Hyperproinsulinemia is commonly present in subjects with impaired glucose tolerance. The present study was undertaken to investigate the proinsulin level in Bangladeshi IGT subjects and to explore its association with insulin resistance. This observational study was conducted under a case-control design with IGT subjects (n=50) and controls (n=44). IGT was diagnosed following the WHO Study Group Criteria. Serum glucose was measured by glucose-oxidase method, serum lipid profile by enzymatic method and serum insulin and serum proinsulin were measured by ELISA method. Insulin secretory capacity (HOMA%B) and insulin sensitivity (HOMA%S) were calculated from fasting serum glucose and fasting serum insulin by homeostasis model assessment. The study subjects were age- and BMI-matched. Mean (±SD) age (yrs) of the control and IGT subjects were 40±6 and 40±5 respectively (p=0.853). Mean (±SD) BMI of the control and IGT subjects were 23±3 and 22±2 respectively (p=0.123). Fasting glucose was not significantly higher in IGT subjects, but serum glucose 2 hours after 75 gm glucose load was significantly higher in IGT subjects. Median (Range) value of fasting serum glucose (mmol/l) of control and IGT subjects were 5.3 (3.8-6) and 5.2 (4-12) respectively; (p=0.297). Median (Range) value of serum glucose (mmol/l) 2 hours after 75 gm glucose load of control and IGT subjects were 6.1 (3-7.8) and 7.9 (5-21) respectively; (p=0.001). Fasting TG was significantly higher in IGT subjects and LDL-c was significantly lower in IGT subjects. Serum Total cholesterol and HDL-c were not significantly different between the IGT and control subjects. Median (Range) value of fasting serum TG (mg/dl) of control and IGT subjects were 119 (51-474) and 178 (82-540) respectively; (p=0.001). Median (Range) value of fasting serum T chol (mg/dl) of control and IGT subjects were 180 (65-272) and 186 (140-400) respectively; (p=0.191). Median (Range) value of fasting serum HDL-C (mg/dl) of control and IGT subjects were 29 (19-45) and 31 (15-78) respectively; (p=0.914). Median (Range) value of fasting serum LDL-C (mg/dl) of control and IGT subjects were 117(29-201) and 111(41-320) respectively; (p=0.001). Fasting serum proinsulin was significantly higher in IGT subjects. Median (Range) value of fasting serum proinsulin (pmol/l) of control and IGT subjects were 9.2(1.8-156) and 17(3-51) respectively; (p=0.001). Insulin secretory capacity (HOMA%B) was higher but insulin sensitivity (HOMA%S) was significantly lower in case of IGT subjects. Median (Range) value of HOMA%B of control and IGT subjects were 97(46-498) and 164(17-300) respectively; (p=0.001). Median (Range) value of HOMA%S of control and IGT subjects were 68(19-270) and 39(15-110) respectively (p=0.001). In multiple regression analysis a significant negative association was found between fasting proinsulin and insulin sensitivity (p=0.037). The data led to the following conclusions: a) Insulin resistance is the predominant defect in Bangladeshi IGT subjects. b) Basal proinsulin level is significantly increased in IGT subjects. c) Insulin resistance is negatively associated with serum proinsulin in IGT subjects.

Key Words: Proinsulin, Hyperproinsulinemia, IGT, Insulin Resistance
tolerant study group. In previous studies no association was found between relative hyperproinsulinaemia and insulin sensitivity, in contrast to another study in which a negative association was found in 138 people with normal glucose tolerance.

Bangladesh has one of the largest diabetic and prediabetic populations in the world, but the pathophysiology of these states in our population has only been started to be investigated. Data from this population shows that both insulin secretory defect and insulin resistance are present in T2DM subjects, but the secretory defect seems to have a predominant role. In case of prediabetes, studies from Bangladeshi population, it was reported that IFG and IGT seemed to be separate disorders where b-cell dysfunction was predominant in IFG and insulin resistance had a major role in IGT. A combined IFG-IGT group has both the defects.

It has been found that the lean and young Bangladeshi diabetic population showed disproportionate rise of proinsulin compared to the healthy counterparts. No study has yet been done to investigate the role of serum proinsulin in the IGT subjects. Studies on prediabetic subjects can give substantial insight on the natural history of the disorders and the present study was undertaken to investigate the association of proinsulin level with insulin resistance in IGT subjects.

Materials and Methods

Ninety four subjects were taken into the study among them 50 were IGT subjects (WHO guidelines) and 44 were control subjects. The study subjects were adult, age ranging from 25-55 years and voluntarily agreed to participate in the study. Patients having any co-morbid diseases and pregnant women were excluded from the study.

Anthropometric measurements such as BMI, percentages of body fat mass (by Omeron body fat monitor, Japan), blood pressure (according to WHO-ISH) were recorded for all study subjects.
Glycemic and lipidemic status of the study subjects

Fasting glucose was not significantly higher in IGT subjects but serum glucose 2 hours after 75 gm glucose load was significantly higher in IGT subjects. Median (Range) value of fasting serum glucose (mmol/l) of control and IGT subjects were 5.3 (3.8-6) and 5.2 (4-12) respectively; (p=0.297). Median (Range) value of serum glucose (mmol/l) 2 hours after 75 gm glucose load of control and IGT subjects were 6.1 (3-7.8) and 7.9 (5-21) respectively; (p=0.001).

Serum Total cholesterol and HDL-c were not significantly different between the IGT and control subjects. Fasting TG was significantly higher in IGT subjects and LDL-c was significantly lower in IGT subjects. Median (Range) value of fasting serum TG (mg/dl) of control and IGT subjects were 119 (51-474) and 178 (82-540) respectively; (p=0.001). Median (Range) value of fasting serum T. chol (mg/dl) of control and IGT subjects were 180 (65-272) and 186 (140-400) respectively; (p=0.191). Median (Range) value of fasting serum HDL-C (mg/dl) of control and IGT subjects were 29 (19-45) and 31 (15-78) respectively; (p=0.914). Median (Range) value of fasting serum LDL-C (mg/dl) of control and IGT subjects were 117(29-201) and 111(41-320) respectively; (p=0.001) as shown in table II.

Table-II: Glycemic and lipidemic status of the study subjects

Results are expressed as median (range). Significance of difference was calculated by Mann -Whitney U test at 5% significance level. n= numbers of subjects; IGT, Impaired glucose tolerance; TG, Triglycerides; HDL-C, high density lipoprotein cholesterol; LDL-C, low density lipoprotein cholesterol.
In multiple regression analysis a significant negative association was found between fasting proinsulin and insulin sensitivity (p=0.037) as shown in table-V.

Table V: Multiple regression analysis taking HOMA%S as a dependent variable in IGT subjects

<table>
<thead>
<tr>
<th>Variable</th>
<th>Value</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMI</td>
<td>β-0.141</td>
<td>0.183</td>
</tr>
<tr>
<td>Proinsulin</td>
<td>-0.228</td>
<td>0.037</td>
</tr>
<tr>
<td>Group (Control/IGT)</td>
<td>0.197</td>
<td>0.065</td>
</tr>
</tbody>
</table>

Multiple regression analysis was done taking HOMA%S as a dependent variable and Group (Control/IGT), BMI, as independent co variables. HOMA%S had significant negative association (p=0.037) with proinsulin.

Discussion

Analysis of the anthropometric data in the present study showed that the IGT and the Control subjects were age and BMI matched. Both the IGT and Controls were in the middle age group (mean age was 40) as shown in table I. Obesity is one of the major risk factors for the development of IGT, but the IGT subjects in the present study did not show any generalized obesity and their BMI were within normal range. Regarding the lipid profile, IGT subjects had significantly higher serum triglyceride level than that of controls. Serum LDL cholesterol was found to be higher both in controls and IGT subjects but difference between controls and the IGT were not significant. This finding is consistent with the finding of a study where it was found that people with IGT had higher fasting plasma triglycerides and non-esterified fatty acids, and lower HDL cholesterol concentrations than people with NGT and with IFG. Blood lipid profiles illustrate that even non-obese people with IGT show several features of metabolic syndrome13.

Insulin secretory defect was not evident in IGT subjects rather a hypersecretory stage was found by increased β-cell function evident by HOMA % B. Wasada et. al also found similar findings and they found that people with IGT
IGT subjects had significantly lower insulin sensitivity (p=0.0001) compared to Controls (Table III) which indicates that IGT subjects had insulin resistance. This finding is consistent with the previous studies done in our IGT population where insulin resistance was found as a primary defect for IGT subjects. Data from the Bangladeshi population indicate that IFG has primarily insulin secretory defect, IGT has primarily insulin resistance, and combined IFG-IGT has both the defects\(^{11}\). Another study in western population showed that insulin resistance is markedly higher in people with isolated IGT and is absent in people with IFG\(^{14}\). In contrast, some studies have reported that people with isolated IFG are more insulin resistant than those with normal glucose tolerance (NGT) and people with isolated IGT exhibited a more severe deficit in insulin secretion than those with IFG\(^{15,16}\). Although both isolated IFG and isolated IGT are insulin-resistant states, they differ in their site of insulin resistance\(^{17}\). People with isolated IFG predominantly have hepatic insulin resistance and normal muscle insulin sensitivity, whereas individuals with isolated IGT have normal to slightly reduced hepatic insulin sensitivity and moderate to severe muscle insulin resistance. Not surprisingly, individuals with both IFG and IGT manifest both muscle and hepatic insulin resistance.

In the present study, the basal plasma proinsulin (pmol/L) level was 9.2 (1.8-156) in control group and 17 (3-51) in IGT. This value is slightly higher compared to the value found in western population where they got 5.8±3.3 pmol/l in control group, 12.6±7.5 pmol/l in IGT group\(^{1}\).

Stumvoll et al. found a contrasting findings and they suggested that the primary lesion resulting in the secretory defect of IGT subjects did not necessarily involve abnormal proinsulin processing\(^{18}\). If this had been the case, more proinsulin per mol insulin should have been cosecreted, resulting in an even greater difference between the two groups during maximal stimulation. It is possible that the activity of the specific endopeptidases and exopeptidases responsible for the enzymatic conversion of proinsulin to insulin increased over proportionately in IGT during maximal stimulation. This could indicate that a defect in the rate of conversion of proinsulin to insulin is overcome when the activity of the β-cell is strongly stimulated\(^{18}\).

In the multiple regression analysis taking insulin secretory defect as dependent variable and age, BMI, proinsulin and control/IGT as independent variables no significant association was found (Table IV).

In the multiple regression analysis taking insulin sensitivity as dependent variable and BMI, proinsulin and control/IGT as independent variables a significant negative association was found with serum proinsulin (p=0.05) as shown in table V. Lele et al. also found elevated proinsulin and its association with insulin resistance in Indian population\(^{19}\). But Wang et al. did not found any such association and they found that, the fasting proinsulin to insulin ratio showed no relationship to the degree of insulin resistance. They suggested that, insulin resistance and the need to secrete more insulin to maintain glucose tolerance did not necessarily lead to abnormal insulin processing by the β-cell\(^{20}\). From this study, it can be concluded that insulin resistance is the predominant defect in Bangladeshi IGT subjects and basal proinsulin level is significantly increased in IGT subjects while insulin resistance is negatively associated with serum proinsulin in IGT subjects.

References


13. Wasada T, Kuroki H, Arii H, Sato A, Aoki K. Who are more insulin resistant, people with IFG or people with IGT? Published online: 2004; 13 February © Springer-Verlag.


