

Original Article:**Fasting glucose to adiponectin ratio is associated with the development of type 2 diabetes mellitus**

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Abstract:

Adiponectin and resistin are inversely associated with type 2 diabetes but it is not yet concluded whether adiponectin and resistin are the causal factors of diabetes. The present study was undertaken to evaluate the association of serum adiponectin and resistin with insulin secretory capacity and insulin resistance in subjects with impaired glucose regulation (IGR). Twenty four subjects with impaired fasting glucose (IFG), 58 with impaired glucose tolerance (IGT) and 30 with IFG-IGT were recruited in this study. Forty four non-diabetic healthy controls with on family history of diabetes or prediabetes were also recruited. Serum insulin, adiponectin and resistin levels were measured using ELISA technique. Serum adiponectin and resistin levels were not significantly different among the study groups. Ratios of fasting insulin with adiponectin and resistin were increased, both in IGT and IFG-IGT subjects. Binary logistic regression analysis have shown that ratio of fasting glucose to Adiponectin was significantly associated ($\beta=1.085$, $p=0.031$) with IGR subjects when age and body mass index were adjusted. Ratios of fasting glucose to adiponectin and resistin were also increased in IFG-IGT subjects. Multiple regression analysis have shown that ratio of fasting insulin to Adiponectin was negatively associated ($\beta=-0.201$, $p=0.034$) with insulin sensitivity (HOMA% S) and positively ($\beta=0.507$, $p=0.0001$) with insulin secretory capacity (HOMA% B) in IGR subjects. On the other hand, ratio of fasting insulin to Resistin showed significant negative association ($\beta=-0.237$, $p=0.015$) with HOMA% S and positive association with HOMA% B, ($\beta=0.506$, $p=0.001$) in IGR subjects. The findings indicate that ratio of fasting glucose to adiponectin may be an important factor for the development of type2 diabetes.

Key words: Adiponectin, Resistin, Insulin sensitivity, Resistance.

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Introduction

The prevalence of diabetes is rapidly increasing with the changes of life style and composition of meals. The high prevalence of diabetes has led to an increase in medical conditions that accompany obesity, hypertension, and cardiovascular disease (CVD) [1]. In the recent years, a line of evidence has demonstrated a much more complex function of adipose tissue, as an endocrine organ that releases hormones into the blood stream to take part in their potential implication in insulin resistance, obesity and diabetes [2]. The recent boom of interest is to identify the role of adipocyte derived factors such as adiponectin and resistin in insulin sensitivity in IGR subjects [3] and in particular, their potential implication in insulin resistance [4]. Reduced levels of serum adiponectin in type 2 diabetes may involve in insulin resistance but it is not concluded whether reduced adiponectin leads to insulin resistance or vice versa [5].

Resistin impairs glucose homeostasis by affecting both insulin-stimulated glucose uptake in adipose

tissue and hepatic glucose production and obesity-induced insulin resistance [6]. Serum resistin levels were found to be related to body mass index (BMI) in human subjects [7-9], but other studies contradict this result [10-12]. Silha et al described a possible impact of resistin on insulin sensitivity [4]. In contrast, a considerable number of studies failed to detect an association between resistin concentration and markers of insulin sensitivity [7-12].

Type 2 diabetes develops through the stage of IFG and/or IGT, which are asymptomatic and unassociated with any manifested morbidity. Their sole significance, lies in the fact that they predict future diabetes or cardiovascular disease [13]. Recently, it has been found that insulin resistance and insulin secretory defect appears in the prediabetes stage i.e., before the onset of diabetes [14]. However, few studies exist which examine whether adiponectin and resistin levels begin to change in prediabetic stage [15-16]. The present study was undertaken to explore the circulating adiponectin and resistin concentration and its association with insulin sensitivity and insulin secretory capacity in prediabetic subjects.

Methodology

Subjects:

The study was conducted at Biomedical Research Group, Research Division, Bangladesh Institute of Research and Rehabilitation in Diabetes, Endocrine and Metabolic Disorders (BIRDEM), Dhaka, Bangladesh. One hundred and twelve (112) IGR subjects (IFG=24, IGT=58, IFG-IGT=30), along with forty-four (44) non-diabetic healthy control subjects were included in this study. There was no specific predilection for race, religion or socioeconomic status. The purpose of the study was explained to all the subjects before taking their consent for recruitment in the study. Anthropometric indices, like, height, weight, waist circumference and hip circumference of the subjects were measured by standard procedures.

Sample collection:

Selection of subjects was purposively made from Bangladesh Institute of Research and Rehabilitation in Diabetes, Endocrine and Metabolic Disorders (BIRDEM), Dhaka, Bangladesh. The subjects were confirmed for IFG, IGT and IFG-IGT according to WHO guideline (17). Forty four healthy subjects from the similar

socio-economic status without any known family history of diabetes or prediabetes were also included in this study to serve as Controls. Subjects with serious comorbidities and pregnant women were not included in the study. On a prescheduled morning, fasting (8-10hrs) venous blood (10 ml) was taken by venepuncture with the subject sitting comfortably in a chair in a quiet room. The subjects (both the prediabetic and control) were then given 75g of glucose in 250-300 ml of water and advised to drink it in 5 min. They were advised not to smoke, not to take any food and to take rest in a chair for 2 hours. The second blood sample was taken 2h after glucose load. After 10-15 minutes blood samples were centrifuged for 10 minutes at 3000 rpm to obtain serum which was kept frozen at -70°C until analysis.

Assay methods:

Serum glucose was estimated by Glucose-Oxidase (GOD-PAP) method. Serum triglyceride (TG), serum cholesterol and serum high-density lipoprotein (HDL) were measured by enzymatic colorimetric (GPO-PAP) method. All these estimations were done by an automatic analyzer (Hitachi 704, Hitachi Ltd., Tokyo, Japan) using reagents of Randox Laboratories Ltd., UK. LDL cholesterol was calculated using the standard formula. Serum insulin level was measured by chemiluminescence based ELISA, using Immulite, DPC, USA. Serum resistin and adiponectin were measured by Enzyme Linked Immunosorbent Assay (Linco Research, Millipore, USA). Insulin sensitivity (HOMA% S) and insulin secretory capacity (HOMA% B) were calculated from by fasting glucose and fasting insulin values using HOMA-CIGMA software.

Statistical Analysis

Statistical analysis was performed using SPSS (Statistical Package for Social Science) software for Windows version 10 (SPSS Inc., Chicago, Illinois, USA). All the data were expressed as mean±SD, median (range) and/or percentage (%) as appropriate. The statistical significance of differences among the groups was assessed by ANOVA Bonferrony test or Mann-Whitney U test (as appropriate). A two-tailed p value of <0.05 was considered statistically significant. Binary logistic regression was done to test the association of adiponectin and resistin with IGR. Multiple linear regression analysis of HOMA% S and HOMA% B was done for adiponectin and resistin adjusted by BMI and waist hip-ratio (WHR).

Table 1: Clinical and Biochemical Characteristics of different study groups (IFG, IGT, IFG-IGT and controls

Variables	Control	IFG	IGT	IFG-IGT	P Value		
					Control vs IFG	Control vs IGT	Control vs IFG-IGT
Age (yrs)	35 ± 9	43 ± 10	45 ± 12	47 ± 9	0.002	0.001	0.0001
Body Mass Index (kg/m ²)	23 ± 3.0	25.8 ± 4.7	25.9 ± 4.8	26.1 ± 3.5	0.013	0.0001	0.0001
Waist-hip Ratio	0.92 ± 0.07	0.91 ± 0.06	0.92 ± 0.06	0.94 ± 0.06	0.628	0.72	0.269
Fasting Glucose (mmol/l)	4.98 ± 0.6	6.23 ± 0.34	5.48 ± 0.44	6.52 ± .25	0.0001	0.0001	0.0001
2 hour Glucose (mmol/l)	5.5 ± 1.12	6.53 ± 0.97	9.0 ± 0.9	9.73 ± 0.84	0.0001	0.0001	0.0001
Fasting Insulin (pmol/l)	47 (15-40)	60 (23-152)	62 (13-225)	78 (39-123)	0.357	0.004	0.006
Triglyceride (mg/dl)	118 (53-75)	133 (59-415)	149 (50-370)	164 (50-401)	0.779	0.247	0.002
Cholesterol (mg/dl)	187 (119-283)	187 (124-259)	186 (108-295)	211 (124-265)	1.000	1.000	0.521
HDL (mg/dl)	35 (22-54)	30 (13-48)	37 (22-61)	34 (21-49)	0.222	1.000	1.000
LDL (mg/dl)	102 (55-149)	118 (63-162)	110 (30-207)	137 (57-191)	1.000	1.000	1.000
HOMA% B	100 (50-159)	74 (39-122)	96 (44-287)	79 (53-117)	0.001	0.734	0.002
HOMA% S	99 (32-268)	69 (28-180)	57 (21-325)	55 (35-107)	0.005	0.001	0.0001
Adiponectin (µg/ml)	6.11 (1.9-19)	6.66 (2.3-15.51)	5.5 (1.85-16.6)	5.84 (1.38-16.09)	0.797	0.680	0.314
Resistin (ng/ml)	18.84 (9.34-86.21)	20.52 (12.9-80.12)	20.2 (9.09-119)	16.87 (9.93-51.32)	0.432	0.402	0.526
Ratio of fasting glucose to adiponectin	0.93 ± 0.41	1.18 ± 0.65	1.08 ± 0.52	1.46 ± 0.94	0.065	0.143	0.002
Ratio of fasting insulin to adiponectin	9.49 ± 6.35	13.86 ± 12.71	15.56 ± 12.9	18.15 ± 13.7	0.072	0.007	0.001
Ratio of fasting glucose to Resistin	0.28 ± 0.13	0.3 ± 0.12	0.28 ± 0.15	0.37 ± 0.14	0.597	0.891	0.007
Ratio of fasting insulin to Resistin	2.55 ± 1.42	2.88 ± 1.62	3.78 ± 2.73	4.62 ± 2.51	0.455	0.012	0.0001

P-value among the groups was calculated using ANOVA Bonferrony test

Results:

Table 1 indicates that BMI (kg/m²) was significantly higher in IFG (p=0.013), IGT (p=0.0001) and IFG-IGT (p=0.0001) subjects compared to controls. Fasting serum insulin levels were significantly higher in IGT (p=0.004) and IFG-IGT (p=0.006) subjects as compared to controls. Fasting serum triglyceride (TG) level were

significantly higher (p=0.002) in IFG-IGT subjects as compared to controls. HOMA% B was significantly lower in IFG (p=0.001) and IFG-IGT (p= 0.002) subjects as compared to controls and HOMA% S was significantly lower in IFG (p=0.005), IGT (p=0.001) and IFG-IGT (p=0.0001) subjects as compared to controls. Fasting serum adiponectin

($\mu\text{g/ml}$) and resistin levels (ng/ml) of the prediabetic subjects were not different from that of controls. Ratios of fasting insulin to adiponectin and resistin were increased both in IGT and IFG-IGT subjects as compared to Controls. Similarly ratios of fasting glucose to adiponectin and resistin were also increased in IFG-IGT subjects.

Binary logistic regression analysis considering IFG, IGT and IFG-IGT as a single IGR group (Table 2), shows that fasting glucose to adiponectin ratio was significantly ($\beta=1.085$, $p=0.03$) associated with IGR subjects when controls were used as

reference value and BMI and age were adjusted. Multiple linear regression analysis have also shown that fasting insulin to adiponectin ratio was negatively ($\beta= -0.201$ $p=0.034$) associated with HOMA% S and positively ($\beta=0.507$, $p=0.0001$) with HOMA% B in IGR subjects, when BMI and WHR were adjusted. On the other hand, in IGR subjects fasting insulin to resistin ratio was negatively ($\beta=-0.237$ $p=0.015$) associated with HOMA% S and positively ($\beta=0.506$, $p=0.0001$) with HOMA% B when BMI and WHR were adjusted.

Table 2: Logistic regression analysis of IGR subjects adjusted with BMI and age considering Controls as reference

Factors	Beta	Stander error	P-value	Odds ratio
Adiponectin	-0.093	0.081	0.250	0.911
Resistin	0.002	0.012	0.897	1.002
Ratio of fasting serum glucose to adiponectin	1.085	0.503	0.031	2.959
Ratio of fasting serum insulin to Resistin	0.201	0.125	0.107	1.223

Table 3: Multiple linear regression analysis of HOMA% S and HOMA% B with each of the dependent variables

Dependent variable	Groups	HOMA% S		HOMA% B	
		Beta	P value	Beta	P value
Adiponectin	control	0.557	0.024	0.250	0.219
	IGR	0.029	0.813	-0.208	0.069
Resistin	control	0.259	0.348	0.514	0.034
	IGR	-0.157	0.234	-0.113	0.357
Ratio of fasting glucose to adiponectin	control	-0.505	0.057	0.252	0.263
	IGR	-0.257	0.035	-0.088	0.458
Ratio of fasting glucose to Resistin	control	-0.632	0.016	-0.686	0.003
	IGR	-0.065	0.616	-0.170	0.158
Ratio of fasting insulin to Adiponectin	control	-0.349	0.085	0.224	0.188
	IGR	-0.201	0.034	0.507	0.0001
Ratio of fasting insulin to Resistin	control	-0.697	0.007	-0.119	0.562
	IGR	-0.237	0.015	0.506	0.001

Adiponectin, Resistin, Ratio of fasting glucose to Adiponectin, Ratio of fasting glucose to Resistin, Ratio of fasting insulin to Adiponectin and Ratio of fasting insulin to Resistin, adjusted by Body mass index and Waist-hip ratio

Discussion:

Adipose tissue plays an important role in insulin resistance through the dysregulated production of a large number of adipocyte hormones; adiponectin and resistin are two important hormones. Accumulating evidence from animal and human studies shows that adiponectin plays an important role in insulin sensitivity [18-22] and lipid metabolism [18,23], and thus influences hyperlipidemia [24] and diabetes. Circulating adiponectin is negatively associated with BMI and WHR suggesting that adiponectin may mediate some effects of adiposity. However, whether central obesity or other unrecognized pathways might play a regulatory role, remains to be elucidated by future studies. In this study prediabetic subjects were targeted to observe whether these two hormones dysregulated before the onset of diabetes. Although our study found no difference between controls and prediabetic or IGR subjects, the ratios of fasting glucose and insulin to adiponectin and resistin were different as compared to healthy subjects. When these ratios were analysed using binary regression between controls and IGR subjects, fasting glucose to adiponectin ratio was found to be positively associated with impaired glucose regulation. This indicates that adiponectin dysregulation commences before the onset of diabetes. In a previous study [25], it has been shown that 44% of patients diagnosed with IFG subsequently developed diabetes and these subjects had lower adiponectin levels compared to those who have not developed diabetes. High levels of adiponectin in IFG subjects may have a protective effect against the development of DM [25]. Increased serum adiponectin concentrations are associated with increased insulin sensitivity and glucose tolerance [26]. It can therefore be speculated that adiponectin, or drugs that stimulate adiponectin secretion or action, could play a role in combinations with insulin resistance; mainly type 2 diabetes mellitus and metabolic syndrome. Low concentrations of adiponectin have also been implicated in the severe insulin resistance in both animal models and humans [27]. Therapy with adiponectin may be advantageous in reversing insulin resistance in lipodystrophic disorders and metabolic syndrome [28]. Thiazolidinediones, a class of insulin-sensitizing antidiabetic drugs, increase adiponectin in insulin-resistant patients. In addition, high adiponectin concentrations are

associated with a reduced risk of type 2 diabetes [29].

In this study when the data were analyzed using multiple linear regression, a negative association between fasting glucose to adiponectin ratio and HOMA% S was found in IGR subjects, when BMI and WHR were adjusted. This indicates that if adiponectin concentration is increased, insulin sensitivity (HOMA% S) will also be increased. The ratio of fasting insulin to adiponectin had also shown significant association with both HOMA % B and HOMA % S in IGR subjects when BMI and WHR were adjusted. Therefore, it could be mentioned that ratio of fasting glucose to adiponectin may be an important factor in prediabetes which involves declined insulin sensitivity. Further studies are needed to know whether adiponectin initiates insulin resistance or vice versa.

Resistin has been proposed to play a role in obesity-mediated insulin resistance. Some studies have found significantly increased serum resistin concentration in association with development of insulin resistance and type 2 diabetes [30-33]. However, in this study, similarly to adiponectin no significant increase in serum resistance was found, which contradicts with other studies. Nevertheless, ratio of fasting insulin to resistin was consistent in multiple linear regression analysis when BMI and WHR were adjusted.

Therefore, based on the results it can be concluded that the ratio of fasting glucose to adiponectin may be an important factor for the development of type 2 diabetes and that the ratio of adiponectin and resistin to fasting insulin and /or glucose are associated with insulin sensitivity and insulin secretory capacity in prediabetic or IGR subjects.

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