi vessels CAD; T2DM: Type 2 diabetes mellitus; HTN: Hypertension. Mean±SD; Chi-square test; independent t-test, and ANOVA; p*<0.05 significant; p**<0.001 highly significant with 95% CI

Significant differences were observed between HbA1c, fasting and post-prandial blood glucose levels in SVD, DVD, TVD/MVD-CAD patients [Table/Fig-3].

Inflammatory markers hsCRP, IL-6 and TNF-α were observed to be significantly associated with severity of CAD and increased with progression of CAD and increase in vessel disease [Table/Fig-4].

Parameters	SVD (n=25, 31.25)	DVD (n=23, 28.75%)	TVD/MVD (n=32, 40%)	f-value	p-value
BMI (kg/m^2)	25.00±2.61	26.4±3.3^a	27.97±1.84^{b**,c}	9.296	0.001
BSL-F (mg/dL)	111.57±40.24	135.5±59.48^{a*}	148.3±59.48^{b**,c*}	3.266	0.001
BSL-PP (mg/dL)	146.28±76.80	179.6±89.2^{a**}	205.4±86.11^{b**,c**}	3.460	0.001
HbA1c (%)	6.32±3.5	7.35±2.74^a	8.5±2.1^{b**,c}	4.419	0.015
Cholesterol (mg/dL)	197.4±19.0	202.09±10.5^a	208.8±21.85^{b,c}	2.779	0.068
Triglyceride (mg/dL)	174.12±10.32	180.52±16.27^a	186.0±12.58b^{**,c}	5.737	0.005
HDL-C (mg/dL)	43.72±7.2	39.5±3.4^{a**}	38.3±2.78b^{**,c}	9.326	0.001
LDL-C (mg/dL)	118.85±21.95	126.46±10.86^{a**}	135.70±20.27b^{**,c*}	5.781	0.005

[Table/Fig-3]: Association of coronary risk factors with severity of CAD.
BMI: Body mass index; BSL-f/PP: Blood sugar fasting/Post prandial; HbA1c: glycosylated haemoglobin; HDL-C: High density lipoprotein cholesterol; LDL-C: Low density lipoprotein cholesterol. Mean±SD; Chi-square test; independent t-test; and ANOVA; p*<0.05 significant; p**<0.001 highly significant with 95% CI. A) Comparison between SVD and DVD; b) Comparison between SVD and TVD/MVD; and c) comparison between DVD and TVD/MVD

Parameters	SVD	DVD	TVD/MVD	f-value	p-value
hs-CRP (mg/l)	7.75±3.2	12.36±2.22a**	16.54±5.44^{b**,c*}	32.78	0.0001
IL-6 (pg/mL)	43.71±17.1	59.5±23.5a**	79.70±14.20^{b**,c**}	27.93	0.0001
TNF-α (pg/mL)	33.76±12.9	48.04±20.8a**	56.56±26.9^{b**,c*}	7.828	0.001

[Table/Fig-4]: Association of inflammatory markers with severity of CAD.
hsCRP: High sensitive C-reactive protein; IL-6: Interleukin-6; TNF-α: Tumour necrosis factor-alpha. Mean±SD, Chi-square test; independent t-test; and ANOVA; p*<0.05 significant; p**<0.001 highly significant with 95 % CI; a) Comparison between SVD and DVD; b) Comparison between SVD and TVD/MVD; and c) comparison between DVD and TVD/MVD

DISCUSSION

In developing countries, lifestyle associated disorders like T2DM increases the risk of development of cardiovascular diseases [6]. In the present study, maximum number of cardiac events were observed in CAD patients (with and without T2DM) aged 55-60 years, suggesting that age is an important risk factor for CAD, apart from higher BMI (>25). These findings were in accordance with Chen Y et al., study that reported an estimated 62.3%, 35.7%, and 92.4% association between higher BMI and the risk of death from CVD, CHD and stroke respectively, which could be attributed to hypertension [7]. The pooled analysis of Western cohorts reported a positive association of BMI and CVD mortality which can be largely accounted by increased blood pressure, lipid profile, and poor management of diabetes [7].

The prevalence of dyslipidemia and hypertension was observed to higher in males as compared to females, thus making them more susceptible to development of CAD. These finding are in agreement with Arumugam C et al., and Girdhar R, studies, that reported higher sex-specific prevalence in male (40.9%, 95% CI) than female (26.0%, 95% CI) [6,8]. Girdhar R et al., assessed fourth national family health survey evaluated hypertension in large population-based sample and reported prevalence rate of 13.8% in men as opposed to 8.8% in women [8].

In the present study, the incidence and severity of CAD based on number of vessels (SVD, DVD, TVD/MVD) involved in CAD patients with and without diabetes were assessed. A majority of TV/MV CAD patients (71.87%) were observed to be diabetic, in comparison to 28% SVD-CAD and 43.47% DVD-CAD patients, suggesting that CAD in diabetics had considerably higher percent of severe and unpredictable presentation. These findings were similar to Malthesh MK et al., Girdhar R, Arif RM et al., and Dubey L et al., results [2,8-10]. Kesani M et al., assessed severity of CAD by Genesini score reported higher incidence and severity of CAD in diabetic individuals as compared to non-diabetic Indian subjects [11]. Arif RM et al., also reported that poor glycaemic control with level of HbA1C >7% are associated with severe CAD in Non-ST-Elevation Myocardial Infarction (NSTEMI) DM patients, and the extent and severity of CAD were significantly high in diabetic patients when compared to non-diabetic subjects [9]. Izadi M et al., reported that proper glycaemic control in T2DM patients prevents formation and progression of atherosclerosis [12]. In our study, 71.87% diabetic patients with poor glycaemic control, i.e., HbA1c >8.5%, had triple/multivessel disease proving that poor glycaemic control (with higher HbA1c levels) leads to higher number of coronary vessels involved and higher severity of the stenosis. In addition, the incidence of TV/MVD was found to be significantly higher in T2DM patients with the duration of diabetes >10 years. This finding in accordance with Saleem T et al., study that showed HbA1C (r=0.427, p=0.001) and

duration of DM (r=0.362, p=0.004) had a positive linear correlation with the Gensini score indicating severity of CAD [13]. Fox CS et al., also reported that the duration of diabetes increases the risk of CHD death independent of coexisting risk factors [14].

In the present, significant increase in levels of TG and LDL-C and decline in HDL-C in SVD, DVD and TVD/MVD CAD with poor glycaemic control was also observed. The deterioration of glycaemic control in T2DM further exacerbates their inherent dyslipidemia, and leads to higher triglyceride levels. Das S, prospective study suggests that MVD development in T2DM patients can be anticipated by hypertriglyceridaemia, which is one of the markers of Insulin Resistance (IR) [15]. IR calculated by the homeostatic model showed significantly high levels of HOMA-IR in CAD patients with diabetes when compared to CAD without DM (p-0.001) suggesting that T2DM patients may have genetic predisposition for hypertriglyceridaemia.

The significance of diabetic dyslipidemia in the pathogenesis of CAD is well known, and Asian Indians have lower HDL-C levels compared to other ethnic populations which often accelerates atherosclerosis and leads to premature CAD [5]. The present findings were in accordance with Singh P et al., and Agarwal M et al., that reported hypertriglyceridemia and high LDL-C levels as the most common mixed lipid abnormality [16,17].

Inflammation plays an essential role in the development of insulin resistance and T2DM, the initiation and progression of atherosclerotic lesions and plaque disruption [18]. The chronic inflammatory process in atherosclerosis usually results in acute clinical events by plaque rupture [19]. Among inflammatory markers, hsCRP, IL-6 and TNF-α levels were significantly associated with severity of CAD, indicating that increased risk of atherosclerotic progression among group of patients with uncontrolled diabetic TVD/MVD CAD can be predicted by elevated levels of hsCRP, TNF-α and IL-6.

Minna S et al., reported that CRP is an independent risk factor for CAD mortality in T2DM patients, and Masood A et al., observed that serum hsCRP levels showed significant correlation with the severity of CAD as assessed by angiographic Gensini Score [20,21]. Sukhija R et al., also reported that hsCRP and IL-6 were associated with CAD severity on coronary angiography [22].

Literature suggest that IL-6 and TNF-α are the main inducer of hepatic acute phase protein including hsCRP and the levels of these cytokines in serum are correlated with various risk factors for CAD such as obesity, IR, DM, hypertension, smoking and hyperlipidemia. IL-6 are subsidises in CAD development that increase blood viscosity and augments platelets activity and number, contributes to deposition of fibrinogen, IL-6 decreases the activity of Lipoprotein Lipase (LPL), and activates Hypothalamic-Pituitary-Adrenal (HPA) axis [23-25]. While several studies reports the positive association between increased IL-6 concentration and development and progression of CAD, the exact mechanism of how elevated IL-6 serum affects CAD mortality remains unclear [26-30]. Owing to the association of IL-6 and CAD, new therapeutic approach for the prevention of coronary heart disease could be provided by targeting IL-6.

Among a multifunctional inflammatory cytokine TNF-α, is mainly produced by monocytes and macrophage; The present authors found a highly significant difference of values of TNF-α in study population (p-value=0.001). TNF-α level were observed to be 56.56±26.9 pg/mL, 48.04±20.8 pg/mL and 33.76±12.9 pg/mL in TVD/MVD, DVD and SVD respectively. The variation in level of TNF-α with severity of CAD can be accounted to differences in variable interval between onset and detection of disease. TNF-α can cause the formation of an inflammatory reaction, cell necrosis and neo-vascularisation, and promote the production of endothelin, leading to vascular injury. TNF-α is also involved in the development of CAD, and its levels are associated with the degree of myocardial ischaemia [31]. The present results were in accordance with Guo M et al., study, that reported that the serum levels of TNF-α increased with severity of CAD, and can be used to predict the severity of coronary artery lesions [32].

LIMITATION

Relatively small sample size and severity of CAD was only assessed by number of vessel involved. Further studies with higher sample size and assessment of severity of CAD by angiographic Gensini score is required.

In the present study, the serum levels of hsCRP, IL-6, and TNF-α were significantly higher with severity of CAD, which was in accordance with previous studies [31]. Indeed, it has been reported that hsCRP, IL-6 and TNF-α are significant predictors of the severity of CAD [32]. By combining serum cytokines and clinical cardiovascular risk factors, cytokines are the "messengers" of inflammation and immunity which are involved in mediating all stages of atherosclerosis.

There is indeed a link between β-cell stress and inflammation in diabetes. Human Islet Amylin Polypeptide (hIAPP), cellular cholesterol, glucotoxicity, lipotoxicity and inflammatory cytokines induce cellular stress through activation of endoplasmic reticular stress or oxidative stress. On the other hand, excessive production of ROS induced by oxidative stress, contributes to inflammation. Expression of pro-inflammatory cytokines that may attracts local inflammatory cells, which leads to local inflammation causing β-cell apoptosis and development of T2DM.

CONCLUSION

The present findings suggest that CAD patients with T2DM have a more active inflammatory state, and high levels of inflammatory mediators with poor glycaemic control are strongly associated with an increased risk and severity of CAD. Thus, routine screening for glycaemic control and inflammatory markers may provide additional prognostic value and assist in stratification of CAD patients during follow-up.

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