Summary/Conclusion
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The large number of rapidly growing diabetic population in India needs immediate and resourceful strategies to arrest the epidemic of diabetes. Indians are prone to the development of diabetes by their genetic programming and the strong influence of environmental factors. Type 2 diabetes mellitus (T2DM) and its associated lipid and vascular disorders including metabolic syndrome (MetS) have been shown to have an inflammatory basis. Inflammatory markers were found to be elevated even in the prediabetes stage.

The present study was taken up; to estimate markers of inflammation in nondiabetic first degree relatives (FDRs) of type 2 diabetes patients and assess their suitability as predictors of diabetes development as compared to the subjects without a family history, to find the differences, if any, between the younger and older subjects, to estimate the prevalence of metabolic syndrome in them, and to understand the correlation of inflammatory markers with anthropometric and metabolic variables.

In all, 301 subjects participated in the study, of which data on 24 subjects was not included for statistical analysis since they did not fulfil the inclusion criteria. Of the 277 participants, 133 were with a positive family history (FH⁺) and 144 without a family history (FH⁻) of diabetes. Both the groups were further divided into the younger group (20-39 yrs) and the older group (40-60 yrs). Demographic details; age, height, weight, waist circumference (WC), hip circumference, waist hip ratio (WHR), body mass index (BMI) and blood pressure (BP) of all these subjects were recorded. Following an overnight fast of 10-12 hrs, blood was drawn by venipuncture for the estimations of fasting plasma glucose (FPG), glycated hemoglobin (HbA₁c), fasting insulin (FIns), lipid profile, total leucocyte count (TLC), erythrocyte sedimentation rate (ESR), highly sensitive C-reactive protein (hsCRP), ceruloplasmin, haptoglobin and fibrinogen. Blood was collected for 2 hr postload glucose, 2 hours after giving 75 g glucose. In 47 subjects with family history and 48 subjects without a
family history of diabetes, additionally interleukin-6 (IL-6) and cortisol were estimated in the morning blood sample collected before 8.30 a.m. Insulin resistance was calculated as homeostasis model assessment for insulin resistance (Homa-IR). The key findings of the study are listed below.

- The levels of inflammatory markers; TLC, ESR, hsCRP, ceruloplasmin, haptoglobin and fibrinogen did not differ in the two groups. Peripheral circulating acute phase proteins may not be suitable assessors of diabetes risk. However, IL-6 and cortisol were significantly elevated in the FH\(^+\) group indicating the activation of the inflammatory process.

- FH\(^+\) subjects were heavier with higher abdominal adiposity, had elevated HbA\(_{1c}\), LDL, TC/HDL ratio, greater degree of peripheral insulin resistance and compensatory hyperinsulinaemia.

- Age, BMI, WC, PPG, HbA\(_{1c}\), FIn and Homa-IR correlated with inflammatory markers including IL-6 in both FH\(^+\) and FH\(^-\). The strength of association was stronger in the FH\(^-\) subjects.

- The results of the above comparison suggest that central adiposity provokes insulin resistance in the FH\(^+\) subjects leading to deleterious lipid, glucose and BP disturbances. These derangements activate the inflammatory process causing elevation of IL-6. The compensatory hyperinsulinaemia and hypercortisolemia by virtue of their anti-inflammatory properties can inhibit the peripheral acute phase response. With a greater degree of metabolic abnormalities and upon chronic stimulation, these mechanisms may fail leading to the elicitation of the active inflammatory process.

- The entire group of FH+ subjects did not exhibit inflammatory milieu. It was hypothesized that dichotomizing the subjects into younger and older groups would highlight the pathophysiology related to inflammation.

- Fibrinogen was found elevated in the older FH\(^+\) and FH\(^-\) subjects compared to their younger counterparts. Since this finding was not
confined to the FH+ subjects, the results do not concur with previous reports that those with a family history of diabetes exhibit higher inflammatory markers.

- The adverse levels of obesity, glycemic and lipid indices, and Homa-IR which were found in the comparison between the whole cohort of FH+ and FH- were re-established in the younger and older subjects with FH+. It is alarming that the younger subjects of FH+ had comparable levels of anthropometric and metabolic alterations with the older subjects putting them at greater diabetes and cardiovascular risk.

- The prevalence of metabolic syndrome in the study groups was assessed and compared using ATP III criteria and SAM-NCEP criteria. By both criteria, the number of MetS cases was higher in the FH+ subjects (27.1% vs 16.6% by ATP III and 39.8% vs 28.5% by SAM-NCEP).

- However, the cardiometabolic risk profile did not vary between MetS-FH+ and MetS-FH- cases implying that although FH+ subjects are prone to MetS, once MetS is established the clinicopathological course does not vary.

- SAM-NCEP criteria were sensitive in identifying MetS cases. Low HDL was the most frequent element found in the MetS cases by both the criteria. Tg was the best predictor of MetS and showed good specificity and sensitivity in both the criteria.

- Inflammatory markers were significantly elevated in the MetS cases and particularly strong correlations were seen with WC.

To conclude, among non-diabetic first degree relatives of type 2 diabetes patients, inflammatory proteins are not elevated and thus can not be used as markers of diabetes risk in the clinical settings. Although significant elevations of IL-6 were observed, it is not possible to favour a unifying hypothesis in this regard because of the representative sample size. The traditional risk factors,
BMI, WC, atherogenic lipids and HbA\textsubscript{1c} routinely measured are better suited as risk predictors. Metabolic syndrome is higher in them and is also associated with inflammation. Waist circumference is the MetS constituent which strongly correlates with inflammation. Since it is said that the FDRs are at 50-70% risk of developing diabetes, it is worthwhile to monitor them especially the younger FDRs who are the most vulnerable group.

Limitations of the study:

1. Family history of diabetes was not ascertained by subjecting the parents and siblings to laboratory tests. Hence, those reporting a negative family history of diabetes could not be definitely confirmed.
2. An unintentional bias was introduced on account of choosing subjects who definitely knew their family history and had some knowledge of diabetes.
3. IL-6 and cortisol were estimated in only 47 FH\textsuperscript{+} and 48 FH\textsuperscript{-} subjects. The extension of the significant findings of these parameters needs to be ascertained in a larger sample size.
4. Immunoturbidimetry assay was used for estimating HbA\textsubscript{1c}. Though the results are reliable it would still have been desirable to use the HPLC method.

Future scope:

In the present study, most of the subjects were non-obese. Since significant results were found with the associations of inflammatory markers and WC, a cohesive group of obese FDRs can be compared with non-obese FDRs. There were a total of 86 subjects with FPG > 100mg/dL in the present study. This group also showed elevated inflammatory markers suggesting that at least a mild aberration in glucose levels is necessary to elicit an inflammatory response which can be further studied. Along the same lines, the role of raised PPG (which is associated with greater CVD risk) which could not be assessed in the present study as there were only 10 subjects with isolated IGT can be explored.