Original Article

Association of insulinotropic hormone with glycemic status in impaired glucose tolerance

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Abstract

Objective : Impaired glucose tolerance means that blood glucose is raised beyond normal levels. The major objective of the present work was to explore the association of GIP with dysglycemia or abnormal insulinemic status.

Methodology : Serum glucose was measured by glucose-oxidase method, serum lipid profile by enzymatic method, and serum C-peptide and serum glucose dependent insulinotropic hormone (GIP) 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 analytic observational study was conducted under a case subjects (n=51) and Controls (n=47). IGT was diagnosed following the WHO study group criteria.

Results : Mean (±SD) age (yrs) of the Control subjects and IGT subjects were 40±6 and 41±5 respectively (p=0.502). Mean (+SD) BMI of the Control and IGT subjects were 24.0±2.9 and 24.0±3.5 respectively (p=0.955). WHR of IGT subjects were statistically higher than the Control subjects, [Mean (+SD), 0.92±0.08 vs 0.88±0.05, (p=0.02)]. Median (Range) value of fasting serum glucose (FSG) of Control and IGT subjects were 5.2 (4.1-6.0) and 5.3 (4.4-6.0) mmol/l respectively. Fasting C-peptide value of IGT subjects was not significantly different from the value of the Controls. Serum (Range) value of fasting serum C-peptide of Control and IGT subjects were 0.64 (0.18-1.62) and 0.68 (0.21-1.39); (p=0.310). A significant positive correlation was found between fasting C-peptide and fasting GIP (p=0.019) in the control subjects. In multiple regression analysis a significant positive association was found between fasting C-peptide and fasting GIP (p<0.01). A significant negative association was found between fasting GIP and insulin sensitivity (HOMA%S) (p=0.05). No association was found between fasting glucose and fasting GIP both in simple correlation and multiple regression.

Conclusion : GIP does not have any association with insulin secretion in IGT subjects, but it has an association with insulin resistance.

Key Words : insulinotropic hormone, glycemic status, impaired glucose tolerance

Introduction

Diabetes mellitus (DM) is a heterogeneous group of metabolic disorders characterized by chronic hyperglycemia with disturbances of carbohydrate, fat and protein metabolism resulting from defects in insulin secretion, insulin action or both. When fully expressed, diabetes is characterized by fasting hyperglycemia, but the disease can also be recognized during less overt stages, most usually by the presence of glucose intolerance.

All forms of diabetes can pass through a stage of IFG and/or IGT. These categories are a part of the natural history of diabetes and not a type of diabetes. That is why they are not included in the classification of diabetes mellitus by ADA.

The pathophysiology of T2DM is a field of rigorous investigations. T2DM is well characterized by defects in insulin secretion, insulin action or both[1]. The progressive deterioration of pancreatic insulin secretion has been implicated as the proximate cause of the progressive increase in plasma glucose level.[2] Thus decrease in insulin secretion is a major contributor to the development of the overt T2DM state.

Two GI peptide hormones (the incretins) GLP-1 and GIP — were found to exert major glucoregulatory actions[3] within minutes of nutrient ingestion, GLP-1 is secreted from intestinal L cells in the distal ileum and colon, while GIP is released by intestinal K cells in the duodenum and jejunum.[3] GLP-1 and GIP trigger their insulinotropic actions by binding beta-cell receptors[3,4]. GLP-1 receptors are

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expressed on pancreatic glucagon-containing alpha and delta cells as well as on beta cells, whereas GIP receptors are expressed primarily on beta cells.[4] GLP-1 receptors are also expressed in the central nervous system (CNS), peripheral nervous system, lung, heart, and GI tract, while GIP receptors are expressed in adipose tissue and the CNS. GLP-1 inhibits glucose-dependent glucagon secretion from alpha cells.[3] In healthy individuals, fasting glucose is managed by tonic insulin/glucagon secretion, but excursions of postprandial glucose (PPG) are controlled by insulin and the incretin hormones.[5]

Methodology

The study was conducted in the Department of Biochemistry, General Medical Hospital, Dhaka during the period of July 2014 to June 2015. It was an observational analytic study with a case-control design. A group of 98 adult subjects with age ranging from 30-55 years and voluntarily agreed to include in this study were included and they were recruited from the Hospital. Of them impaired glucose tolerance (IGT) 51 were taken as study subjects and 47 as control. Patients with serious co-morbid diseases (severe infection, stroke, myocardial infarction, major surgery, mal-absorption etc) were excluded.

Fasting blood was collected between 8.00-9.00 am. Venous blood (05 ml) was taken with the subject sitting comfortably in a chair. After 30 minutes blood samples were centrifuged for 10 minutes at 3000 rpm to obtain serum. Separated serum was adequate and preserved in a freezer (-27° C) for future biochemical analysis. Fasting serum glucose, triglyceride, total cholesterol, HDL cholesterol, creatinine and SGPT were measured in the same day. Homeostasis Model Assessment (HOMA) is a simple widely used method which derives separate indices of B cell secretion (HOMA-B) and insulin sensitivity (HOMA-S) from the serum glucose and serum insulin concentrations under basal conditions by using HOMA CIGMA software.[6] Data were expressed as mean ±SD and/or median (range) where appropriate. Comparison between two groups was done using Students't' test (paired and unpaired), Mann-Whitney 'U' test and Wilcoxon 'Z' test. Bivariatte correlation analysis was done by using Spearman's Correlation analysis. Data were managed and statistical analyses were performed using Statistical Package for Social Science (SPSS) for Windows version 18. p value <0.05 was taken as level of significance.

Results

Table-1 : Clinical and anthropometric measurements of the study subjects

Variables	Control (n=47)	IGT (n=51)	t/p value
Age (yrs)	40+6	41+5	0.673/0.502
BMI (kg/m2)	24.0+2.9	24.0+3.5	0.570/0.955
WHR	0.88+0.05	0 .92+0.08	2.340/0.02
S Creatinine (mg/dl)	1.03±0.12	1.06±0.24	0.43/0.597
SGPT (U/L)	29.5±21.5	27.4±15.3	0.568/0.571

Table-2 : Glycemic and Insulinemic status of the subjects

Variables	Control (n=47)	IGT (n=51)	z/p value
FSG (mmol/l)	5.2 (4.1-6.0)	5.3 (4.4-6.0)	0.502 /0.615
PSG (mmol/ l)	6.3 (4.8-7.8)	9.3 (7.9-11.0)	**8.502/0.001**
FCPEP (pmol/l)	0.64 (0.18-1.62)	0.68 (0.21-1.39)	1.000/0.310
HOMA%B	117 (58.4-461)	117 (39.4-455)	0.109/0.914
HOMA%S	71 (27-247)	65 (22-222)	**1.890/0.050**

Table-3 : Lipidemic status of the study subjects

Variables	Control (n=47)	IGT (n=51)	t/p value
TG (mg/dl)	159±101	186±116	0.229/0.819
T Chol (mg/dl)	190±36	190±50	0.004/0.997
HDL-C (mg/dl)	36.3±6.6	38.2±5.7	1.56/0.121
LDL-C (mg/dl)	122±31	114±44	0.951/0.344

Table-4 : Absolute levels of glucose dependent insulinotropic polypeptide (GIP) of the study subjects

Variables	Control (n=47)	IGT (n=51)	z/p value
F GIP (ng/ml)	49.62 (6.10-278.0)	74.21 (10.0-189.9)	3.30/0.001
P GIP (ng/ml)	267 (37.76-700.36)	254.95 (130.9-616.3)	0.175/0.861
PGIP:FGIP	5.14 (0.96-19.85)	3.47 (0.98-22.0)	4.469/0.001
FGIP (0 min)	49.6 (6.10-278)	74.21 (10.0-190)	
PGIP (120 min)	267 (37.76-700)	254.95 (131-616)	
z/p value	**5.958/0.001**	**6.205/0.001**	

Discussion

Type 2 Diabetes Mellitus is a major health problem all over the world and its rise in epidemic proportion warrants urgent measures for its prevention. This, in turn, presupposes evidence based knowledge on the predisposing factors of the disorder in individual population. IGT is thought to be an intermediate stage in the natural history of diabetes and intervention at this stage has been proven to be a highly cost-effective measure in combating diabetes. Data on the pathophysiology of IGT in Bangladeshi population is relatively scarce and the present study is the first one exploring its association with GIP. Analysis of the anthropometric data in the present study shows that the IGT subjects do not have generalized obesity as evident by no difference in BMI between control and IGT groups. IGT, however, is associated with central obesity as evident by the higher WHR in these subjects compared to control. The finding is consistent with the observations in a previous study conducted on the same population.[7,8] Central obesity is known to be more specifically related to the increased secretion of adipocytokines (like resistin and adiponectin) and inflammatory markers (like hs CRP) which, in turn, are associated with insulin resistance. Thus, consistent finding of central obesity in the IGT population can be a central issue in designing preventing campaigns for reducing abdominal fat through lifestyle and dietary modifications.

Although prediabetic stages (IFG, IGT and IFG-IGT) are getting increased importance in the prevention of T2DM, their pathophysiology is still not fully understood. For example, it is still not fully decided whether isolated IFG, isolated IGT and combined IFG-IGT should be treated as etiologically separated disorders[9] 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[7,8] There are similar heterogenecity in the Bangladeshi diabetic population with different kinds of abnormalities being predominant in different patient groups[10-12]. There is no insulin secretory abnormality in the present IGT group, but there is significant insulin resistance in IGT (p=0.05) compared to Control (Table 2). Insulin resistance in IGT has been reported by many authors in other populations[13].

The major objective of the present work was to explore the association of GIP with dysglycemia or abnormal insulinemic status. GIP was found to be raised in T2DM as well as in IGT[14] but some authors reported reduced GIP in IGT cases[15,16] In the present study the fasting level of GIP in IGT cases were significantly higher than Control and both the groups showed acute rise in the GIP values in response to oral glucose. However, the difference between the two groups were totally lost at the postprandial stage because there was a proportionately higher rise (about 5 times) in the Control compared to a blunted response (about 4 times) in the IGT group. A ratio analysis also reveals that relative GIP values are already higher at the fasting stage compared to the Control; however, the scenario becomes reverse at the postprandial state with the corresponding ratio being significantly less in IGT compared to Control. The significance of the higher GIP values in the fasting state is currently unknown as focus have been mostly given to the GIP values after nutrient intake. This issue, however, now needs to be investigated further.

GIP is known to have a considerable insulinotropic effect and, along with GLP -1, it is thought to be a major contributor of the 50-60% additional rise of insulin secretion through incretin effect in response to oral diet. The effect of oral glucose on GIP release in the Control group could be observed by about 5 fold rise of GIP in postprandial state, but it was about 4 times in case of IGT subjects. It would have been interesting to see how it affected serum C-peptide levels, but the postprandial C-peptide value was not available for analysis. The fasting C-peptide level however was not different between the Control and IGT groups although the GIP was higher in IGT cases. Consequently, the FC-peptide to GIP ratio is significantly lower in IGT compared to Control ($p< 0.05$). It is thus evident that the insulinotropic effect of GIP seems to be already diminished at the fasting stage. The data is in conformity with the observations of decreased activity of GIP in both prediabetic and diabetic subjects.[13,14] In support of the finding in univariate analysis, multiple regression showed a significant association of glucose and C-peptide with GIP. The present data also showed a significant negative association of insulin sensitivity (HOMA%S) with GIP. The mechanism of insulin resistance from deficient GIP action is still uncertain & this needs to be studied further.

Conclusion

IGT subjects have insulin resistance but their pancreatic β cell function seems to be still uncompromised. GIP secretion in IGT subjects is probably upregulated at the fasting state and it has a blunted response to oral glucose in this disorder. The incretin effect of GIP is diminished in

impaired glucose tolerance. GIP does not have any association with insulin secretion in IGT subjects, but it has an association with insulin resistance.

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