Lipid Abnormalities in the Natural History of Diabetes
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Abstract:
Objective: To explore lipid abnormalities in normoglycemic first-degree diabetic relatives (FDRs) and prediabetic and diabetic subjects in the natural history of diabetes.

Research design and methods: Thirty six impaired fasting glucose (IFG), 61 isolated impaired glucose tolerance (I-IGT), 64 combined IFG-IGT, 73 diabetic, and 32 FDRs along with 57 normoglycemic healthy controls without family history of diabetes in 1st degree relatives, were selected purposively following 2003 ADA cut-off values and 2006 WHO/IDF grouping. Anthropometry and blood pressure of the subjects were taken. Fasting and 2-h plasma glucose and HbA1c were measured. Fasting plasma triglyceride, total cholesterol and HDL cholesterol were measured by enzymatic colorimetric method.

Results: Serum triglyceride was higher in IFG, I-IGT, IFG-IGT, diabetic and FDRs compared to Control [145 (59-307), 128 (66-584), 166 (68-764), 161 (69-750) and 130 (81-281) vs. 108 (47-219) mg/dl, P<0.01, P<0.01, P<0.001, P<0.001 and P<0.05]. Total cholesterol was raised in IFG-IGT and diabetes compared to Control [185 (105-310), 185 (123-326) vs. 171 (101-235) mg/dl, P<0.05] and FDRs. But HDL did not differ among the groups. Prevalence of metabolic syndrome was higher in IFG, I-IGT, IFG-IGT and diabetes and FDRs than Control [55%, 38%, 57%, 58% and 36% vs. 15%, P<0.001, P<0.01, P<0.001, P<0.001 and P<0.05] and also in IFG-IGT and diabetic compared to I-IGT and FDRs (P<0.05).

Conclusions: Higher prevalence of metabolic syndrome and raised serum triglyceride is seen among diabetic, prediabetic and 1st degree diabetic-relatives. Total cholesterol and non-HDL cholesterol is raised only in IFG-IGT and diabetes, the more decompensated glycemic states.

Key words: IFG, IGT, combined IFG-IGT, normoglycemic first-degree diabetic relatives, serum triglyceride, metabolic syndrome.

Introduction
Individuals in the natural history of type 2 diabetes pass through different stages.1 The first stage begins at birth, when glucose homeostasis is normal but individuals are at risk for developing diabetes because of inherited non-specific diabetogenic genes or a compromised intrauterine environment predisposing them to limit the ability of their pancreatic b cells to compensate for insulin resistance. In the next stage, insulin resistance emerge, probably due to interaction of environmental factors with genetic factors, which are initially compensated for by an increase in b-cell function, so that glycemic profile is normal even with glucose challange. The next stage is prediabetic stage, collectively termed as ‘prediabetes’ or ‘categories of increased risk for diabetes’ by ADA Expert Committee2,3 and ‘Intermediate

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Hyperglycemia’ by WHO/IDF Technical Advisory Group.4 In this stage b-cell function and insulin sensitivity both deteriorate, so both challenged (with glucose or meal) and basal blood glucose is raised above the normal range but below the diagnostic cut point for diabetes. When fasting plasma glucose (FPG) is raised it is termed as ‘impaired fasting glucose’ (IFG), and when 2-h plasma glucose (2-h PG) value in the oral glucose tolerance test is raised it is termed as ‘isolated impaired glucose tolerance’ (I-IGT). When both fasting and 2-h value is raised it is termed as combined IFG-IGT. Ultimately, as a result of further deterioration in b-cell function, subjects enter into diabetic stage when fasting and/or postprandial glucose levels reach diabetic range.

Diabetes mellitus is associated with multiple abnormalities in lipid metabolism but the underlying mechanisms are complex. Type 2 diabetic subjects show mild hypertriglycerideremia accompanied by reduced HDL cholesterol.5-7 LDL cholesterol is normal or only slightly raised, but total cholesterol is similar to general population.5,6 Diabetic hypertriglycerideremia results from excessive production of VLDLs by the liver, as well as reduced clearence of TG-rich lipoproteins due to decreased activity
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16 and low HDL in IFG and IGT.13-15 Probably insulin resistance and/or secretion defect in these subjects have role for this dyslipidemia. There are also genetic factors and ethnic influence on lipid abnormalities. The present study was undertaken to explore lipid abnormalities in Bangladeshi prediabetic and diabetic subjects and FDRs.

Research design and methods
All newly detected prediabetic and diabetic subjects alone with FDRs were selected from the out-patient department of BIRDEM (the tertiary hospital of Bangladesh Diabetic Somity) every 3rd working days during the period of January to June, 2005. Following the cut-off values of 2003 ADA Follow-up Report2 and grouping of 2006 WHO/IDF Consultation Report,4 36 IFG (FPG 5.6 – 6.9 mmol/l and 2-h PG <7.8 mmol/l), 61 I-IGT (FPG <5.6 mmol/l and 2-h PG 7.8 – 11.0 mmol/l), 64 IFG-IGT (FPG 5.6 –6.9 mmol/l and 2-h PG 7.8 – 11.0 mmol/l), 73 diabetic subjects (FPG >6.9 mmol/l and 2-h PG >11.0 mmol/l), and 32 FDRs along with 57 normoglycemic healthy controls with no family history of diabetes in first degree relatives (FPG < 5.6 mmol/l and 2-h PG <7.8 mmol/l), were selected. Patients with serious comorbid diseases or using drugs significantly affecting glucose metabolism (like glucocorticoids, oral contraceptives containing levonorgestrel or high-dose estrogen, phenytoin, high-dose thiazide diuretics etc.) or lipid metabolism (like lipid lowering drugs, beta blockers, diuretics, hormones etc.) or history of gestational diabetes mellitus and pregnant women were excluded. The purpose of the study was explained in details to each subject and informed written consent was taken. The study protocol was approved by the Ethical Committee of the Association.

Anthropometric Measurements
Height, weight, waist circumference (WC), neck circumference (NC) and blood pressure were measured using standard procedure. Then BMI of the subjects were calculated as weight/height² (kg/m²). Subjects with higher diastolic and/or systolic blood pressure or under treatment with hypotensive drugs were considered hypertensive. Body fat mass was measured by Omron Body Fat Monitor.

Oral glucose tolerance test
After at least 3 days of unrestricted carbohydrate diet, avoiding strenuous exercise and fasting for 8-14 hours, the subjects underwent 75-g 2-h OGTT following WHO Guidelines.17 Blood was collected at fasting between 8.00-9.00 AM and then 2-h after 75-g glucose load.

Laboratory data, analytical procedure and calculations
Fasting and 2-h plasma glucose was measured by Glucose Oxidase method (Randox Laboratories Ltd., Co. Antrim, UK) and HbA1c by VARIANT Hemoglobin A1c Program (Bio-Rad Laboratories, CA, USA) on the same day. Fasting plasma TG, TC and HDL cholesterol were measured by enzymatic colorimetric method (Randox Laboratories Ltd., UK).

Non-HDL cholesterol (=TC-HDL cholesterol), ratio of total cholesterol to HDL cholesterol (TC/HDL) and ratio of TG to HDL cholesterol (TG/HDL), markers of cardiovascular risk, were determined. Metabolic Syndrome (MetS), a cluster of risk factors for coronary artery disease, was defined using the IDF Consensus Worldwide definition of metabolic syndrome in 2006.18 The prevalence of MetS and its components were evaluated.

Statistical analysis
Statistical analysis was performed using SPSS software for Windows version 11.0 (SPSS Inc., Chicago, IL, USA). Sex, high WC, arterial blood pressure and TG, low HDL and MetS distribution were expressed as percent and compared in different groups by Chi Squared (χ²) test. Age, BMI, NC and BFM were expressed as mean±SD and the statistical difference between the groups were assessed by One-Way ANOVA with Post-Hoc Benferroni. WC, fasting and 2h plasma glucose, HbA1c, TG, TC, HDL, non-HDL cholesterol, TC/HDL and TG/HDL were not normally distributed and were expressed as median (range) and analysis for statistical difference were done by Mann-Whitney U test. P values less than 0.05 were considered significant.

Results
Clinical and glycemic status of the study subjects are shown in Table I. Diabetic subjects were a bit older than Control subjects. There were more female subjects in I-IGT group than Control, IFG, IFG-IGT and diabetic groups and also in
FDRs than Control, IFG-IGT and diabetic subjects. BMI was higher only in diabetic subjects, and waist circumference was higher in IFG-IGT and diabetic subjects compared to Control. Neck circumference was higher in IFG-IGT and diabetic subjects than I-IGT subjects and FDRs, but not compared to Control. HbA1c was higher in IFG-IGT and diabetic subjects than Control and FDRs and also higher in diabetic subjects than I-IGT subjects.

Table I

Clinical and glyceric profile of the study subjects (n =323)

<table>
<thead>
<tr>
<th></th>
<th>Control (n =57)</th>
<th>IFG (n =36)</th>
<th>I-IGT (n =61)</th>
<th>IFG-IGT (n =64)</th>
<th>DM (n =73)</th>
<th>FHO-DM (n =32)</th>
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<tbody>
<tr>
<td>Female (%)</td>
<td>20 (35%)</td>
<td>18 (50%)</td>
<td>46 (74%)</td>
<td>31 (48%)</td>
<td>29 (39%)</td>
<td>23 (69%)</td>
</tr>
<tr>
<td>Age (yrs)</td>
<td>39±11</td>
<td>43±11</td>
<td>40±11</td>
<td>43±9</td>
<td>45±10*</td>
<td>39±9</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>23.3±3.9</td>
<td>25.2±3.3</td>
<td>24.8±4.2</td>
<td>25.4±3.9</td>
<td>25.6±3.5*</td>
<td>24.9±3.5</td>
</tr>
<tr>
<td>WC (cm)</td>
<td>80(57-106)</td>
<td>90(61-104)*</td>
<td>86(59-108)</td>
<td>90(59-110)‡‡‡</td>
<td>90(61-110)**‡‡‡</td>
<td>85(58-98)§</td>
</tr>
<tr>
<td>NC (cm)</td>
<td>34±3</td>
<td>35±3</td>
<td>33±3</td>
<td>36±3‡‡</td>
<td>35±3‡‡</td>
<td>33±3‡‡</td>
</tr>
<tr>
<td>BFMI (%)</td>
<td>27.9±7.2</td>
<td>31.0±6.0</td>
<td>31.0±6.2</td>
<td>30.3±6.6</td>
<td>30.6±6.2</td>
<td>30.3±7.0</td>
</tr>
<tr>
<td>F-Glu (mmol/l)</td>
<td>4.9(2.8-5.5)***</td>
<td>5.9(5.6-6.9)***</td>
<td>5.0(4.1-5.5)†††</td>
<td>5.9(5.6-6.9)***</td>
<td>6.3(3.6-10.0)</td>
<td>5.0(3.8-5.5)†‡‡</td>
</tr>
<tr>
<td>2-h-Glu (mmol/l)</td>
<td>6.0(3.4-7.6)‡‡</td>
<td>6.8(4.2-7.7)‡‡</td>
<td>9.0(7.8-11.0)‡‡‡</td>
<td>9.7(7.9-11.0)***</td>
<td>12.3(8.3-18.7)§</td>
<td>6.3(3.6-7.6)‡‡‡</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>5.6(4.5-6.5)‡‡</td>
<td>5.5(4.7-7.1)‡‡</td>
<td>5.7(4.3-7.9)‡‡</td>
<td>5.8(4.3-7.3)‡‡</td>
<td>5.9(4.8-8.2)‡‡</td>
<td>5.4(4.7-6.1)‡‡‡</td>
</tr>
</tbody>
</table>

Data are n (%), mean±SD or median (range). *P<0.05, **P<0.01 and ***P<0.001 vs. Control, †P<0.05 and ††P<0.001 vs. IFG, ‡P<0.05, ‡‡P<0.01 and ‡‡‡P<0.001 vs. I-IGT, §P<0.05, §§P<0.01 and §§§P<0.001 vs. IFG-IGT, and ¶P<0.05 and ¶¶¶P<0.001 vs. DM. n = number of subjects. BMI, body mass index; WC, waist circumference; NC, neck circumference; BFMI, body fat mass; F, fasting; 2-h, 2 hour after 75-g glucose, Glu, glucose.
Conclusions

Our study finding shows higher TG in IFG, I-IGT, IFG-IGT, diabetes and FDRs (Table II). Hypertriglyceridemia is a feature of type 2 diabetes.5,8 Higher TG is also a feature of prediabetic subjects.12-16 Insulin resistance and/or B-cell failure in prediabetic and diabetic subjects may be responsible for higher TG in these subjects. Studied in FDRs have shown raised TG9,10 and insulin resistance.10,19 Higher TG in FDRs may be due to insulin resistance. Our study finding also shows raised TG in IFG-IGT and diabetes compared to I-IGT and FDRs. As HbA1C levels are higher in IFG-IGT and diabetes than Control (Table I), I-IGT and FDRs, IFG-IGT and diabetes are more decompensated glycemic states, which may explain higher TG in these subjects.

HDL level does not differ among the groups. But TG/HDL ratio is a better marker of dyslipidemia, which, like TG, is higher in prediabetic and diabetic subjects and FDRs and also higher in IFG-IGT and diabetic subjects than I-IGT subjects.

In the study, we have also found that prevalence of MetS is higher in prediabetic and diabetic subjects and FDRs (Table III). It is well accepted that MetS is associated with insulin resistance. So insulin resistance in these subjects may be responsible for higher prevalence of MetS in them and also explain raised TG in these subjects.

Total cholesterol and non-HDL cholesterol is higher in IFG-IGT and diabetic subjects than control and FDRs. TC/HDL ratio is also raised in IFG-IGT and diabetes than control. As mentioned before, IFG-IGT and diabetes are more decompensated glycemic states. So total cholesterol, non-HDL cholesterol and TC/HDL ratio is raised only in more decompensated glycemic states of IFG-IGT and diabetes.

In our study, FDRs have raised TG and TG/HDL ratio, even though blood glucose level is within normal range. So raised TG may be the earliest metabolic change in FDRs. Prediabetic subjects (IFG, I-IGT and IFG-IGT) have raised blood glucose but within prediabetic range. Among the measured parameters of lipid profile, only TG is raised in

<table>
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<th>Table II</th>
<th>Lipid profile of the study subjects</th>
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<tbody>
<tr>
<td></td>
<td>Control</td>
</tr>
<tr>
<td>TG (mg/dl)</td>
<td>108(47-219)</td>
</tr>
<tr>
<td>HDL(mg/dl)</td>
<td>38(24-62)</td>
</tr>
<tr>
<td>TC(mg/dl)</td>
<td>171(101-235)</td>
</tr>
<tr>
<td>Non HDL(mg/dl)</td>
<td>131(66-198)</td>
</tr>
<tr>
<td>TC/HDL(mg/dl)</td>
<td>4.6(2.2-7.9)</td>
</tr>
<tr>
<td>TG/HDL(mg/dl)</td>
<td>2.9(1.0-6.7)</td>
</tr>
</tbody>
</table>

Data are median (range). * P<0.05,** P<0.01 and *** P<0.001 vs. Control, ‡‡‡ P<0.05 and ‡‡‡‡ P<0.001 vs. I-IGT, $ P<0.05 vs. IFG-IGT, and ¶¶¶ P<0.05 vs. DM. TG, triglyceride; TC, total cholesterol.

<table>
<thead>
<tr>
<th>Table III</th>
<th>Frequency of abnormal cardiometabolic variables of the study subjects</th>
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<tbody>
<tr>
<td></td>
<td>Control</td>
</tr>
<tr>
<td>High WC</td>
<td>22 (38%)</td>
</tr>
<tr>
<td>Arterial Hypertension</td>
<td>17 (29%)</td>
</tr>
<tr>
<td>High TG</td>
<td>11 (19%)</td>
</tr>
<tr>
<td>Low HDL</td>
<td>40 (70%)</td>
</tr>
<tr>
<td>High F-Glu</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>MetS</td>
<td>9 (15%)</td>
</tr>
</tbody>
</table>

Data are n (%). * P<0.05, ** P<0.01 and *** P<0.001 vs. Control, ††† P<0.001 vs. IFG, ‡‡‡ P<0.05 and ‡‡‡‡ P<0.001 vs. I-IGT, § P<0.05, and §§§ P<0.001 vs. IFG-IGT, and ¶¶¶ P<0.001 vs. DM. WC, waist circumference; TG, triglyceride; F, fasting; Glu, glucose; MetS, metabolic syndrome.
all prediabetic subgroups. So raised TG is the earliest lipid abnormality in prediabetic subjects. Among the prediabetic subgroups, only IFG-IGT has raised total cholesterol, non-HDL cholesterol and TC/HDL ratio, which is also seen in diabetic subjects. As IFG-IGT and diabetes are more decompensated glycemic states, total cholesterol and non-HDL cholesterol is raised only in more decompensated glycemic states, viz. IFG-IGT and diabetes.

Using cut off values of the IDF Consensus Worldwide definition of metabolic syndrome, high WC is more prevalent in I-IGT, IFG-IGT and diabetes, and hypertension is more prevalent in IFG-IGT and diabetes. In lipid profile, high TG is prevalent in prediabetic and diabetic subjects and FDRs and low HDL cholesterol in I-IGT and FDRs. High fasting plasma glucose is prevalent in IFG, IFG-IGT and diabetes, as defined in case selection. When MetS is defined from its components, it is found that prevalence of MetS is higher in prediabetic and diabetic subjects and FDRs. Although absolute value of HDL cholesterol did not vary among the groups, but when subjects were grouped as having low and high HDL cholesterol, it was evident that low HDL cholesterol was more prevalent in I-IGT and FDRs. We know that FDRs suffer insulin resistance. In a Bangladeshi population, it was found that IFG subjects have B-cell dysfunction, I-IGT subjects suffer insulin resistance, and IFG-IGT subjects suffer both B-cell dysfunction and insulin resistance. It is well known that type 2 diabetic patients suffer both B-cell failure and insulin resistance. So low HDL cholesterol is prevalent only in those Bangladeshi subjects which have pure insulin resistance and not accompanied by B-cell failure.

So, in conclusion, it is evident from the study that raised serum triglyceride level is the earliest metabolic derangement in 1st degree diabetic-relatives and the earliest lipid abnormality in prediabetic subjects. Total cholesterol and non-HDL cholesterol is raised in IFG-IGT and diabetes, the more decompensated glycemic states. Higher prevalence of metabolic syndrome is seen among diabetic, prediabetic and 1st degree diabetic-relatives.

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Conflict of Interest: None

References


