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# Significance of Inflammatory Markers in Type 2 Diabetes Mellitus With and Without Coronary Artery Disease

Biochemistry

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## ABSTRACT

Diabetic patients are prone to develop coronary artery disease. Low degree of inflammation may play central role in type 2 diabetes & CAD.

**Aim:** To find significance of inflammatory markers in T2DM with & without CAD.

**Material and Method:** Total 210 subjects including control, T2DM with & without CAD were assessed for hsCRP, IL6 & TNFα. Patients with chronic renal/liver diseases & inflammatory disorders were excluded. Study was approved by institutional Ethics Committee & statistics done on SPSS-20, Chi-square & Independent t-test applied, *p <0.05

**Result:** Significant increased inflammatory mediators, due to cytokines released by monocytes/macrophages which initiate process of β cell damage. hsCRP, IL6 & TNFα induces local inflammation & independently predict atherosclerotic burden manifested by number of obstructed vessels & its severity.

**Conclusion:** Our study highlights inflammatory mediators are strong indicator for future risk & severity & CAD in DM.

## KEYWORDS

Diabetes, coronary disease, inflammatory markers

## INTRODUCTION

Diabetes mellitus is a heterogeneous group of metabolic disorders caused by either lack of insulin or decreased insulin sensitivity or both [1]. Global estimated prevalence of diabetes in adult was 422 million in 2014. The disease currently affects more than 62 million Indians, which is more than 7.1% of adult Population [2, 3] and it is projected to 109 million individuals with diabetes by 2035. Diabetes causes secondary pathological changes in multiple organ system that imposes remarkable burden on the diabetic individual and on health care system. T2DM developed by various risk factors includes obesity, ethnicity, sedentary life style, gender, family history, smoking [4] and chronic stress. Diabetic dyslipidemia are more prone to develops CAD and atherosclerotic complications [5]. With an increasing incidence worldwide, CAD is the leading cause of morbidity and mortality in diabetic patients [4]. Increased risk of T2DM contributed by their underlying pro-inflammatory state. Various mechanisms have been indicated by which prolonged low grade inflammation contributed to the clinical expression of T2DM [4, 6]. The increase in inflammatory cytokines is the essential step in glucotoxicity and lipotoxicity induced mitochondrial injury and beta cell apoptosis in T2DM indicating role of inflammation in pathogenesis of the disease [7].

Furthermore, inflammatory mediators are implicated in the initiation and progressive development of CAD [8]. Though, earlier studies have paid more attention on the relationship between inflammatory markers and the atherosclerotic progression and instability. However, evidence is scare about the relationship between inflammatory status in diabetes and coronary artery disease. We aimed to evaluate significant association of inflammatory cytokines and to find whether they act as predictive biomarker for future risk of CAD in diabetes.

## MATERIAL AND METHODS

Present prospective study carried out in Departments of Biochemistry, OPD & IPD of CVTS and General Medicine, MGM Medical College and Hospital, Navi Mumbai. Study comprised 210 subjects (> 30 years); are stratified into control and two study groups: known cases of diabetes without CAD and with angiographically proven CAD (n=70 in each group). The diabetic cases confirmed as per WHO criteria and lipid profile was assessed by Adult Treatement Panel III. After clarifying about study, informed consent was taken. Patients with ACS, chronic renal & liver diseases, inflammatory disorders, were excluded. The BMI was calculated by formula, weight (kg)/height (m2) & WHO classification as normal 18.5-24.9, overweight 25-29.9 and ≥ 30 for obese. All patients were advised for 10-12 hours overnight fasting and the 5-8ml of venous blood sample were collected under aseptic condition. All known cases of T2DM also evaluated for their blood sugar levels by GOD-POD method and HbA1c done on Nycocard reader. Among lipid profile, serum level of total cholesterol, triglyceride, and HDL-C was measured using commercially available kits. Friedewald formula used for calculating LDL-C = [TC–(TG/5) –HDL] and VLDL-C = TG/5. The upper normal levels for total cholesterol, TG and LDL-C, were considered 200 mg/dl, 150 mg/dl, and 100 mg/dl respectively. Serum Insulin, hsCRP, IL-6, TNF-α levels were estimated by ELISA [Chemux Bioscience, Cal-biotech, Krishgen BioSyatems resp.] & homeostasis model used for IR. Statistical analysis done on SPSS version 20 by using Chi-square and independent t-test applied and result express in mean ± SD with 95% CI.

## RESULT

Comparison of Inflammatory Markers, Glycaemic control and lipid profile in healthy controls and study groups. We have demonstrated statistical differences between a-Control and T2DM without CAD; b-Control and T2DM with CAD; c-T2DM without and with CAD.

| Variables | controls | T2DM without CAD | T2DM with CAD | p-value |
|---|---|---|---|---|
| Age (years) | 52.0±6.5 | 55.0±5.8 | 53.3±6.75 | 0.615 |
| Sex | M-42, F-28 | M-45, F-25 | M-40, F 30 | 0.320 |
| BMI | 22.9±2.15 | 25.4±3.08 a* | 26.09±3.25 b* | <0.147 |
| BSL-F (mg/dl) | 91.8±6.3 | 169.0±45 a** | 176.1±49.7b** | 0.766 |
| BSL-PP (mg/dl) | 108.5±6.0 | 240.4±84.12 a** | 253.7±62.5 b** | 0.30 |
| HbA1c (%) | 4.9±0.32 | 8.8±1.5 a** | 9.7±2.23 b** c* | 0.040 |
| HOMA-IR | 2.75±0.82 | 5.45±2a* | 6.01±2.5 b* | 0.217 |
| Cholesterol (mg/dl) | 165.5±35.1 | 188.3±32.3 a** | 206.8±22.1 b** c* | <0.014 |
| Triglyceride (mg/dl) | 114.5±9.17 | 158.2±24.36 a** | 172±12.21 b** c** | 0.001 |
| HDL-C (mg/dl) | 48.1±3.0 | 42.1±3.19 a** | 39.9±5.7 b** c** | 0.001 |
| LDL-C (mg/dl) | 94.4± 34.0 | 115.5±30.6 a** | 132.4±22.5 b** c* | 0.044 |

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|---|---|---|---|---|
| VLDL-C (mg/dl) | 22.9±1.83 | 31.6±4.8 a** | 54.4±2.44 b** c** | 0.001 |
| TG/HDL-C | 3.4±0.7 | 3.8±0.6 | 4.3±0.4 | 0.057 |
| hs-CRP (mg/l) | 1.8±0.62 | 4.3±1.6 a** | 8.4±3.5 b**c** | 0.001 |
| TNF-α (pg/ml) | 35.0±26.3 | 37.3±19.1 a** | 53±25.2 b**c** | 0.001 |
| IL-6 (pg/ml) | 33.2±17.16 | 47.2±25.7 a** | 71.5±14.7 b**c** | 0.001 |

*p- value <0.05 considered statistically significant and **p value <0.001 is highly significant.

## DISCUSSION

In present study mean age of participants was 53.4±6.35 year (male 60.5% & female 39.5%). The previous studies showed that age has important role in the risk of development of diabetes and diabetic dyslipidaemia. Metabolic disturbances linked with central place of IR for T2DM and obesity [9]. BMI of participants from both study groups are overweight, in diabetes the possibilities of obesity and activation of adipose tissue may enhance release of inflammatory mediators. Among glycemic control we found significant difference of HbA1c (<0.05) when compared within the study groups. Determination of HbA1c in diabetes gives an idea regarding glycaemic control during the last three months and values >7% indicate poor glycemic control. Our findings were in agreement with Uttara K et al [5], Sultania S et al [10]. We observed (HOMA-IR) index of IR is 6.01±2.5 Vs 5.45±2.0 in diabetics with Vs without CAD; significantly high when compared with control (2.75±0.82), IR begins prior to the onset of T2DM.

Furthermore, among lipid profile we found significant high levels of serum total cholesterol 206.8±22.1 Vs 188.3±32.3, triglyceride 172±12.21 Vs 158.2±24.36, and LDL-C 132.4±22.5 Vs 115.5±30.6 whereas low level of HDL-C 39.9±5.7 Vs 42.1±3.19 in diabetics with CAD Vs without CAD, P<0.01, which was found to be in accordance with Gamit DN et al [11], Nariman M [12]. These are known risk factors for cardiac disorders, are the leading cause of death in patients with type 2 DM. In diabetic dyslipidemia the prominent features are hypertriglyceridemia which is frequently associated with decreased HDL-C. The possible mechanism responsible for hypertriglyceridemia is increased VLDL-C secretion and decreased its clearance which is mainly due to increased availability of substrates for triglyceride synthesis (FFAs and glucose) [13]. Low HDL-C due to number of HDL-C particles functions that possibly contribute to direct cardio-protective effects, including promotion of cellular cholesterol efflux and anti-oxidative and anti-inflammatory properties [14]. Every diabetic patient in our study had at least one kind of dyslipidemia, and 41.2% of them had combined dyslipidemia. Dyslipidemias make diabetics more prone to develop CAD and other complications of atherosclerosis found to be strongly associated with subclinical low grade of systemic inflammation indicating that the role of inflammation in pathogenesis of these diseases.

However, we found significant increased inflammatory markers, in diabetes with CAD Vs without CAD: hsCRP 8.4±3.5 Vs 4.3±3.5, IL-6 71.05±14.7 Vs 47.2±25.7 and TNF-α 53.0±25.2 Vs 37.3±19 when compared within the study groups <0.001, our results in accordance with Israel G et al [15] & Potani s et al [16]. This may be due to augmented levels of glucose and FFAs that are toxic to β-cells for destruction & stimulates various pro-inflammatory mediators. It has been suggested that cytokines released by monocytes/macrophages, including TNF-α stimulated by stress hyperglycemia [17]. IL6 has been speculated to play a key role in the development of CAD through a number of metabolic, endothelial and pro-coagulant mechanisms. By damaging the vessel wall results in exposure of the underlying vascular smooth muscle cells which produces IL-6 and IL-6 gene transcript that are expressed in atherosclerotic legion. A surrogate of IL6 activity predicted cardiovascular mortality and future myocardial infarction. CRP not only powerful inflammatory markers but also directly participate in the inflammatory process of atherogenesis [18]. Also poor glycemic control and higher hs-CRP levels is the harbinger of complications of Type 2 Diabetes Mellitus.

**Conclusion:**

Chronic low grade inflammation with deterioration of the glycemic control aggravates lipid and lipoprotein abnormalities, and accelerates the atherosclerotic process. Thus, identifying uncontrolled diabetic patients with dyslipidemia associated increased inflammatory mediators provide an opportunity to reduce the incidence of future risk of coronary artery disease.

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