Introduction
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Type 2 Diabetes Mellitus (T2DM) is a growing health problem around the world affecting nearly 336 million of the world’s population. The number is expected to increase to 552 million persons by 2030. Until recently India was the worst affected, it is now only next to China. The actual number of people with diabetes has far exceeded the projected values. In the year 2000, it was projected that India will harbor approximately 50 million diabetes patients by 2025. In 2006, this number was revised and it was estimated that India will have nearly 70 million diabetics by 2025. Recent release by the International Diabetes Federation (IDF) puts the number of people affected by diabetes in India at 61.3 million and the estimate for 2030 is 101.2 million.

Although prevalence of T2DM is generally high in older adults, young T2DM patients are increasingly being reported. Because of the resultant macrovascular and microvascular injury typical of this disease, the economic and functional burdens are greatest during mid to late adulthood. Compounding these issues, as many as 1/3 of individuals with T2DM are undiagnosed and approximately 20% have diabetic complications at clinical presentation.

It is well known that type 2 diabetes (T2D) is a polygenetic disease and environmental factors such as sedentary life style, a high calorie intake and consequent obesity interact strongly with genetic predisposition. The term ‘Diabesity’ has been created to express that T2D is obesity dependent and is the main etiologic cause. It has been observed for some time that South Asians including Indians have a high rate of insulin resistance and hyperinsulinemia, higher incidence of T2D and coronary artery diseases (CAD) in comparison with Caucasians and other ethnic groups. The higher prevalence is not completely explained by the traditional risk factors such as hypertension (HTN), dyslipidemia and smoking. Indians are also more likely to have increased waist-hip ratio (WHR), glucose intolerance and higher abdominal adiposity for a given body mass index (BMI) as compared to
Caucasians. They are described thus as ‘metabolically obese normal weight Indians’.\textsuperscript{7}

Family history (FH) of diabetes is a strong factor associated with T2DM development. In a population survey done in South India, it was noted that 47\% of diabetic patients had first degree FH of diabetes. The offspring of diabetic parents develop diabetes at least a decade earlier than their parents.\textsuperscript{8}

A long prediabetes period where glucose levels are above the normal range but below the diabetes cut off levels [impaired fasting glucose (IFG) and impaired glucose tolerance (IGT)] came to be increasingly recognized and treatment and lifestyle modifications recommended in them to arrest the progress or regress the disease process.\textsuperscript{9} Insulin resistance (IR), deficiency in insulin secretion, abdominal obesity and metabolic syndrome (MetS), the important risk factors for diabetes and cardiovascular diseases (CVD) were observed to be inherited. Still, only about 50\% of first degree relatives (FDRs) develop diabetes. Also, not all people with diabetes are insulin resistant.\textsuperscript{10,11} Hence what triggers the disease process is as yet unclear.

Growing evidence suggest that subclinical inflammation and endothelial dysfunction may represent potentially important mechanisms leading to T2D. Circulating markers of inflammation like tumor necrosis factor-\(\alpha\) (TNF-\(\alpha\)), interleukin-6 (IL-6), acute phase proteins like C-reactive protein (CRP), fibrinogen, haptoglobin etc, non specific markers like white blood cell count and erythrocyte sedimentation rate (ESR) were elevated in patients of type 2 diabetes.\textsuperscript{12-14} They were also strong predictors of the development of diabetes in subjects with high baseline values.\textsuperscript{15,16} Studies in prediabetes also brought out similar findings suggesting that ‘inflammatory process’ may be appreciated before pathological hyperglycemia.\textsuperscript{17}

Cytokine mediated inflammatory response is also found in the commonly coexisting conditions of diabetes like HTN, dyslipidemia, CVD and obesity. Thus, inflammation is thought to be the link between them.\textsuperscript{18} Adipose tissue was shown to express and secrete different hormones, cytokines and metabolites that play a role in the development of IR and atherosclerosis.
These include TNF-α, IL-6, angiotensin II, leptin, plasminogen activator inhibitor-1 (PAI-1) and complement C₃.¹⁹,²⁰ These proinflammatory markers thought to be released mainly by the visceral fat induce an inflammatory response resulting in increased hepatic synthesis of acute phase proteins like CRP. The chronic inflammatory response if present for a prolonged period of time can lead to detrimental consequences to the host.²¹

The MetS is a constellation of interrelated risk factors that confer an increased risk to develop T2D and CVD. The previous research into the relationship between genetic predisposing factors and MetS suggest that individuals with a parental history of HTN, stroke or diabetes are more likely to develop MetS or IR than people without a familial history of these diseases. The predominant underlying mechanisms of MetS appear to be IR, leptin resistance, abdominal obesity, autonomic dysfunction, endothelial dysfunction and inflammation. Factors that influence the development of MetS include, adipose tissue and hormones secreted by it, abnormality of the hypothalamo-pituitary-adrenal (HPA) axis, advancing age, genetic and environmental factors, perinatal malnutrition and low grade systemic inflammation.²²-²⁵

Cortisol has potent effects on adipose tissue, influencing insulin sensitivity, fatty acid metabolism, adipocyte differentiation, adipokine expression and body fat distribution.²⁶ In adults, both T2DM and MetS have been linked to chronic stress and abnormalities in the activity of the HPA axis resulting in mild form of hypercortisolism. Another route of activation of HPA axis is by the cytokines particularly IL-6. IL-6, the mediator of inflammatory response also stimulates the HPA axis as part of the link that exists between the neuroendocrine-immune axis. However, chronic activation of the stress system by IL-6 is associated with many negative manifestations and sequelae including obesity, MetS, atherosclerosis, T2DM etc.²⁷

Presence of complications at the time of diagnosis, co-morbidities like HTN, obesity and dyslipidemia, presence of endothelial dysfunction and IR point to the possibility that the clock for the pathogenesis of T2DM starts ticking long before clinical hyperglycemia sets in.²⁸ All the above are independently associated with chronic low grade inflammation. Thus, it could be expected
that inflammation is the earliest sign in asymptomatic nondiabetic subjects at high risk of developing diabetes (the FDRs). Nondiabetic FDRs are a valuable model for studying the pathogenic mechanisms without the confounding effect of hyperglycemia.\textsuperscript{29}

Mounting evidence supports the fact that by the time glucose tolerance or fasting plasma glucose (FPG) levels become impaired, appreciable β-cell destruction may have already occurred. Thus, it seems likely that attempts to prevent T2D will be more successful if intervention is commenced when blood glucose levels are still in the normal range.\textsuperscript{30}

The purpose of this study was therefore to investigate the association between FH of diabetes and MetS and a panel of inflammation sensitive parameters in normoglycemic FDRs of T2DM patients.