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ORIGINAL ARTICLE

Evaluation of progression in metabolic parameters along with markers of subclinical inflammation and atherosclerosis among normoglycemic first degree relatives of type 2 diabetes mellitus patients

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Abstract

Background The aim of this study is to assess for the change in progression of inflammatory, adiposity, and atherosclerotic markers in first degree relatives of type 2 diabetes mellitus patients.

Methods Normal glucose tolerant (NGT) individuals (20–40 years) who had positive family history of T2DM (FHP) were enrolled in this prospective study based on ADA 2015 criteria. Age, sex, and BMI matched controls without any history of diabetes in their parents referred as family history negative (FHN) were taken for comparison. At baseline, detailed clinical assessment and requisite blood/imaging investigations were done. All the available subjects from the original cohort (FHN-32 and FHP-46) were studied after 2 years with recording of the clinical, biochemical and imaging parameters.

Results A total of 64 cases (FHP) and 42 controls (FHN) were enrolled at baseline. FHP group had significantly higher hsCRP ($p = 0.039$) and cIMT ($p = 0.003$) than that of FHN group. No significant difference in the rate of conversion of NGT to prediabetes (using multiple criteria) was found after 2 years between the two groups. cIMT was increased significantly from baseline in FHP group than FHN group at the end of the study(0.02 ± 0.03 vs. 0.01 ± 0.02 mm, $p = 0.002$). But there was no significant difference for changes in glycemic status, lipid parameters, HOMA IR, hsCRP, and adiposity markers between the two groups at the end of the study.

Conclusion Despite no significant differences in change in glycemic parameters or rates of conversion from NGT to pre diabetes, cIMT increased significantly in the normoglycemic offspring of T2DM subjects than those without history of T2DM in their parents.

Keywords Insulin resistance · High sensitive C reactive protein (hsCRP) · Visceral adiposity · First degree relatives · Type 2 diabetes mellitus

Introduction

Type 2 diabetes mellitus (T2DM) is characterized by chronic hyperglycemia and its detrimental effects on major organ systems. The etiopathogenesis of T2DM is complex and is still incompletely understood despite decades of research. Interaction between the genetic and environmental factors is incriminated in the development of T2DM in a susceptible individual. The risk of development of T2DM is around 40% for offspring having history of T2DM in one parent whereas it is almost 70% if both parents are affected [1]. Obesity plays a major role in accentuating the risk of T2DM in susceptible individuals.

Insulin resistance plays a major role in the pathogenesis of metabolic syndrome as well as T2DM and is

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transmissible from parent to their offspring [2]. So the metabolic consequences of insulin resistance may be demonstrated in the first degree relatives of T2DM subjects before they develop overt diabetes. It is well evident that in most populations, those who evolve into frank T2DM usually demonstrate insulin resistance at an earlier time [3]. To overcome this insulin resistance, increased secretion of insulin occurs from the pancreatic beta cell resulting in hyperinsulinemia, which is capable of maintaining a relatively normal glucose tolerance state. However, in a subpopulation of these subjects impaired glucose tolerance (IGT) develops eventually as the hyperinsulinemic response is insufficient to fully compensate for the prevailing insulin resistant state. The proportion of conversion of IGT subjects to frank T2DM depends on the ethnicity of the individuals studied and the assay methods used. In the Chennai Urban Rural Epidemiology Study(CURES) after a follow-up of 10 years, conversion rate of NGT to prediabetes and diabetes was 25.7% and 19.4% respectively [4]. In this study, family history of diabetes was one of the major predictors of progression to dysglycemia [4].

Inflammatory cytokines are implicated in the pathogenesis of T2DM [5]. But it is uncertain whether inflammation causes insulin resistance, or is a secondary effect of obesity itself [6]. C-reactive protein (CRP), a nonspecific inflammatory marker, is most strongly associated with the development of T2DM [7]. However, the causal association has not been proved conveniently yet [8].

Apart from genetic factors, obesity (visceral adiposity in particular), has been incriminated in the development of insulin resistance and T2DM [9]. Increased flux of free fatty acid (FFA) into the circulation from the visceral adipose tissue is mainly responsible for insulin resistance [10]. Visceral obesity has also been associated with increased production of various adipocytokines, reduction of insulin sensitivity and an increased risk for development of diabetes as well as dyslipidemia [11]. Non-diabetic offspring of T2DM subjects have been found to have increased abdominal fat content and making them more prone for the development of various cardiometabolic diseases [12]. Ultrasound (USG) is a cost-effective and reliable method for the measurement of abdominal fat with a very good diagnostic accuracy compared with that of computerized tomography (CT) scan [13].

The risk of coronary heart disease (CHD) development is increased in their offspring of diabetic parents [14]. Differences in the body composition and metabolic and cardiovascular parameters may be responsible for this triggering effect. Carotid intima media thickness (cIMT) assessment is a well-studied tool and can be used as an indicator for future development of cardiovascular diseases like myocardial infarction and stroke [15]. Various studies have revealed a comparatively higher degree of subclinical inflammation and visceral adiposity in the offspring of T2DM subjects than that of nondiabetic parents [14, 16]. There is limited data available regarding the progression of glycemic status, inflammatory markers, and cIMT in first degree relatives of T2DM individuals in our population and hence the current prospective study was carried out.

Material and methods

Normal glucose tolerant (NGT) adults belonging to 20–40 years [family history positive (FHP)] were recruited at baseline. Age, sex, and body mass index (BMI) matched controls without any history of T2DM in their parents and relatives up to third generation were taken for comparison [family history negative (FHN)]. Individuals with history of hypertension, cardiac disease, stroke, smoking, dyslipidemia, renal disease, liver disease, thyroid illness, presence of any acute infection/illness, connective tissue disorder, chronic medication intake, polycystic ovary syndrome, pregnancy, and lactation were excluded from the study.

A total of 100 healthy individuals (aged 20–40 years) with a parental history of T2DM were enrolled. Similarly, around 100 healthy individuals without parental history were also enrolled to serve as control. All enrolled individuals underwent detailed screening tests as per inclusion and exclusion criteria for fulfilling eligibility for the study. NGT was detected as per the American Diabetic Association (ADA) guideline, i.e., fasting plasma glucose (FPG) < 100 mg/dl, 2-h post glucose plasma glucose (PGPG) < 140 mg/dl, and HbA1C < 5.6% [17]. Only euglycemic healthy adults were recruited at baseline (total = 106) which was based on sample size derived from earlier available literature. This group consisted of 64 in FHP group and 42 in FHN group. After baseline clinical, biochemical and radiological investigations, all subjects were asked to review at periodic intervals. At the end of the study (after 2 years), detailed clinical, biochemical, and imaging parameters were recorded for all available subjects of original cohort (46 in FHP group and 32 in FHN group) (Fig. 1).

All participants had undergone detailed clinical examinations to look for physical signs like acanthosis nigricans or skin tags. Body weight, height, waist circumference, hip circumference, and blood pressure were measured. Measurement of height and weight were done by using a standard apparatus. The point midway between the lowest rib margin and the iliac crest was taken for the measurement of waist circumference, whereas hip circumference was assessed along the widest portion of buttocks. BMI was calculated by using the formula as weight in kg divided by the height in m2. After resting for at least 5 min, measurement of blood pressure was done by using a mercury sphygmomanometer in supine position.

A standard 75 g oral glucose tolerance test (OGTT) with FPG, 2 h PGPG, and HbA1C testing were done in each subject after an overnight fast for at least 8 h.

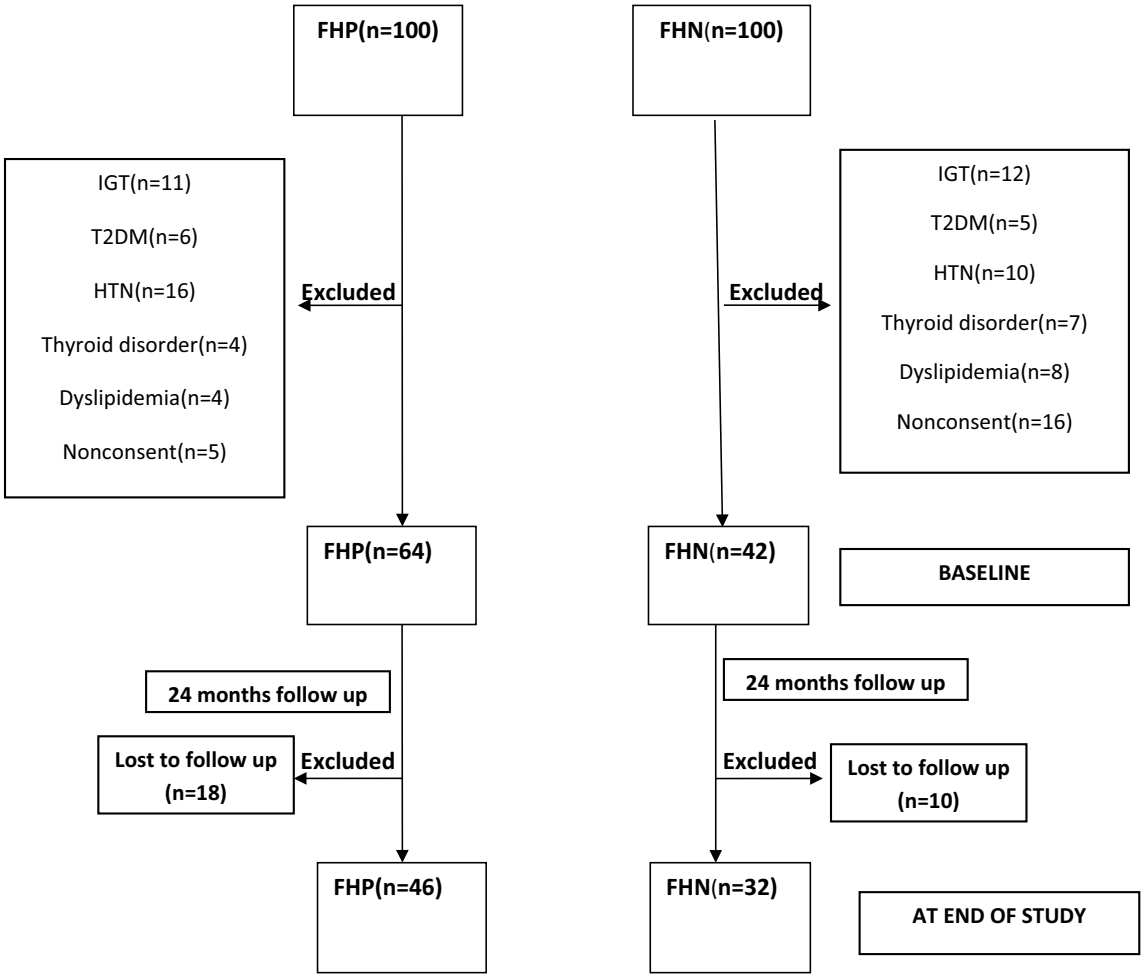

Fig. 1 Flow diagram depicting study design

Estimation of lipid profile [serum total cholesterol (TC), TG, LDL, HDL], fasting insulin and hsCRP were performed by taking the fasting blood sample in the morning. The plasma glucose was estimated with glucose oxidase-peroxidase method. Serum total cholesterol was measured by cholesterol esterase oxidase peroxidase method and TG by colormetric enzymatic method. HDL was estimated by direct enzymatic method. LDL was calculated by using Friedewald formula [18]. High-pressure liquid chromatography (HPLC) was used for HbA1C estimation. Serum insulin was estimated by chemiluminescent microparticle immunoassay (CMIA) method and nephelometry method was used for the measurement of serum hsCRP. For detection of insulin resistance, Homeostasis Model Assessment of Insulin Resistance (HOMA IR) was calculated by using the formula as [FPG (mg/dl) × fasting insulin (mU/L)]/405 [19].

Carotid intima media thickness (cIMT) was estimated by using high resolution B mode ultrasound with electrical linear transducer (5 to 9 MHz). Measurement was done in supine position at a point just proximal to the carotid bulb in the common carotid arteries with patient's head turned slightly to the contra lateral side. Mean value of the bilateral measurements was taken for reporting the cIMT. Measurement of subcutaneous tissue thickness denoted as SAT was done by taking the vertical distance from skin to the linea alba with a 9 L transducer (2.5 to 8.0 MHz). Similarly, visceral adipose tissue thickness denoted as VAT was estimated as the vertical distance from the peritoneum up to the front edge of the lumbar vertebra with a 5C transducer (1.5 to 4.5 MHz) [20]. Both SAT and VAT were measured three times and the average of the three readings was taken for reporting. The recording of the images was done by a single radiologist who was blinded regarding the group allocation.

At the end of the study, body weight, height, waist circumference, hip circumference, and blood pressure were measured in all available subjects in both groups. Glycemic status was evaluated in all subjects by doing a 75 g OGTT and HbA1C testing. Lipid profile, fasting insulin, hsCRP, cIMT, VAT, and SAT were also measured in each subject at the end of the study. Prediabetes and diabetes mellitus (DM) were detected by using ADA guideline (2015) criteria, i.e., prediabetes:FPG-

100–125 mg/dl (IFG) or 2 h PGPG-140–199 mg/dl (IGT) or HbA1C- 5.7–6.4% and DM: FPG ≥ 126 mg/dl or 2 h PGPG ≥ 200 mg/dl or HbA1C ≥ 6.5% or RPG ≥ 200 mg/dl with symptoms of diabetes [17].

Statistical analysis

Mean and standard deviation were used to summarize the continuous variables. Categorical data were reported as percentages or proportions. Normality distribution was assessed by using Shapiro-Wilk test. Nonparametric tests (Mann-Whitney *U* test) and parametric tests (independent *t* test) were performed for comparison between the variables. Data analysis was done by IBM SPSS 21 statistical software (IBM Corp., Armonk, NY, USA).

Results

At baseline, total number of individuals recruited in FHP group and FHN group were 64 and 42 respectively. FHP group had a mean age of 28.31 ± 4.91 years as that of 28 ± 4.23 years in FHN group ($p = 0.538$). There was no significant difference with regards to physical activity, BMI, blood pressure, and WHR between the two groups. However, mean total cholesterol and LDL levels were significantly higher in the FHP group than that of FHN group ($p < 0.01$ for both). No significant difference was observed with regards to glycemic parameters like FPG, 2 h PPG, and HbA1C between the two groups at baseline (*p*-non significant). We also did not find any significant difference in insulin resistance markers (fasting insulin and HOMA IR) and adiposity indices (SAT, VAT) ($p > 0.05$ for each parameter) between the two groups. However, individuals in the FHP group had significantly elevated hsCRP ($p = 0.039$) and cIMT ($p = 0.003$) than that of FHN group at baseline.

To look for progression of various metabolic parameters, inflammatory markers, insulin resistance, and intima media thickness in both FHP and FHN individuals, reassessment of these individuals was done (after 2 years). Ten subjects in FHN group and 18 subjects in FHP group were lost to follow-up during this period. Hence, comparison was made between 32 subjects and 46 subjects in FHN group and FHP group respectively (Fig. 1). Four subjects (8.7%) in FHP group and two subjects (6.25%) in FHN group transitioned into IFG from NGT based on FPG criteria respectively ($p = 1.000$). Similarly based on 2 h PGPG criteria, four subjects (8.7%) in FHP group and two subjects (6.25%) in FHN group transitioned into IGT from NGT ($p = 1.000$). During the same period, 11 subjects (23.91%) in FHP group and six subjects (18.75%) in FHN group became pre-diabetic based on HbA1C recommended criteria ($p = 0.78$) (Fig. 2). Hence, it was observed that numerically higher number of individuals met the criteria of pre diabetes from FHP group versus FHN group but statistical significance was not achieved. Similarly, we noted that there was no significant difference in the change (Δ) in BMI, WHR, and blood pressure (SBP, DBP) from baseline to the end of the study among the two groups. The two groups did not differ significantly in terms of change in glycemic status (FPG, 2 h PGPG, and HbA1C) and lipid parameters (TG, LDL, and HDL) from base line (Table 1). Also, HOMA-IR did not change significantly from baseline in FHP group (1.25 ± 3.46 vs. 0.32 ± 0.61, $p = 0.056$). We also noted that hsCRP was not significantly changed from baseline in both groups at the end of the study (*p*-non significant for change). No significant change in adiposity markers like SAT (0.08 ± 0.19 vs. 0.04 ± 0.12 cm, $p = 0.159$) and VAT (0.33 ± 0.42 vs. 0.22 ± 0.22 cm, $p = 0.213$) from baseline was observed in FHP group in comparison to FHN group. However, cIMT was increased significantly from baseline in FHP group in comparison to FHN group at the end of the study (0.02 ± 0.03 vs. 0.01 ± 0.02 mm, $p = 0.002$) (Table 1).

Discussion

We have previously reported certain noteworthy differences in our population with regards to inflammation, markers of insulin resistance, adiposity indices, and cIMT between non diabetic offspring of T2DM patients and age, sex, and BMI matched controls without having history of T2DM in their parents [21]. We found that cIMT was significantly higher in the offspring of T2DM patient [21]. This finding has been also reported by earlier studies suggesting that possibly genetic predisposition may accelerate the development of atherosclerosis [22–25].

Similarly, we found that the first degree relatives of T2DM patients had significantly higher hsCRP levels than controls in our population [21]. This finding of chronic low-grade inflammation in normoglycemic subjects with parental history of T2DM has been observed in other studies including one from Indian subcontinent [22, 24]. It may be plausible that this chronic low-grade inflammation might accentuate atherosclerosis risk in T2DM patients' offspring. Certain important perturbations in lipid metabolism have been reported among normoglycemic offspring of parents with T2DM which include elevated TG and increased total cholesterol and LDL with decreased HDL levels [21].

Importantly and interestingly, we did not observe any significant difference with regard to glycemic status, insulin resistance or blood pressure between the first degree relatives of T2DM subjects and controls at baseline [21]. Similar to our study, few authors also did not find any significant difference in glycemic parameters, degree of insulin resistance (HOMA IR), or blood pressure in the offspring of T2DM subjects than those without having diabetic history in their parents [10, 22,

Table 1 Comparison of anthropometric, biochemical, hormonal, and radiological parameters in FHP and FHN groups at the end of the study

Parameters	Change from baseline (Δ)		*p* value for change (Δ)
	FHN group (*n* = 32)	FHP group (*n* = 46)	
BMI (kg/m^2)	0.76 ± 0.99	0.71 ± 1.08	0.764
WHR	0.03 ± 0.06	0.03 ± 0.05	0.545
SBP (mmHg)	1.56 ± 4.94	3.52 ± 5.35	0.135
DBP (mmHg)	1.63 ± 3.95	1.26 ± 3.51	0.652
FPG (mg/dL)	5.03 ± 4.98	7.93 ± 8.02	0.073
2hrPGPG (mg/dL)	9.94 ± 22.43	7.09 ± 20.33	0.633
HbA1C (mmol/mol)	2.51 ± 1.79	2.62 ± 3.14	0.859
TC (mg/dl)	10.31 ± 6.1	9.36 ± 16.23	0.160
TG (mg/dl)	10.88 ± 13.09	8.98 ± 15.6	0.089
LDL (mg/dl)	9.47 ± 7.59	8.48 ± 14.74	0.163
HDL (mg/dl)	-0.34 ± 4.01	-0.7 ± 3.35	0.866
hsCRP (mg/L)	0.66 ± 0.8	0.61 ± 1.36	0.388
Fasting insulin (mIU/L)	0.88 ± 2.69	4.43 ± 13.9	0.111
HOMA IR	0.32 ± 0.61	1.25 ± 3.46	0.056
SAT (cm)	0.04 ± 0.12	0.08 ± 0.19	0.159
VAT (cm)	0.22 ± 0.22	0.33 ± 0.42	0.213
cIMT (mm)	0.01 ± 0.02	0.02 ± 0.03	**0.002**

Data are expressed as mean ± S.D, $p < 0.05$- significant

BMI body mass index, *WHR* waist hip ratio, *SBP* systolic blood pressure, *DBP* diastolic blood pressure, *FPG* fasting plasma glucose, *PGPG* post glucose plasma glucose, *TC* total cholesterol, *TG* triglyceride, *LDL* low-density lipoprotein, *HDL* high-density lipoprotein, *hsCRP* high sensitive C-reactive protein, *HOMA IR* homeostasis model assessment for insulin resistance, *VAT* visceral adipose tissue thickness, *SAT* subcutaneous adipose tissue thickness, *cIMT* carotid intima media thickness

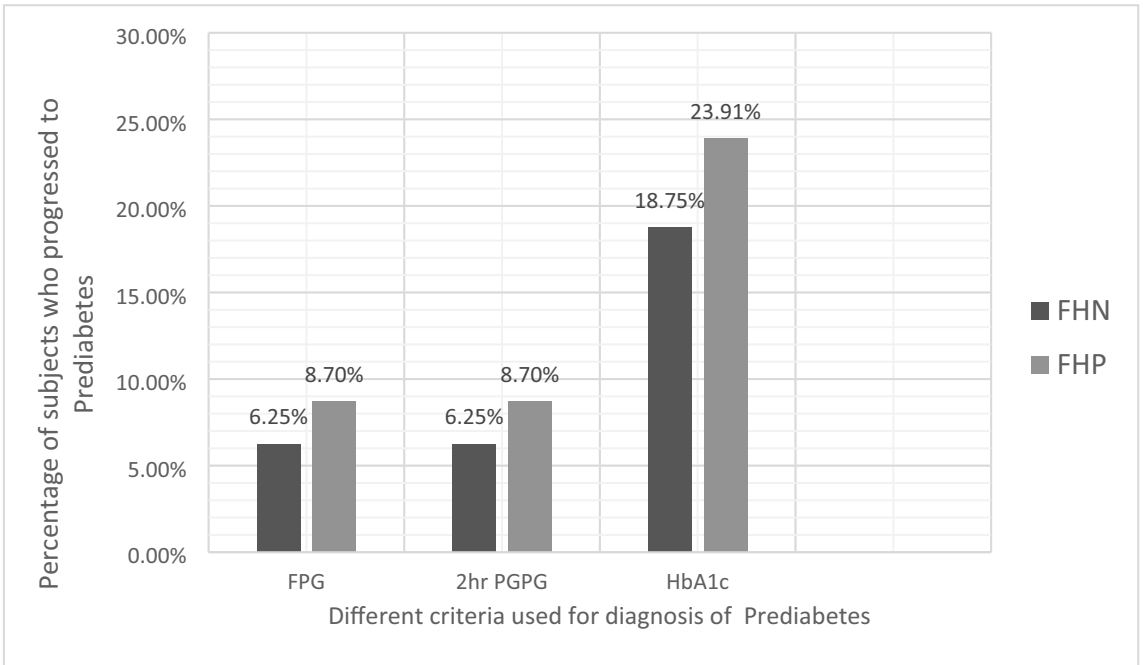

Fig. 2 Progression to prediabetes in FHP and FHN groups at the end of the study. *FPG* fasting plasma glucose, *PGPG* post glucose plasma glucose

23]. However, Ustun et al. reported significantly higher fasting blood glucose, blood pressure, serum insulin, and HOMA IR levels in the offspring of T2DM patients [24].

To look for progression of various metabolic indices including glycemic parameters, insulin resistance, and intima media thickness in both FHP and FHN individuals, we evaluated all available subjects from the original cohort at the end of the study. However, after a follow-up of 2 years, there was no significant difference for change (Δ) in glycemic status (FPG, 2hrPGPG & HbA1C) and insulin resistance marker (fasting insulin, HOMA IR) between the two groups at the end of the study. Moreover, no significant difference in the rate of conversion of NGT to IGT, IFG, or T2DM between FHP and FHN individuals was noted. In the Chennai Urban Rural Epidemiology Study(CURES) after a follow-up period of 10 years, conversion rate of NGT to prediabetes and diabetes was 25.7% and 19.4% respectively [4]. In our study, we evaluated the individuals after 2 years which is much shorter duration to look for the conversion of NGT to IGT or DM than the previous Indian study [4]. Similarly, an Iranian study carried out in the offspring of T2DM subjects reported the progression rate from NGT to IFG, IGT and diabetes were 8.6%, 3.7%, and 0.5% per year after a follow-up period of 27.6 months, respectively [26].

Our previous findings suggested no significant differences in adiposity indices among FHP and FHN subjects. FHP subjects had similar levels of SAT as well as VAT in comparison to that of FHN individuals [21]. In agreement to our findings, Kriketos et al. also did not find any significant difference in subcutaneous as well as visceral adipose tissue depots in the first degree relatives with history of T2DM in their parents [10]. Apart from genetic factors, central adiposity may play a role in the development of insulin resistance. In this study (after completion of follow-up period), no significant difference in the change from baseline for adiposity markers (SAT/VAT) between the two groups was found.

As previously discussed, we reported significantly higher cIMT and hsCRP among FHP subjects than FHN subjects in our cohort at baseline. Hence, it was worthwhile to explore whether any difference in progression of cIMT would be observed between these two groups. Surprisingly, we found that cIMT was increased significantly from baseline in FHP group in comparison to FHN group even in a relatively short span of 2 years. In the IMPROVE study, Baldassarre et al. found significant progression of cIMT in subjects with three or more vascular risk factors to the tune of 0.005 mm/year during the first 15 months of follow-up [27]. In the PROG-IMT Collaboration study, it was found that the average annual mean cIMT progression was 0.009 mm/year in T2DM patients, whereas the progression was 0.010 mm/year in the non-diabetic individuals [28]. No significant difference for hsCRP change (Δ) was observed at the end of the study between the two groups.

The limitations of the study include a relatively small sample size limiting the generalizability of our results. Only hsCRP was assessed as surrogate inflammatory marker. We used USG for the measurement of adiposity indices instead of CT or MRI. We have preferred USG because it is inexpensive and non-ionizing and adiposity indices measurement can be done in the same sitting along with the cIMT assessment. However, study of hepatic steatosis/fibrosis was not done. The study follow-up period is short, i.e., 2 years, which may be insufficient to look for the progression of NGT to either IGT or DM. Lastly, many confounding factors like diet pattern, recruitment based on parental diabetic history, and physical activity level have not been adequately studied during follow-up. However, despite these limitations, we have reported data of these two matched groups in a prospective fashion which would be definitely helpful in understanding influence of family history of T2DM on progression of various metabolic parameters in our population.

In conclusion, our study reports that T2DM subject's offsprings have significantly elevated hsCRP levels and increased cIMT than those without diabetic history in their parents at baseline. There were no significant differences with regards to change of glycemic parameters or rates of conversion from NGT to pre diabetes among the two groups. In contrast to above finding, cIMT increased significantly in the normoglycemic offspring of T2DM subjects than those without history of T2DM in their parents. Hence, perhaps mere presence of family history of T2DM in normoglycemic individuals may result in important metabolic perturbations and differential progression of atherosclerotic process in this vulnerable population. These findings may have significant bearing on their future cardiovascular health status.

Declarations

Ethics approval and consent to participate Written informed consent was obtained from the study participants and institutional ethical committee clearance was taken.

Conflicting interest Nil.

Financial disclosure All authors have no financial relationship related to this article to disclose.

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