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A STUDY OF DYSLIPEDEMIA IN PREDIABETES

Cardiology

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KEYWORDS

INTRODUCTION :

Prediabetic state is the intermediate phase between the normoglycemic state and frank diabetes. It may be impaired fasting glucose (IFG) or impaired glucose tolerance (IGT) either singly or in combinations depending on the type of blood test used to diagnose the aforementioned condition. [1,2] .Prevalence of IGT varies as low as 6.3% in a Chinese population to as high as 20.3% in a Swedish population.[3]. In India prevalence of IFG and IGT are 3.6 % and 5.2 % respectively with significant difference in urban and rural population.[4]. *In general, epidemiological studies indicate that approximately 25% of subjects with IFG or IGT progress to type 2 diabetes in 5 years, whereas about 50% remain prediabetics and 25% revert back to normal*. [5] . Rate of progression to type 2 diabetes may be higher, averaging 10-12% per year and the risk of eventually developing type 2 diabetes may be as high as 70% in persons with IFG or IGT.[6,7,8] . The combination of IFG and IGT confers a greater risk of diabetes than either category alone. Overall, prediabetes confers about a six fold increased risk of diabetes compared with normal glucose tolerance.

Premature and accelerated atherosclerosis often starts before the diagnosis of type 2 diabetes mellitus and coronary artery disease is increased two to three fold and is responsible for more than 75% of cardiovascular death in T2DM patients[9,10,11]. The macrovascular disease in T2DM though depend on multiple factors but dyslipidemia is most important factor and coronary artery disease occurs rarely in its absence. Dyslipidemia is present in many cases of T2DM at onset and also in the stage of prediabetes or simple metabolic syndrome[12,13]. In T2DM and metabolic syndrome, the pattern of dyslipidemia is atherogenic dyslipidemia which is characterized by high TG, low HDL, high small dense LDL.

Individual with IFG and IGT are usually associated with obesity (especially abdominal), dyslipidemia with high TG and low HDL and hypertension. [14,15] The presence of dyslipidemia in diabetes is very well studied and since macrovascular disease in diabetes precedes the diagnosis of diabetes, it is likely that prediabetics are also at increased risk of the same. So far very few studies have examined the presence of dyslipidemia in individuals with IFG and/or IGT and our study is an attempt to do the same. Presence of dyslipidemia in diabetes is well studied but the occurrence of dyslipidemia in prediabetes is not well studied till now. The study aims were if we can detect dyslipidemia early in the sequence of IFG→IGT→ Diabetes, then specific intervention may be instituted to check the progression of coronary atherosclerosis.

AIMS AND OBJECTIVES :

The primary objective of the study was to determine the actual prevalence of dyslipidemia in prediabetes. For this purpose, we tried to investigate the pattern of dyslipidemia in prediabetes , whether dyslipidemia is more prevalent in IFG or IGT or both , the variation of lipid changes in IFG and IGT and to evaluate the cardiovascular risk in prediabetes as assessed by serum lipid levels.

MATERIALS AND METHODS

Subjects with pre-diabetes in the age-group 18-60 years were selected from those attending the medicine OPD and from those admitted in medicine ward or attending the Cardio-Diabetes clinic at the R G KAR Medical college and Hospital, Kolkata. 75 prediabetic patients were compared with 75 properly age and sex matched normal control (NFG/NGT) . The prediabetic patients were divided into 3 groups of 25 each- .the first group consisted of patients with IFG, the second IGT and the third consisting of patients with both IFG and IGT. Acutely ill patients such as overt cardiac, renal, respiratory failure or recent stroke, alcoholic subjects, smokers, pregnant females, patients of Cushing's Syndrome and Acromegaly, Lipodystrophy Syndromes, Glycogen Storage disorders, Hypothyroidism, Nephrotic syndrome, Obstructive jaundice were excluded from the study.

After exclusion of other causes of dyslipidemia, fasting serum lipid profile that includes Total Cholesterol, LDL, HDL, VLDL, TG and HDL (after 12 hrs fasting), fasting blood sugar after 8 to 10 hrs overnight fast were analysed by the XL-600 (ERBA autoanalyser) by standard methods in the Biochemistry department in R.G.Kar Medical College. The OGTT was also performed on these patients. The data thus compiled was analysed statistically by the Standard Statistical Software (SPSS) version 16.

NGT is defined as fasting plasma glucose level less than 100 mg/dl and 2 hour plasma glucose less than 140 mg/dl in oral glucose tolerance test by giving 75 gm of anhydrous glucose load. Fasting plasma glucose in the range of **100 – 125 mg/dl** (5.6-6.9 mmol/l) is classified as **IFG or impaired fasting glucose and** 2-h plasma glucose in the 75-g OGTT **140 – 199 mg/dl** (7.8 – 11.0 mmol/l) is classified as **IGT.**

RESULT AND ANALYSIS :

The results obtained after statistical analysis are given below.

TABLE 1: table showing mean age and BMI of the subjects.

	GROUP			
	TEST/ PREDIABETES	CONTROL	p VALUE	Significance
AGE	41.69 ± 12.28	38.47 ± 11.8	0.103	Not Significant
BMI	24.93 ± 3.19	24.28 ± 2.77	0.183	Not Significant

Sex distribution between prediabetes and control group were also evenly poised. There were 38.7 % and 42.7% female in test and control group respectively. Similarly, percentages of male subjects were 61.3 % and 57.3 % in test and control respectively.

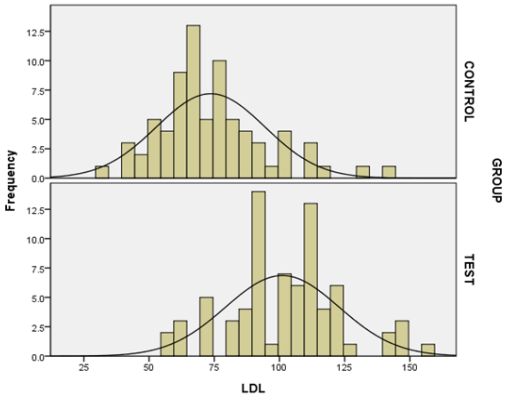
TABLE 2: table showing Distribution of fasting blood sugar and OGTT between prediabetes and control group

	GROUP			
	TEST/ PREDIABETES	CONTROL	p VALUE	Significance
FBS	105.08 ± 11.04	81.21 ± 11.61	<0.001	**Significant**
OGTT	148.44 ± 13.25	117.67 ± 11.22	<0.001	**Significant**

TABLE 3: table showing the mean values of the parameters of lipid profile among cases and controls.

	GROUP			
	TEST/PREDIABETES	CONTROL	p VALUE	Significance
Total Cholesterol	185.67 ± 31.36	136.99 ± 28.11	<0.001	**Significant**
LDL	101.09 ± 21.8	73.63 ± 20.81	<0.001	**Significant**
HDL	42.85 ± 9.4	43.35 ± 8.69	0.739	Not Significant
Triglyceride	206.39 ± 86.29	100.59 ± 45.86	<0.001	**Significant**
VLDL	40.49 ± 17.85	20.25 ± 9.53	<0.001	**Significant**
NHDL	142.81 ± 32.83	92.69 ± 25.84	<0.001	**Significant**

LDL Distribution in Control and Test (Study) Groups



72% prediabetes subjects were dyslipidemic as compared to 25.3 % dyslipidemic normal controls and p value was highly significant (< 0.001).

TABLE 4: Table showing mean values of age and BMI among the 3 groups of pre-diabetics.

	IFG	IGT	IFG_IGT	p VALUE	Significance
AGE	40.2 ± 12.75	40.2 ± 12.42	44.68 ± 11.58	0.334	Not Significant
BMI	25.26 ± 3.1	23.95 ± 3.08	25.58 ± 3.27	0.159	Not Significant

TABLE 5: table showing the comparision of Fasting sugar and OGTT among the 3 groups using ANOVA.

	IFG	IGT	IFG_IGT	p VALUE	Significance
FBS	111.08 ± 8.05	92.88 ± 5.04	111.28 ± 7.31	<0.001	**Significant**
OGTT	133.68 ± 5.65	156.2 ± 8.3	155.44 ± 9.98	<0.001	**Significant**

TABLE 6: Table showing Lipid Profile abnormalities among IFG, IGT & IFG and IGT :

	IFG	IGT	IFG_IGT	p VALUE	Significance
Total Cholesterol	161.56 ± 24.68	197.4 ± 19.61	198.04 ± 33.61	<0.001	**Significant**
LDL	85.6 ± 17.4	109.8 ± 16.76	107.88 ± 22.48	<0.001	**Significant**
HDL	46.24 ± 9.32	41.28 ± 9.3	41.04 ± 9	0.086	*Not Significant*
Triglyceride	148.72 ± 63.13	228 ± 72.76	242.44 ± 91.49	<0.001	**Significant**
VLDL	28 ± 10.87	44.44 ± 16	49.04 ± 18.8	<0.001	**Significant**
NHDL	115.32 ± 23.23	156.12 ± 19.09	157 ± 35.17	<0.001	**Significant**

Analysis of dyslipidemia showed that 96% of IGT subjects were dyslipidemic whereas 36 % and 84 % subjects were dyslipidemic in the IFG and IFG_IGT groups respectively and P value was signifcant (< 0.001)

Only 12% of IFG_IGT group were found to have high Total Cholesterol as compared to 4% in IGT group. 88% of IFG subjects had total cholesterol in the desirable range. and p value was significant (0.006).

Optimal LDL was observed in 80%, 20% and 28 % of subjects with IFG, IGT and IFG & IGT group respectively. 12% of both IGT and IFG & IGT showed high LDL. p value is significant.Low HDL was found in 12%, 48% and 52% of IFG, IGT and IFG & IGT respectively.and they were significantly different from each other. Analysis of TG level showed that 68 % of both IGT and IFG & IGT groups were having high TG as compared to 20% of IFG subjects.and it was statistically significant.

DISCUSSION :

The result from present study provides conclusive evidence that all the three groups viz. IFG, IGT & both IFG and IGT are associated with elevated cardiovascular risk as assessed by serum lipid levels. When the prediabetes group and normal control population were compared, it is seen that mean value of total cholesterol, LDL, HDL, TG are 185.6, 101, 42.8 and 206.4 respectively in the prediabetes group. Analysis has shown that every parameter mentioned above are significantly different from normal control except for HDL. This is probably due to a smaller sample size. 5.3% prediabetic population in our study group has high total cholesterol (> 240 mg/ dl) as per NCEP ATP III category. 8% prediabetics in our study have their LDL in the high range (160 – 189 mg/ dl). Though 37.3% prediabetics are found to have low HDL (< 40 mg/dl) as compared to 22.7% of normal control, the values are not statistically significant. 52% of prediabetic population in our study have high TG level (200 – 499 mg/dl). This result is consistent with atherogenic dyslipidemia of low HDL, high TG, and small dense LDL. Here, we could not measure the density of LDL. **As a whole, 72% of prediabetic population in our study is dyslipidemic as compared to 25.3% of normal control subjects and the difference is significant (p value < 0.001)**

The IFG group *shows significant change in lipid parameter in all respects in comparison to normal control population*. Mean value of total cholesterol, LDL, HDL and TG are 161.6 mg/dl, 85.6 mg/dl, 46.2mg/dl and 146.7mg/dl respectively. The value of the total cholesterol falls in the desirable range (< 200 mg/dl) of NCEP ATP III category. The value of LDL also falls in the optimal range (< 100 mg/dl). The value of TG is in the borderline high range (150 – 199 mg/dl). *12% of IFG group has borderline high total cholesterol (200- 239 mg/dl). 20% of IFG population has near optimal LDL (100 -129 mg/dl) and high TG (200-499 mg/dl). 12% of IFG population in our study has low HDL (< 40 mg/dl).* **The reason behind this observation is that insulin resistance usually predates frank diabetes by years**. **Overall, 36% of IFG population in our study is dyslipidemic which is quite high**.

The published data on this issue is quite discrepant and ranges from lack of difference in the lipid profile between IFG and NGT to similar changes to those in diabetes [16,17]. The result of our study is in corroboration with the study done by D.M. Nathan et al where they had opined that only IGT was found to be associated with increased cardiovascular risk. [23]

The IGT group also shows significant changes in the lipid parameters in comparison with NGT. Significantly higher levels of triglyceride and lower level of HDL are found in IGT as compared to NGT. Mean value of total cholesterol, LDL, HDL, TG are 197.4mg/dl, 109.8mg/dl, 41.28mg/dl and 228mg/dl respectively. The value of total cholesterol falls in the desirable range of NCEP category. But the value of LDL falls in the near optimal range (100 – 129 mg/dl). The LDL cholesterol in insulin resistance is small and dense which is not shown here. The TG is within high range.(200-499 mg/dl). *4% of IGT group is found to have high cholesterol (> 240 mg /dl). 12% of IGT population also has high LDL (160 – 189 mg /dl). 48% of IGT population is having low HDL (< 40 mg/dl) which is expected in atherogenic dyslipidemia. 68% of the IGT population also has high TG (200 - 499 mg/dl).***Overall, 96% of IGT population in our study is dyslipidemic.** This is in accordance with the results from other studies which are much more alike and have found decreased HDL-c and increased triglycerides and total cholesterol to HDL-c ratio to be the main differences between IGT and NGT [18,19,20].

In the combined IFG & IGT group, the result is also like the IGT group. Mean value of total cholesterol, LDL, HDL and TG are

198mg/dl, 107.8mg/dl, 41.04mg/dl and 242.44mg/dl respectively. Like IGT, mean values of total cholesterol and LDL fall in desirable and near optimal range respectively. TG is in high range as in IGT. *12% of combined IFG & IGT group has high total cholesterol (> 240 mg/dl) and high LDL (160 – 189 mg/dl). 52% and 68% of the combined IFG & IGT group has low HDL (< 40 mg/dl) and high TG (200 – 499 mg/dl) respectively*. **Overall, 84 % of the combined IFG & IGT population in our study is dyslipidemic**.

When IFG, IGT and combined IFG & IGT are compared among each other, it is seen that the major alterations are found in the latter two groups. Total cholesterol, LDL and TG are significantly different across the three groups while HDL has no significant difference. This may be due to the smaller sample size. *However, when low HDl category is analysed across the three study groups, it is found that the values are significantly different from each other with p value < 0.006. The mean values of total cholesterol and TG progressively increase from IFG → IGT → Combined IFG & IGT. The mean value of HDL progressively declines from IFG → IGT → Combined IFG & IGT, with lowest mean shown in combined IFG & IGT group (41.04) which is very close to the upper limit of cutoff value for low HDL (< 40 mg/dl) as per NCEP ATP III guidelines. The different lipid profiles of NGT, IFG, IGT and combined IFG & IGT cannot be explained by a difference in body weight as the four groups appeared to be quite well BMI-matched.*

So, it is concluded that atherogenic risk profile in prediabetes definitely increases from IFG → IGT → Combined IFG & IGT, with lowest risk in IFG and probably the highest risk in combined IFG & IGT.

The results from our study are also in support of the concept for different cardiovascular risk in IFG and IGT. This conclusion can be made on the basis of the direct comparison of the two prediabetic states to each other. The number of studies comparing the lipid profile in IFG and IGT is relatively small. The reported data is controversial–some of the studies have found no significant difference in the cardiovascular risk between IFG and IGT as assessed by serum lipid levels [21,22,23], while others have pointed out just increased triglyceride levels in IGT as the main significant difference between IFG and IGT [24,25].

Our study has shown that atherogenecity or increased cardiovascular risk is progressively increasing from IFG → IGT → Combined IFG & IGT. In our study population, no significant difference is found in mean HDL value in between the groups, whereas all other lipid parameters are significantly different amongst each other. The probable reason for this difference may be due to ethnic variation and smaller sample size of our population.

Some unique features of our study are noteworthy. The prediabetes group and control population are compared and subgroup analysis of the same comparison was done as per NCEP ATP III standard guidelines. This is probably the first study of its kind. The prediabetes population has been subclassified into three groups viz. IFG, IGT and Combined IFG & IGT and compared among each other to show different patterns of dyslipidemia prevalent in them. The dyslipidemia has also been analysed with standard NCEP ATP III guidelines and extrapolated in the three study groups. Though our study has small sample size, still it clearly depicts the trend of lipid profile changes in prediabetes.

Our results are also in support of the concept that IFG and IGT are two phenotypically different categories of prediabetes with different underlying pathophysiological mechanisms resulting in different cardiovascular risk and risk for future progression to diabetes.

***Several limitations of our study** are smaller sample size, nonmeasurement of LDL particle size, hsCRP and free fatty acids.*

In future projection from our study, it can be suggested that serum lipid profile must be included in the evaluation of prediabetes population. The pattern of dyslipidemia is to be noted and carefully followed up in long term and appropriate measures should be taken as per national guidelines or standard lipid goals.

CONCLUSION :

The present study indicates that the cardiovascular risk increases from prediabetic state as assessed by serum lipid levels. The risk appears not to be same in different classes of prediabetes ; IGT and combined IFG & IGT are being characterized by higher risk as compared to IFG. The risk assessment would have been more ideal if the lipid profile was also measured in newly diagnosed diabetes. The reason behind this observation cannot be commented from our study, probably more research will be needed in this aspect. But, it can be said that IFG and IGT are two different phenotypic manifestations of insulin resistance at different sites. IFG is characterized by hepatic insulin resistance predominantly and IGT shows insulin resistance at peripheral tissues viz. muscle and adipose tissue.

Risk of macrovascular disease predates the diagnosis of T2 DM by years and it is worth mentioning that cardiovascular risk assessment should be started early in the course of prediabetes.

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