Discussion
Categorical data

301 subjects participated in the study. The demographic details of the participants are presented in Table-1. There were 75 subjects in FHY\(^+\), 76 in FHE\(^-\), and 75 each in FHY\(^-\) and FHE\(^+\) groups. The number of male and female participants in the four groups, their physical activity and knowledge of diabetes did not differ significantly. In all, 24 subjects were excluded from the study (18 from FH\(^+\) and 6 from FH\(^-\)). One of the FHY\(^+\) subjects had very high CRP levels and was later found to have gouty arthritis. Another subject in the FHE\(^-\) group also had high CRP but was lost to follow up. The remaining 22 subjects were found to have diabetes by laboratory data and were hence excluded from the study.

17 (11.2\%) incident cases of diabetes were detected among subjects with a familial disposition to diabetes as compared to 5 cases (3.3\%) among the subjects without a FH. Researchers conducting cross sectional studies have noted that type 2 diabetes is hereditary and the offspring are at 50-70\% risk of developing diabetes.\(^{59,60}\) In the selected population of people with a known FH\(^+\) and who themselves are not yet diagnosed with diabetes, 11.2\% had plasma glucose and corroborating HbA\(_{1c}\) values in the diabetes range. The strong familial aggregation has been particularly observed in Asian Indians through studies comparing the prevalence in migrated Indians and native Caucasian population.\(^{44}\)

The number of subjects with FH of HTN and IHD (Table-2) was also significantly higher among the subjects with FH of diabetes (50.3\% Vs 29.1\% and 22.5\% Vs 15.9\%). These findings are in agreement with the previous reports that those with diabetes are more likely to develop HTN and IHD.\(^{29,30,60,63}\) More number of younger subjects of the FH\(^+\) group reported FH of HTN, whereas the older subjects of FH\(^+\) had higher number of IHD in the immediate family. The number of subjects reporting a history of HTN and IHD in the family was larger among the older subjects without a FH of diabetes.
Family History

Anthropometric measures (age, BMI, WC, WHR, SBP, DBP), glycemic indices (FPG, PPG, HbA1c, Fln, insulin resistance by Homa-IR), lipid parameters (TC, Tg, HDL, LDL, VLDL & TC/HDL) and inflammatory markers (TLC, ESR, hsCRP, ceruloplasmin, haptoglobin and fibrinogen) were measured/estimated in 133 non-diabetic first degree relatives (FDRs) of type 2 diabetes patients and were compared with 144 non-diabetic FDRs without a FH of diabetes.

FH of diabetes and inflammation:

The present study was taken up primarily to know if a cohort of individuals at high risk of developing diabetes (FDRs with FH of diabetes) manifest an inflammatory milieu. About 40-50% of FDRs (upto 70% in some ethnic populations), 8,46,47 are known to develop diabetes. The plasma glucose level of the prediabetes range is the earliest diagnostic marker available to identify converters. Even when subjects develop prediabetes, there is 20-50% chance of reverting to normoglycemia156 or remaining as prediabetics. Thus it was of interest to know, if by the use of these markers, the sensitivity of identifying individuals converting to diabetes can be improved. The results (Table-3) show that FDRs of T2D patients do not have marked elevation of inflammatory markers compared to age matched FDRs without a FH of diabetes.

Several experimental and prospective epidemiological studies have shown an association of elevated serum levels of acute phase proteins (APPs), indicating chronic sub-clinical inflammation in the pathogenesis of diabetes and CVD.12-17 Although visceral fat,204 hyperglycemia,281 endothelial dysfunction,297 adrenal steroids,233 and birth weight57 have been implicated in the activation of the low grade inflammation, the pathophysiology still remain elusive. The role of glucotoxicity in inflammation was further supported, when the subjects with mild hyperglycemia in the prediabetes range also showed elevated inflammation markers.127,293
These studies were mostly the prospective follow up studies\textsuperscript{16,251}, where a baseline value was noted and serial estimations during a follow up period showed raised levels. But such serial estimations may not be feasible in clinical set up. Instead, demonstration of higher absolute concentrations/cut off values would be easy to adopt. Gokulakrishnan et al\textsuperscript{252} found a significant association of leukocyte count and hsCRP with metabolic syndrome and cardiovascular risk factors in Asian Indians even among non-diabetic subjects. It has been previously demonstrated that a family history of type 2 diabetes is associated with increased plasma levels of CRP in apparently healthy adult women\textsuperscript{15} and in NGT subjects with 1 hr PG >155mg/dL.\textsuperscript{167} Such a finding however was not noted in the present study.

In a subset of 47 FH\textsuperscript{+} and 48 FH\textsuperscript{-} subjects chosen randomly from the original cohort, IL-6 and cortisol levels were additionally estimated in the morning samples (collected before 8.30 am). The results of these groups are presented in Table-4. IL-6 and cortisol levels were significantly elevated in the FH\textsuperscript{+} group. These findings suggest that the inflammation process has begun with the activation of the cytokine cascade, but it is not sufficient to elicit an acute phase response. IL-6 induces the synthesis of APPs by hepatocytes. An indirect effect of IL-6 is also through the ACTH stimulation which in turn produces glucocorticoids. The glucocorticoids negatively control levels of IL-6 such that a feedback loop is completed and the acute phase response subsides.\textsuperscript{230}

The HPA axis and cortisol secretion are known to play a significant inhibitory role in the manifestation of the acute phase response.\textsuperscript{230} Only upon chronic stimulation of the HPA axis, the inhibitory effect fails and hyper-cortisolemia may not be able to suppress the acute phase response.\textsuperscript{233,234}

Insulin is also a potent inhibitor of inflammation and a suppressor of hepatic APP synthesis. Insulin regulates the expression of cytokine mediated APPs at the transcription level, thus inhibiting their rise in the blood.\textsuperscript{308,309} Pearson's correlational analysis of these inflammatory markers was performed with anthropometric and metabolic indices. In the FH\textsuperscript{+} group (Table-5) Age, BMI, WC, PPG, HbA\textsubscript{1c}, FIn and Homa-IR showed a significant positive correlation
A strong association ($r > 0.3$) was found between BMI and TLC and that of HbA$_{1C}$ and fibrinogen. In the subset with IL-6 and cortisol (Table-6) BMI, WC and PPG correlated significantly with IL-6, and WHR correlated with cortisol. In the FH$^-$ group (Table-7), Age, BMI, WC, SBP, DBP, PPG, HbA$_{1C}$, FIn, Homa-IR, Tg and HDL correlated ($r > 0.2$) with the inflammatory markers with strong association ($r > 0.3$) found between BMI, WC, FIn and Homa-IR with CRP. Among the sub group with IL-6 and cortisol (Table-8) BMI, WC, PPG, FIn and Homa-IR all correlated significantly with IL-6 ($r = 0.381-0.471$).

The strength of association of the inflammatory markers with metabolic and anthropometric indices was stronger in the FH$^+$ groups. This points to the possibility of a more complex involvement of the inflammatory mechanisms in the FH$^+$ subjects. Highlight of the study was that, although mean FPG showed a nonsignificant elevation in the FH$^+$ subjects, correlations with inflammatory markers were found only with PPG in both FH$^+$ and FH$^-$.

To summarise, among the nondiabetic FDRs with a FH of diabetes, IL-6 levels were elevated as compared to age and sex matched subjects without a FH of diabetes. Based on linear correlations, it may be presumed that obesity indices, IR, HbA$_{1C}$ and PPG are the major contributors to inflammation. The peripheral acute phase response however was probably kept under wraps by hypercortisolemia and hyperinsulinemia. It appears that only when these mechanisms fail and the plasma glucose levels (especially PPG) start rising, the inflammatory protein markers manifest.

**Anthropometric indices and FH of diabetes:**

In recent years evidences have been built to say that subjects with FH of diabetes are heavier, with a larger WC and WHR. The same was reflected in the present study also. BMI (not significant), WC and WHR were higher in the FH$^+$ group. In the cohort in whom IL-6 and cortisol were also measured, significant difference was observed for BMI too. (Tables-9 and 10). Central/visceral obesity is the major contributor of CVD, metabolic syndrome, diabetes, hypertension, IR and inflammatory risk. WC and WHR predicted diabetes in prospective studies. Based on these findings and given the
genetic background, normal range of WC for Asians were redefined as <90 cms for men and <80 cms for women.\textsuperscript{199}

BMI and WC correlated with inflammatory markers in both the FH\textsuperscript{+} and FH\textsuperscript{-} groups (Tables-5, 6, 7 and 8). However, the strength of association was stronger, in the FH\textsuperscript{-} group. Longitudinal studies like the ‘Atherosclerosis Risk in Communities’ (ARIC)\textsuperscript{251} study and the ‘Insulin Resistance Atherosclerosis Study’ (IRAS)\textsuperscript{287} have shown that incident diabetes subjects had baseline higher inflammatory markers. In the ARIC study, of the 12,330 men and women followed up for a mean of 7 years, 1,335 had incident diabetes. The odds ratio for WBC and fibrinogen remained significant when adjusted for the known risk factors for T2D. When further adjusted for BMI and WHR, the associations lessened substantially but still remained significant. In the IRAS, 144 incident cases were detected after a mean follow up of 5.2 years from 1,047 participating non-diabetic subjects. These had higher baseline levels of fibrinogen, CRP and PAI-1. The association of CRP and fibrinogen was significantly altered after adjustment for BMI, WC and insulin sensitivity. Only PAI-1 remained significantly related to the incident T2D.

Results of the more recent report from the ‘Western New York Health Study’\textsuperscript{18} (Average follow up of 5.9 years) support the role of endothelial dysfunction and sub-clinical inflammation as important mechanisms in the etiopathogenesis of T2D and that these markers improve prediction of T2D beyond the use of traditional risk factors alone. Here again, hsCRP and IL-6 were not significant after adjusting for BMI and other risk factors. WBC, E-Selectin and albumin remained significant. These reports and several others\textsuperscript{12,139,169,202,204} suggest that the association between markers of inflammation and risk of T2D may be significantly reduced after accounting for measures of obesity. It was also suggested by stranges \textit{et al}\textsuperscript{18} that the associations in fact may be stronger in leaner individuals. The results of the present study also support this suggestion. The FH\textsuperscript{-} subjects had lower WC, WHR and BMI (not significant) as compared to FH\textsuperscript{+} but stronger associations were found with inflammatory markers. Rosenzweig \textit{et al}\textsuperscript{183} proposed clinical practice guidelines for the primary prevention of CVD and T2DM in patients at
metabolic risk. They found that CRP and such other markers do not add any extra benefit for risk engines compared to routinely measured parameters like BP, WC, lipid profile and FPG.

The BP in two groups FH\textsuperscript{+} and FH\textsuperscript{-} did not differ significantly. Kumar \textit{et al}\textsuperscript{80} and Gupta \textit{et al}\textsuperscript{77} have found raised BP in FDRs of T2D patients. Even in normoglycemic FDRs, BP was higher in the study by Gupta \textit{et al.}\textsuperscript{77} The same was not found in the present study. The reason for this could be that, there were only 20 known hypertensives in the present study whose BP was >130/85 mmHg even in those who were on treatment. Of these, 8 were in the FH\textsuperscript{+} group and 12 in the FH\textsuperscript{-} group. Similarly, the number of subjects who had not reported hypertension but were found to have raised BP during the study were distributed in approximately the same ratio in the two groups. Natali and Ferrannini\textsuperscript{24} suggest that two types of HTN exist; one with a strong genetic background largely independent of diabetes and MetS, and the other whose clinical manifestation needs the milieu of the MetS. Also, there was no significant association of BP with any of the inflammatory markers in FH\textsuperscript{+} groups. Among FH\textsuperscript{-} subjects (Table-7) both SBP and DBP correlated with hsCRP (r=0.224 and 0.201 respectively). Inflammation has been reported earlier in prehypertensives and hypertensives.\textsuperscript{305,306} However, in a study conducted in White and Black post-menopausal women inflammatory markers, hsCRP, IL-6, IL-1\textbeta, TNF-r2 or sICAM-1 associated with incident hypertension but the results attenuated after adjusting for BMI.\textsuperscript{311}

**Glycemic indices and FH:**

HbA\textsubscript{1c}, fasting insulin (FIn) levels and insulin resistance calculated as Homa-IR were significantly elevated in subjects with FH\textsuperscript{+} (Table-11). These results concur with the findings reported by Gong \textit{et al,}\textsuperscript{46} Sarlund \textit{et al}\textsuperscript{65} and Balletshofer \textit{et al.}\textsuperscript{312} FPG and PPG were also higher (not statistically so) than in the FH\textsuperscript{-} group, but still within the normal reference range of <100 mg/dl and <140 mg / dl respectively as the subjects chosen were those who had no history of clinical diabetes. HbA\textsubscript{1c} is a function of both FPG and PPG.\textsuperscript{149} It has been documented that, in individuals who are likely to convert to diabetes, even when the FPG and PPG fall within the normal reference intervals there
are hyperglycemic excursions of plasma glucose levels throughout the day and especially following a meal that significantly contribute to the levels of HbA$_{1c}$.\textsuperscript{313} The body however can still maintain the absolute FPG and PPG levels probably through hyperinsulinemia. These and such other studies drive the need to include HbA$_{1c}$ also as a diagnostic tool for diabetes. There are researchers and clinicians against the use of HbA$_{1c}$ majorly because of inconsistencies of its estimation methods.\textsuperscript{154} From the results of the current study, it has to be appreciated that before changes in FPG and PPG fall even in the prediabetes range, HbA$_{1c}$ levels are elevated. Thus, this can be used in the work up of patients at risk of developing diabetes. Wang et al\textsuperscript{150} from the Strong Heart Study found that the use of FPG in detecting new diabetes has a low sensitivity of 62.8\% and recommended the use of HbA$_{1c}$ with FPG to detect undiagnosed diabetes. The results of several other studies\textsuperscript{151-153} in agreement with the above are strongly in favour of using HbA$_{1c}$ for the diagnosis of diabetes to bring all the suspected cases with inconclusive plasma glucose values within the ambit and do away with the oral glucose tolerance test. ADA has now accepted the use of HbA$_{1c}$ for diagnosis. A value > 5.6\% and < 6.1\% represents prediabetes and value > 6.1\% indicates diabetes.\textsuperscript{37}

Between FPG and PPG, the values of FPG were closer to attaining statistical significance between the two groups (Table-11). Differing views are existent on whether FPG is the first to deteriorate or PPG in subjects at risk of developing T2D.\textsuperscript{160,162,164} Several studies have found an aberration of PPG in the development of T2D.\textsuperscript{102,162,163} The subjects in such studies were generally overweight and insulin resistant. A hyperinsulinemic state was also found in the initial stages in such cases which is said to overcome the peripheral insulin resistance. It was postulated that only when the compensatory hyperinsulinemia fails to regulate the plasma glucose values and β-cell failure begins, FPG starts rising.\textsuperscript{62} The fairly well controlled PPG levels and altered FPG levels found in the FH$^+$ group in the present study point to the fact that subjects with a FH of diabetes must be more prone to β-cell damage early in the process of diabetes development irrespective of the insulin action.\textsuperscript{61,103}
The FH+ group showed significant elevations in fasting insulin levels and insulin resistance calculated as Homa-IR. Sarlund et al\textsuperscript{65} have reported that an early sign that characterises the risk of developing diabetes in FH+ is hyperinsulinemia and IR. These can predict conversion to T2D. Hyperinsulinemia is also a risk factor for CHD. Such findings have been reported in prediabetes patients\textsuperscript{30} and in normoglycemic subjects\textsuperscript{11} with FH. The role of IR and elicitation of compensatory hyperinsulinemia in the pathology of fasting and postprandial hyperglycemia is also debatable. Several studies purport that raised PPG is more closely related to IR.\textsuperscript{129,164}

In the studies on FDRs of T2D, however, mixed results have been reported.\textsuperscript{29,30,61} Decline in β-cell functioning has been recognised early in them.\textsuperscript{99} It has been found that the defects are seen much before decline in the glycemic control. Another evidence in support of this is the fact that FDRs develop diabetes atleast a decade earlier than their parents.\textsuperscript{8} As has been described under inflammation and FH, FPG did not correlate with inflammatory markers but PPG did.

Another important observation in studies involving Asian Indians is that the extent and pathology of IR and insulin sensitivity also differs in them as compared to Caucasians.\textsuperscript{7,97,132}

Thus, in the FDRs of T2D, higher insulin levels were found in the face of well-controlled PPG levels. Insulin resistance was higher implying its role in the development of abnormal FPG also.

Table-12 shows the correlation coefficients of FPG, PPG, HbA\textsubscript{1c}, Insulin and IR with BMI, WC, WHR, SBP and DBP. Although significant ‘p’ value was obtained for several of the parameters, only those with a ‘r’ value >0.2 were considered significant and those with a ‘r’ value >0.3 as strongly associated. FPG, PPG, HbA\textsubscript{1c}, FIn and Homa-IR showed a positive correlation with BMI, WC and SBP (except HbA\textsubscript{1c}). WHR and DBP correlated with FIn and IR only. Whenever an association was found in the FH group, the ‘r’ value was either comparable or lower than in the FH+ group. The strongest association was of BMI with FIn (r=0.525) and Homa-IR (r=0.507) and of WC with FIn (r=0.487) and Homa-IR (r=0.480) in the FH+ group. Equally strong association of WC
with FIn and Homa-IR was found in the FH+ group, indicating that glycemic indices are largely governed by changes in body composition and BP particularly in the FH+ subjects. Confusion exists regarding the use of BMI, WC and WHR for risk assessment. There are studies supporting BMI, WC or both and very few in favour of WHR. Ethnic differences and the type of the study also influence the results. In the present study comprising of a cross section of non-diabetic FDRs of T2D patients, matched for age with non-diabetic FDRs without a FH of diabetes, BMI, WC and SBP strongly influenced glycemic parameters like FPG, PPG and HbA1c probably via the hyperinsulinemic/IR derangements.

When FPG, PPG and HbA1c were correlated with FIn and Homa-IR (Table-13), all the 3 showed significant associations in both FH+ and FH- groups. Of particular note was the stronger association with Homa-IR in the FH+ group. The ‘r’ value for PPG was only marginally higher with Homa-IR than the ‘r’ value for FPG. Appreciable difference was observed in the ‘r’ values of FPG and PPG with FIn levels. It is therefore possible that both FPG and PPG contribute to Homa-IR but PPG is the major determinant of insulin levels (Table-13). Thus it can be said that increased body weight (BMI) and abdominal obesity (WC and WHR) seen in the FH+ subjects induce peripheral IR and consequent hyperinsulinemia which affect the HbA1c levels, and in due course of time the absolute FPG and PPG levels also. As is well known, HTN is a comorbidity associated with T2DM and shares an insulin resistance pathology. The IR seen in the FH+ group may ultimately lead to derangements in BP also (Tables-13). Correlation of WC, BMI, WHR, BP, FPG, PPG and HbA1c with IR strengthen the IR basis for all these.

Lipid profile and FH:

Another comorbidity frequently associated with DM is the atherogenic lipid profile including raised Tg and LDL levels, and lower HDL levels. Such lipid alterations have been reported in prediabetes patients also. In the present study involving non-diabetic FDRs, significant increase was seen in the levels of total and LDL cholesterol, and the TC/HDL ratio (Table-14). Though not significant, Tg values showed a higher trend and HDL-C a lower
trend in the FH\textsuperscript{+} group. No significant correlation of the lipid parameters was found with inflammatory markers among the FH\textsuperscript{+} subjects. Upon Pearson's analysis, TLC showed a correlation with Tg (+ve) and HDL-C (-ve) among the FH\textsuperscript{+} group, again emphasising an appreciable relation of inflammation in the FH\textsuperscript{+} subjects (Table 5 & 7).

Table-15 shows a weak albeit significant association of TC, Tg, LDL (+ve) and HDL (-ve) with WC in both the groups. The strength of association also was not very different in the two groups. Tg (+ve) and HDL (-ve) were associated with BMI and WHR also. The association of Tg with WHR showed a high significance with \( r=0.457 \) in FH\textsuperscript{+} and \( r=0.401 \) in FH\textsuperscript{-}. A correlation of TC with WHR and that of Tg (+ve) and HDL (-ve) with SBP and DBP, however was observed only among the FH\textsuperscript{+} group. From the above findings it can be inferred that obesity indices affect lipid levels adversely to similar extents in both FH\textsuperscript{+} and FH\textsuperscript{-} group, whereas BP has a small but significant adverse effect on Tg and HDL in FH\textsuperscript{+} subjects only.

To know if this effect also shared the IR pathology, the lipid levels were correlated with Fln and Homa-IR (Table-13). A significant direct association of Tg and inverse association of HDL with Fln and Homa-IR \( (r>0.3) \) was found in both the FH\textsuperscript{+} and FH\textsuperscript{-} groups and the values were comparable, emphasising the role of IR in lipid derangements also.\textsuperscript{124} But the FH of diabetes did not confer any additional risk. However, higher mean, total and LDL-C, and TC/HDL-C ratio (Table-14) are in support of the fact that dyslipidemia is a significant contribution to CVD risk in normoglycemic FDRs and T2D patients.\textsuperscript{63} Most of the prior results published described alterations in Tg and HDL.\textsuperscript{10,15,30,69} In the present study LDL was elevated. In a study\textsuperscript{312} assessing endothelial dysfunction in young normotensive FDRs also LDL was raised but no differences were found in Tg and HDL.

Although significant differences were seen in LDL-C levels and TC/HDL-C ratio between FH\textsuperscript{+} and FH\textsuperscript{-}; upon correlation analysis, Tg and HDL-C showed a correlation with BMI, WC, WHR, SBP, DBP, Fln and Homa-IR. LDL significantly correlated with WC (FH\textsuperscript{+} had significantly higher mean WC also).
Insulin resistance has been suggested as the underlying pathology for the derangement in carbohydrate and lipid metabolisms and dysregulation of the blood pressure control. IR in turn is brought on by an expanding WC. The results of the present study are in agreement with the above hypotheses and the mechanisms are more pronounced in the FH+ group at risk of developing diabetes.

To summarise the important conclusions drawn from FH+ and FH− groups:

1. IL-6 and cortisol were found elevated in FH+. Mean values of TLC, ESR, hsCRP, ceruloplasmin, haptoglobin and fibrinogen did not differ in the two groups. Peripheral circulating acute phase proteins may not be suitable predictors of diabetes development in non-diabetic FDRs. The use of IL-6 needs to be confirmed in larger sample size.

2. FH+ subjects are heavier, have significantly more abdominal fats as compared to FH− subjects.

3. They have elevated HbA1c levels indicating higher mean plasma glucose with greater degree of peripheral IR and compensatory hyperinsulinemia. Higher LDL-C and greater TC/HDL ratio points to proatherogenic lipid perturbations in them.

4. Age, BMI, WC, PPG, HbA1c, Insulin and Homa-IR correlated with inflammation markers in FH+. Among FH− subjects, along with the above, SBP, DBP, Tg & HDL also correlated with inflammatory markers and the strength of association was stronger in the FH− group.

5. In the sub-group with additional cortisol and IL-6 estimations, IL-6 correlated with BMI, WC and PPG in the FH+ and with BMI, WC, PPG, FIn and Homa-IR in the FH− groups. Again the strength of association was stronger in the FH− group.

6. BMI and WC strongly affected changes in PPG, FIn, Insulin and Homa-IR among the FH+ subjects. SBP and DBP also correlated with FIn and Homa-IR.

7. Strong positive associations of FPG, PPG, HbA1c, SBP, DBP, Tg and negative association of HDL-C was seen with FIn and IR in the FH+ group as compared to FH− group, reiterating the common soil hypothesis that even mild alterations in the glycemic, lipid and blood pressure status
share an underlying insulin resistance pathology in the nondiabetic subjects and the mechanism is pronounced in those with a family history of diabetes.

In conclusion, gain in weight and central fat deposition provokes insulin resistance and hyperinsulinemia which contributes to deleterious lipid disturbances. Both these bring about disharmony of the glucose homeostasis and blood pressure control. The above derangements are probably the earliest noticeable changes in subjects at risk of developing diabetes i.e., FDRs of T2D patients. These derangements activate the inflammatory process causing elevations of IL-6. But, counter regulatory mechanisms like hypercortisolemia and hyperinsulinemia can still control the inflammation and inhibit the peripheral acute phase response. The chick and egg theory exists with inflammation markers and hyperglycemia. It has been proposed by a few that hyperglycemia invokes/exacerbates an inflammatory response, while the converse is advocated by some. The results of the present study conducted in nondiabetic FDRs of T2DM patients support the theory that inflammation (if any) is a consequence of excess adiposity, abnormal glucose homeostasis and lipid aberrations.
Influence of FH on younger and older subjects

It has been discussed that the FH group (Table-3) who were normoglycemic FDRs did not manifest an inflammatory milieu in the form of acute phase proteins, whereas levels of IL-6 were found to be elevated. To address one of the secondary outcomes viz., ‘How early the inflammation process begins?’, the subjects of the groups FH$^+$ and FH$^-$ were divided further into two groups based on their age. FHY$^+$ and FHY$^-$ represented subjects in the age group of 20-39 years with a FH and without a FH respectively. FHE$^+$ and FHE$^-$ were subjects in the age group 40-60 years with and without a FH respectively. Previously reported results indicate a higher adverse cardiometabolic and proinflammatory changes with advancing age. Hence, presuming that differences may be obtained upon subgrouping the study population based on age, (in keeping with the objective), analysis was carried out by dividing the subjects into younger age group (20-39 years) and elder age group (40-60 years).

Table-16 shows a comparison of FHY$^+$ and FHE$^+$. Among subjects with a FH, the older subjects were significantly obese, had higher blood pressure (BP), plasma glucose values and HbA$_1$c, TC and LDL-C. Among the inflammatory markers, the only significant difference was found in the levels of fibrinogen. All these parameters are known to be affected by advancing age. To know whether this difference was restricted to the subjects with FH alone, FHY$^-$ and FHE$^-$ subjects were compared (Table-17). Similar differences were observed among subjects without FH. Additionally, the FHE$^-$ had higher levels of Tg, TC/HDL and ESR.

The inflammatory basis that was proposed as a pathophysiologic phenomenon in the development of diabetes was found to exist even in the normoglycemic FDRs by a few. Elevated levels of TLC, ESR, hsCRP, IL-6, fibrinogen etc have been reported$^{15,29,296,297}$ In this study significantly higher levels of fibrinogen were found in older subjects (both FHE$^+$ and FHE$^-$). Fibrinogen levels are affected by age, raised BP, BMI, WC, WHR, glycemic status and lipids.$^{276,278}$ It is a measure of the viscosity of blood accounting for
other inflammation proteins also. The findings in this study corroborate the earlier reported data.\textsuperscript{277,278} In FHE\textsuperscript{−} the ‘p’ value for ESR and fibrinogen was more significant than for those in FHE\textsuperscript{+}. Thus, as discussed in the whole cohort of FH subjects, inflammation markers may correlate better in those without a FH especially in the older group.

Subclinical rise in inflammatory markers are found to be associated with several conditions like natural aging, hypertension, obesity, diabetes, dyslipidemia, insulin resistance, metabolic syndrome, CVD, etc. Some authors strongly implicate the resistance to insulin action as the underlying cause of all afore mentioned conditions and hence inflammation is evident when associated with IR.\textsuperscript{136-138} FIn and Homa-IR level were comparable between the younger and older subjects with a FH of diabetes. Similarly, no appreciable difference was found between FHY\textsuperscript{−} and FHE\textsuperscript{−}.

Visceral fat accumulation is proportionally dependent on age. Hence it is not surprising that the older subjects in both the groups (FHE\textsuperscript{+} and FHE\textsuperscript{−}) were significantly more obese than the younger subjects in their respective groups (FHY\textsuperscript{+} and FHY\textsuperscript{−}). The genetic programming in the FDRs of T2DM patients predisposes them to the accumulation of visceral fat and consequent IR.\textsuperscript{132,201} This IR stemming from obesity is said to have a cascading effect on the glycemic, lipid and BP regulation, leading in due course of time under the influence of environmental factors, to diabetes, dyslipidemia, hypertension, CVD and other morbidities.

The greater and additional differences in Tg, TC/HDL and ESR among the older subjects of the FH\textsuperscript{−} group point to the fact that the differences in the various studied parameters between the younger and older subjects with a positive FH were not significant implying an already existing subtle lipid alteration and the activation of an inflammatory status in the FHY\textsuperscript{−} group. This is in accord with the findings of previously reported data.\textsuperscript{70}

To test this further, the younger group of FH\textsuperscript{+} and the younger group of FH\textsuperscript{−} (FHY\textsuperscript{+} and FHY\textsuperscript{−}) subjects were compared (Table-18). Significant higher levels of WC, WHR and TC/HDL were found in the FHY\textsuperscript{+} group. In fact, except SBP,
ceruloplasmin and Haptoglobin all the parameters were higher and HDL lower in the FHY group but not statistically so. Several studies have reported these findings in the young diabetic subjects with a FH of diabetes. The results of this study lend credence to these reports and also demonstrate that what was observed in diabetic subjects is in fact present even before clinical hyperglycemia sets in. It is said that the visceral fat is a dangerous storehouse of pro-inflammatory factors. Despite larger WC, significant higher concentration of the inflammatory factors was not observed among the FHY subjects. It must be appreciated that the mean WC was 87.34±11.15 cm which is not morbidly high as has been found in the subjects of studies reporting higher inflammatory markers in the non-diabetic individuals.

Table-19 depicts the comparison of FHE+ and FHE-. With almost significant difference in WC and statistically significant higher WHR, the FHE+ also displayed higher concentrations of FPG, HbA1c, fasting plasma insulin and Homa-IR. These findings provide additional evidence to the previous reports. With advancing age, deterioration in the glycemic profile is expected consequent upon the higher abdominal fat and increasing peripheral insulin resistance. Results of this comparison also reiterate the findings that FPG is the first to be altered in subjects at risk with a positive FH and that dysregulated FPG also has an insulin resistance/hyperinsulinemic basis.

From the comparisons of the younger and the older subjects among and between the groups with and without FH of diabetes, a logical sequence of metabolic aberrations unfolds where the FHY showed a greater amount of abdominal adiposity than FHY-. The FHE+ compared to FHE- had in addition to higher WHR, significant hyperinsulinemia associated with higher IR. As a sign of β-cell failure, FPG and HbA1c were higher in them, strengthening the pathologic mechanisms proposed for diabetes development. Thus, the earliest changes are seen in the form of raised WC in the young FH+ group which goes on to induce IR. Hyperinsulinemia, possibly helps in overcoming the IR and rising FPG and HbA1c.

These findings are relevant in the context of the influence of the FH of diabetes on the outcome in the offsprings and siblings. In age and gender
matched groups, those with a FH positive for diabetes have a larger WC and WHR and this could be the beginning of the spiraling derangements and dysregulations that may be observed in future with regards to carbohydrate, lipid metabolisms and the inflammatory process.

Studies undertaken in diabetic patients developing diabetes early in life have found that those patients differ in their anthropometric and clinical characteristics from those developing diabetes later in life. Pathogenesis of T2D in subjects who develop diabetes at younger age is different from that of elder subjects. Age of onset in subsequent generations decreases in siblings and offsprings of diabetic families. β-cell function declines as early as 12 years before diagnosis and continues despite treatment. Worse glycemic status has been found in them. It is also well understood that those developing diabetes early in life have a more severe and protracted course of the disease and are more likely to develop complications owing to severity, duration and the strong genetic component.

The insignificant differences in the inflammatory markers (other than fibrinogen) can be due to the fact that these FDRs were nondiabetic. The mean values of BP, WC, WHR, FPG, A1C, TC and LDL although statistically higher in the FDRs as compared to the control group, were either within or close to the acceptable clinical reference intervals of the respective parameters. Parallel associations have been found between inflammation and age and it was thought to be due to the accumulation of several cardiometabolic risk factors as age advances. The results of the present study lend support to the above hypothesis and provide data to show that apparently healthy older subjects (40-60 years) who have not yet demonstrated clinically morbid cardiometabolic risk factors show a rise in inflammatory status in the form of fibrinogen irrespective of their FH.

The mean age for developing diabetes in India is found to be around 45 years. The FHE+ group were subjects of 40-60 years with a mean age of 46.91 years. These subjects as and if they develop diabetes could have a less severe course. Alternately, it is well known that only about 50% of the offsprings of T2DM patients develop diabetes. A large proportion of the
subjects in the FHE\textsuperscript{+} group could be the offsprings/siblings who may never develop diabetes. This hypothesis is also supported by the data on FH reported by the FHE\textsuperscript{+} group. Of the 62 participants, 30.6\% reported a history among siblings followed by mother (17.7\%), father (14.5\%), mother and sibling (14.5\%), father and mother (11.3\%), father, mother and sibling (6.5\%) and father and sibling (4.8\%) (Table-20).

Among the FHY\textsuperscript{+} group, of the 71 participants included in the study, 42.2\% reported a history of diabetes in the mother. Close behind was a history in the father at 39.4\% followed by father and mother (9.9\%), father and sibling (4.2\%), sibling (2.8\%) and mother and sibling (1.4\%). Higher maternal transmission has been observed by several researchers studying diabetic patients and their parental history of the same.\textsuperscript{75,89} It is important to note that these studies were conducted in diabetic patients whereas the current study was in non-diabetic individuals where similar pattern of history is observed.

Another alarming observation is that, from the findings it clearly emerges that there were no drastic differences in the two age groups (20-39 years and 40-60 years) with a positive FH. A statistically nonsignificant but adverse profile in FHY\textsuperscript{+} was observed in comparison to FHY\textsuperscript{−}. Thus, caution has to be exercised with the younger group with FH who may be at larger chances of being affected by the genetic and environmental factors contributing to their conversion to the diabetes state with the possible longer duration of the disease and potentially unfavorable outcomes.

Cumulative evidence from the comparisons of FHY\textsuperscript{+}, FHY\textsuperscript{−}, FHE\textsuperscript{+} and FHE\textsuperscript{−} groups suggest that,

1. The FH\textsuperscript{+} subjects – both FHY\textsuperscript{+} and FHE\textsuperscript{+} have higher visceral fat as compared to FHY\textsuperscript{−} and FHE\textsuperscript{−} respectively.
2. Although not statistically significant, with the sample size chosen here, adverse alterations in most of the studied parameters were observed in the FH\textsuperscript{+} group.
3. The FHY\textsuperscript{+} group is a particularly susceptible one and the findings imply a more profound and protracted effect on the course of diabetes as and
when they convert.

4. In due course, among the plasma glucose, FPG is the first to alter associated with hyperinsulinemia/insulin resistance.

5. The extent to which WC, FPG, HbA$_1c$ and IR were elevated in the FHE$^+$ group was not sufficient to provoke a strong inflammatory response in them although these factors are implied in many studies, thus necessitating a higher degree of impairment of the above parameters to provoke a inflammatory response.

6. Inflammatory markers may not be suitable as predictors of diabetes development in both younger and older individuals with a FH of diabetes. Their role, however, in older individuals without a FH needs to be ascertained with a larger sampling.

In conclusion, drastic differences were not found in the anthropometric and the metabolic variables between the younger and the older subjects with a FH of diabetes. Similar comparisons in the subjects without a FH of diabetes showed significant age related adverse changes in the older individuals. The younger group with FH already have a deranged anthropo-metabolic profile because of which they do not differ significantly from their older counterparts. This indicates a possibility of the FHY$^+$ subjects developing diabetes early thereby having a prolonged and protracted course of the disease with impending complications. The findings impress the need to particularly monitor this group.
To understand metabolic syndrome (MetS) among the subjects with FH of diabetes, the NCEP ATP III criteria and SAM-NCEP criteria were used to categorize the subjects.

NCEP-ATP III Criteria:

On dichotomizing the subjects of FH⁺ and FH⁻ meeting the criteria for MetS, 36 subjects (27.1%) in the FH⁺ group and 24 (16.6%) in the FH⁻ group were segregated. These findings concur with the prior reports that have found a higher incidence of MetS in subjects with a FH of diabetes. The metabolic and anthropometric characteristics of the MetS subjects in the FH⁺ group compared with the rest of the subjects in their respective groups are shown in Tables-21 and 22. Other than the obvious difference in the 5 MetS components of raised WC, BP, FPG, Tg, and lowered HDL, statistical significance was also observed in BMI, WHR, PPG, FIn, IR and TC/HDL in the MetS-FH⁺ cases. No rise was observed in any of the inflammatory markers studied. The components of the MetS are also known to be associated with an underlying inflammatory pathology. In this group of nondiabetic FDRs of type2 DM patients however, those meeting the MetS criteria did not show appreciable rise in the inflammatory markers.

When the subjects with MetS in the FH⁻ group (Tables-23 and 24) were studied with their group controls, the MetS subjects were older and did not show difference in BMI, and PPG as with MetS subjects of FH⁺ group. To check for differences among the MetS subjects in the two groups, the groups were compared and statistical significance was found only in WHR with the value being higher in the FH⁺ group (Table-25), confirming previous previous findings of higher degree of visceral adiposity in them. From the above findings it can be concluded that the FDRs of FH⁺ subjects are at greater risk of developing MetS than that of FH⁻ subjects. But the clinical and metabolic profiles do not differ in the two groups once MetS is established (except WHR).
Certain important aspects to be considered are:

a) The subjects were not morbidly obese as in certain studies reporting contrary results. WC was 94.09 ± 10.5 cm in MetS-FH\(^+\) and 93.93 ± 9.78 cm in MetS-FH\(^-\).

b) The mean BP was also 132.55 ± 13.48/86.83 ± 0.91 as against 117.44 ± 11.53/76.43 ± 9.30 (cut off is 135/85).

c) The subjects were not diabetic, but IFG and IGT subjects as per ADA guidelines were included. The mean FPG was 100.30 ± 11.93 mg/dL.

d) Tg and HDL only were well above and below the cutoff of >150 mg/dL and <40/50 mg/dL (in males and females) respectively.

It is possible that mere meeting the criteria with borderline values may not elicit an acute phase response.

Since individually the sample size with MetS in the two groups FH\(^+\) and FH\(^-\) were small (36 and 24) and because there was no appreciable difference between the MetS subjects (except in WHR), the two groups were pooled to study the relation of MetS per se with inflammation. Table-26 depicts the same. With the sample of 60 subjects with MetS compared to 217 subjects without MetS, TLC and CRP levels were statistically higher in the MetS group. This is in agreement with previous studies\(^{254,298}\) and also implies the importance of the sample size. In a larger cohort of FH\(^+\) - MetS cases, raised inflammatory markers probably may be appreciated.

Another possibility is that, the control group comprised of subjects who could be having one or two components of MetS which may interfere with bringing about a difference.

To address this, from the 217 subjects who served as controls and who could be having one or two components of MetS, only those subjects termed ‘absolute controls’ were chosen to mean subjects not meeting any MetS component. These (n=42) were compared with MetS subjects (Table-27). (The number would be too small to carry out such an analysis individually among FH\(^+\) and FH\(^-\). Hence the whole cohort of MetS subjects was considered).
The only difference found between Table-26 and Table-27 was the additional significant rise in Haptoglobin levels. Even though statistical difference was seen in Table-26, the difference was drastically enhanced in the levels of BMI, WC, FIn, IR, Tg, HDL, CRP and haptoglobin when MetS subjects were compared with absolute controls.

Several researchers have highlighted the seriousness of each additional component comprising the MetS.\textsuperscript{27,66,227} When subjects having one or two components of the Mets but not meeting the criteria (3 of 5 components) were deleted from the control group, it was clear that BMI, WC, FIn, IR, Tg, HDL, CRP and haptoglobin are associated with at least one component of MetS. Several definitions of MetS exist.\textsuperscript{185} For example, WHO has DM, IGT, IFG or IR as a mandatory criterion, European Group for the study of Insulin Resistance has IR as the mandatory criterion and IDF has central obesity. Many definitions have undergone revision based on epidemiological and observational studies. WHO dropped ‘microalbuminuria’ from its list of MetS constituents.\textsuperscript{219} ATP III criteria that was first proposed (and used in the present study) was modified to include FPG $\geq 100$ mg/dL instead of $\geq 110$ mg/dL.\textsuperscript{199} With accumulating evidence of ethnic differences, the SAM-NCEP criteria\textsuperscript{190} were proposed with ethnic specific cut points of 90 cm (men) and 80 cm (women) for WC and FPG $\geq 100$ mg/dL. IDF has adopted ethnic cut points and in an attempt to harmonise the definitions of MetS, has recently in its interim statement has proposed dropping the mandatory criterion of WC.\textsuperscript{187} In the present study 21.66% (60/277) had MetS by ATP III criteria, 15.16% (42/277) were absolute controls and 63.18% (175/277) had one or two components of MetS (Fig-1). In India, reported prevalence rates range from 24.9% to 70%. Differences have been observed in north and south Indians, males and females, overweight and lean, diabetics and non-diabetics and by using different criteria.\textsuperscript{214,219,220,223}

Pearsons correlation analysis of inflammatory markers was carried out with the components of MetS. ESR, TLC, hsCRP, haptoglobin, ceruloplasmin and fibrinogen were correlated with WC, HDL, Tg, FPG and BP. Only the significant univariate associations are shown in Table-28. Tg and HDL did not
correlate with any of the inflammatory markers in MetS subjects. Also, there was no definite pattern of the other correlations. FPG correlated with ESR in the FH + MetS subjects and in the whole cohort of MetS subjects. Similarly, TLC with WC. CRP correlated with DBP and haptoglobin with SBP only in the FH - and whole cohort of MetS. Fibrinogen significantly associated with WC only in the whole cohort.

Previous studies have reported association between inflammatory markers and the individual constituents of MetS. Particularly strong correlations have been found with increasing levels of WC and FPG. The results of the present study are in agreement with those. However, a clear pattern does not emerge. It has been previously discussed (under FH discussion) that inflammatory markers could be more strongly associated in the FH - group. Such an observation was not made here. This could be possible due to the fact that although the number of MetS cases were higher in the FH + group, the metabolic and inflammatory profiles did not differ between those with FH + and FH - once MetS is diagnosed. Another limitation could be the sample numbers in each of the groups (36 in FH +, 24 in FH - and 60 in the whole cohort).

Table-29 shows the significant results of the multiple regression analysis of the inflammatory markers as dependent variables and, BMI, WC, SBP, DBP, FPG, PPG, A1c, In, IR, Tg and HDL as independent variables among the entire cohort of MetS subjects (n=60) by ATP III criteria. While there were no independent predictors for TLC, hsCRP and haptoglobin; PPG predicted ceruloplasmin and, HbA1c and Tg predicted fibrinogen. From these results it is difficult to point to any single metabolic or anthropometric variable capable of eliciting an inflammatory response. However, the parameters of glycemic control (PPG, In, IR and HbA1c) could be closer predictors in nondiabetic individuals.

Multiple regression analysis was also carried out with MetS components as dependent variables and, age, BMI, SBP, DBP, WC, insulin, IR, FPG, Tg, HDL and HbA1c as independent variables. Only the significant associations are shown in Table-30. The determinants of each component were different. It
is said that the MetS constituents are united by IR. In the present study fasting FIn levels and IR were determinants of FPG only. Reaven\textsuperscript{217} has shown that FPG is the strongest correlate of IR and BP, the weakest. The same is endorsed by the current findings. SBP was a significant independent variable for WC only. SBP and DBP did not predict any other MetS component. Similarly, none of the independent variables studied predicted BP. The highest number of metabolic predictors were for FPG (BMI, WC, In and IR). Tg and HDL were interrelated as is well understood.\textsuperscript{210} Tg also predicted WC.\textsuperscript{210} Correlation of BMI and WC is also well appreciated.\textsuperscript{170,315} An interesting finding however, is the prediction of HDL by HbA\textsubscript{1c}. This should be probed further to monitor the subjects at risk of DM. A decreasing HDL and increasing HbA\textsubscript{1c} may mark the onset of clinical diabetes. Another deduction from these findings is that the parameters that were considered here as independent variables and the generally accepted ones may not be necessarily important in our population. It may be worthwhile to consider certain other parameters as have been proposed by some researchers.\textsuperscript{212,316,317}

**SAM–NCEP criteria:**

With advancing understanding in the pathophysiology of MetS and its constituents, it was emphasized that ethnic and racial differences in the genetic and phenotypic make up be appreciated and considerations be made for them in the definition, prevalence, diagnosis and management of MetS and its components. Thus, SAM-NCEP criteria were proposed for Asians where MetS is diagnosed when 3 or more of the following are present.

1. WC $\geq$ 90 cm in men and $\geq$ 80 cm in women.
2. BP $\geq$ 130/85 mmHg.
3. Tg $\geq$ 150 mg/dL.
4. HDL $\leq$ 40 mg/dL for men and $\leq$ 50 mg/dL for women.
5. FPG $\geq$ 100 mg/dL.

By this criteria, 39.84% of subjects with a FH of diabetes were found to have MetS as compared to 28.47% among subjects without a FH of diabetes.
(Table-31 and-33). Among the FDRs, those with MetS were older and heavier with greater degree of visceral obesity and higher BP as compared to those without the MetS. All parameters assessing glycemic status were worse among the MetS FDRs (FPG, PPG, HbA1c, insulin and Homa-IR) (Table-32). In keeping with the criteria for MetS diagnosis, Tg was higher and HDL lower in them. They also had higher TC/HDL ratio. Of the inflammatory markers studied, hsCRP levels were significantly higher in the MetS cases. This finding was in difference to the findings in ATP II I cases. Lowering the WC and FPG cut points shifted the individuals with WC ≥90/80 cm in men/women and FPG ≥100 mg/dL to the MetS group thereby refining the group which served as controls (non-MetS subjects).

Among the MetS cases without a FH of diabetes, other than the differences in the parameters constituting MetS (WC, BP, FPG, Tg and HDL), significant higher levels of WHR, PPG, insulin, HOMA-IR, TC/HDL and hsCRP were noticed (Table-34).

A very pertinent observation while comparing ATP III criteria and SAM-NCEP criteria is that, the mean values of most of the parameters studied are similar in the MetS cases diagnosed by the two criteria (Tables-31 to 34) except for age, SBP and hsCRP. The ATP III subjects had higher SBP (132.55 ± 13.48 mmHg) compared to SAM-NCEP subjects (128.86 ± 13.43 mmHg). The subjects of SAM-NCEP were older and the difference in hsCRP levels which was not significant between the MetS cases and non-MetS cases in ATP III turned significant between the MetS and non-MetS cases in SAM-NCEP. A portion of the subjects who constituted the non-MetS control group in ATP III, by virtue of the defining criteria (WC ≥ 90 cm in men and ≥ 80 cm in women, and FPG ≥ 100 mg/dL) moved to the MetS group of SAM-NCEP. The mean hsCRP level in the non-MetS subjects in the ATP III group was 1.75 ± 2.42 mg/L which decreased to 1.50±2.32 mg/L in the non-MetS subjects in the SAM-NCEP group and the value for those with MetS rose from 1.93 ± 1.63 mg/L to 2.18 ± 1.89 mg/L showing that inflammation is associated with rising WC and FPG. This reiterates the importance of ethnic specific cut points of WC and of sample size where a sample number 53 in SAM-NCEP as against
36 in ATP III brought out a larger and significant difference. It is also noteworthy that the distribution of hsCRP normalizes in the MetS cases compared to the skewed distribution in the non-MetS cases in both the criteria.

When the subjects with MetS among FDRs and those without a FH of diabetes were compared (Table-35), as in the ATP III groups, the only difference was a significant higher mean WHR showing that MetS subjects with a FH of diabetes have higher visceral fat compared to MetS subjects without a FH of diabetes and are comparable in all other parameters. Hence, the two groups were pooled and the whole MetS cohort of SAM-NCEP subjects were compared with those not meeting the criteria in Table-36. The differences noted in Table-26 was further enhanced by this comparison with significant differences in TC and LDL also. Lowering the cut points for FPG and WC thus increases the sensitivity of identifying MetS cases.

As with the ATP III group, when the subjects with one or two components of the MetS who could be constituting the non-MetS control group were deleted and the whole cohort of SAM-NCEP MetS cases (n=94) was compared with the ‘absolute controls’ (n=29) in Table-37, drastic differences were observed in all demographic, metabolic and inflammatory variables (except TLC). The findings in the present study extend prior reports that inflammatory markers are associated with MetS and its candidate components more so with WC and FPG. More over the results become obvious as the control group gets refined. The differences are best appreciated when MetS cases are compared with subjects not harbouring even a single component of MetS – the absolute controls.

To highlight the significance of even a single constituent of MetS, if the hsCRP values are studied; the mean hsCRP value in the ‘absolute control’ group in ATP III criteria was 0.90 ± 0.95 mg/L whereas, that in the SAM-NCEP criteria was 0.76 ± 0.77 mg/L. A difference of 8-12 cm in WC (102/88 Vs 90/80 cm) and 10 mg/dL in FPG (110 Vs 100 mg/dL) contribute significantly to the inflammatory response.
By the SAM-NCEP criteria 39.84% (53/133) of FH+ subjects had MetS, 28.47% (41/144) of FH− subjects had MetS and together they accounted for 33.93% (94/277). The number of subjects who had one or two components of MetS but did not meet the MetS definition were 55.61% and the subjects who did not manifest even a single component of MetS, the ‘absolute controls’, were a mere 10.46% (29/277) (Fig-2).

Pearsons correlation of inflammatory markers with components of MetS was carried out and the significant results only are shown in Table-38. Tg correlated with TLC in the FH+ MetS cases and in the whole cohort. SBP correlated with fibrinogen in the entire cohort of MetS cases only. The findings suggest that FH of diabetes does not have a bearing once MetS is diagnosed. The correlation analysis findings do not match the corresponding findings in ATP III criteria (Table-28).

The significant findings of multiple regression analysis with inflammatory markers as dependent variables and BMI, WC, SBP, DBP, FPG, PPG, A1c, Fln, IR, Tg and HDL as independent variables are depicted in Table-39. As compared to similar analysis with ATP III subjects, higher number of independent variables predicted inflammatory markers, except for hsCRP which did not have any significant predictors. Here again, the significant predictors of inflammation were BMI, WC, FPG, HbA1c, Fln, Homa-IR, HDL and Tg. BP was not a predictor of any of the acute phase markers.

Regression analysis with MetS components as dependent variables showed an interdependency of WC and BMI. Unlike in the ATP III group; BP was predicted by A1c, IR and Tg (Tables-30 and 40) and HDL did not have any significant determinants. FPG had Fln and IR as significant determinants and, Tg had FPG and HDL. It appears that the nondiabetic MetS cases have a higher HbA1c despite physiological values of FPG and PPG. This rising A1c brings about adverse alterations in Tg, HDL and BP. Fln and IR are responsible for rising FPG and in individuals with larger WC, WC and BMI also contribute to the dyshomeostasis of FPG (Tables-27, 30, 37 and 40).
When the distribution of the candidate components of MetS was studied in the two groups (Table-41), it was found that low HDL was the most frequently occurring constituent in both the groups (96.7% and 96.8%). Tg was found in 78.3% and 64.9% of ATP III and SAM-NCEP MetS subjects respectively. The occurrence of BP was fairly comparable with 50% subjects in ATP III and 46.8% in SAM-NCEP. The number of subjects exhibiting a raised WC and raised FPG however did not match as the defining cut point were different. The frequency of the MetS constituents in order of their occurrence in the ATP III group was low HDL followed by raised Tg, BP, WC and FPG. That for SAM-NCEP was low HDL followed by raised WC, Tg, FPG and BP.

Various studies have reported different patterns of the MetS constituents’ frequencies in their study populations. Caucasians mainly show dyslipidemia, African populations show HTN, native Americans show hyperglycemia and south Asians show both hyperglycemia and accelerated CHD. Low HDL was the most frequent prevalence in a study from south India and the least was raised BP. However, in a study from Delhi, the most common MetS elements were BP and obesity. In another study low HDL was the most common in women and high Tg was the most common in men.

The prescribed cut off values of the MetS components were tested for their predictive ability as sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) (Table-42). While HDL enjoyed the best sensitivity in both criteria, FPG showed excellent specificity in ATP III and Tg showed good specificity in SAM-NCEP group. Together, Tg had good specificity and sensitivity in both criteria. In the ATP III group, FPG had good PPV and NPV, and in the SAM-NCEP group, it was Tg. Over all, both FPG and Tg showed good PPV and NPV in both groups. Dhanaraj et al from Chandigarh have also found good predictive value for Tg. They reported a cut off of 153 mg/dL and 150 mg/dL in men and women respectively with newly detected T2D.

Recommendations have been made by some researchers for the inclusion of newer indices as MetS constituents. E.g., Wasir et al – BMI, Pratyush et al – LDL and Misra et al – Acanthosis Nigricans, subscapular skin fold
thickness, buffalo hump, double chin etc. In the present study, of the 277 included subjects, 201 (72.6%) had HbA$_{1c}$ $\geq$ 5.6% (Table-43). 66.4% had HDL $\leq$ 40/50 mg/dL in men/women, 62.8% had WC $\geq$ 90/80 cm for men/women and those with BMI $\geq$ 23 kg/m$^2$ were 59.6%. As has been used by some workers, in the absence of WC measures, BMI can be used as a surrogate. The possibility of including HbA$_{1c}$ can be probed particularly considering its relation to Tg, HDL and BP (as discussed earlier) in subjects not overly obese and not diabetic. Osei et al$^{82}$ found HbA$_{1c}$ a surrogate for MetS in non-diabetic FDRs of African-American patients with T2D.

Some researchers are of the opinion that since each individual components is an established independent CVD risk factor, the concept of MetS should not be propagated as it may result in serious consequences to the individual. Although not a part of the defined objectives, the participants in the present study were grouped using cut points for the individual candidate constituent of MetS without regard to the others. There were 86 with FPG $\geq$ 100 mg/dL, 174 with WC $\geq$ 90/80 cm (men/women), 71 with WC $\geq$ 102/88 cm (men/women), 81 with Tg $\geq$ 150 mg/dL, 147 with BP $\geq$ 130/85 mmHg and 184 with HDL $\leq$ 40/50 mg/dL (men/women). The inflammatory markers were studied in these groups compared to the rest of the subjects in each categorizations. The results are shown in Figs-3 to 8. It can be observed that the group with WC $\geq$ 102/88 cm shows the highest levels of all markers (except TLC) compared to all others groups and also MetS groups. The group with WC $\geq$ 90/80 cm was the next in line. This impresses the role of central adiposity in instigating the inflammatory process even defeating the classification of MetS.

To summarize, the subjects with FH of diabetes are more prone to MetS compared to those without a FH. But once MetS develops, the clinic-biochemical profile does not vary between the two sets of individuals. However, those with a FH have greater visceral adiposity. Inflammatory markers are raised in MetS cases classified by both ATP III and SAM-NCEP criteria. Application of the SAM-NCEP criteria to non-diabetic, not so obese subjects improves the sensitivity of identifying the MetS cases. WC appears to be the single most MetS candidate constituent to be associated with
inflammation. Hence, this alone may suffice in the determination of CVD risk said to be conferred by MetS.