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RESEARCH PAPER

Impact of Adipokines and Inflammatory Cytokines on Abnormal Glucose Tolerance in Young

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Abstract

Background: Adipokines and inflammatory cytokines may have an important impact on rising trend of obesity and abnormal glucose tolerance (AGT) in young across the globe.

Objectives: The aim of the study was to see serum adiponectin, leptin, resistin, tumor necrosis factor-alpha (TNF-α) and C-reactive protein (CRP) in young Bangladeshi with AGT.

Methods: This case-control study included 40 young participants with AGT [age 26 years (IQR 24-29); 60.0% female] and 40 with normal glucose tolerance [NGT; age 25 years (IQR 22-28); 44.0% female] encompassed following the oral glucose tolerance test (OGTT) and HbA1c. Insulin resistance (IR) was calculated by homeostasis model assessment (HOMA). The measurement of serum adiponectin, leptin, resistin and TNF-á was done by ELISA whereas CRP by Chemiluminescent test.

Results: Level of TNF-α, leptin, and adiponectin as well as frequency of raised resistin and CRP were statistically similar between AGT and NGT (p=NS for all). Positive correlation of TNF-á [body mass index (BMI) in AGT: r=0.354, p=0.025)], leptin [BMI in AGT r=0.760, p<0.001 and NGT 0.675, p<0.001; waist circumference (WC) in AGT: r=0.675, p<0.001 and NGT 0.493, p=0.001] and CRP (NGT group: BMI: 0.579, p<0.001; WC: 0.553, p<0.001) but negative correlation of adiponectin [waist-hip ratio (WHR) in NGT: r=-413, p=0.008] and resistin (WHR in AGT: r=-0.607, p=0.003) with measures of obesity were observed. No adipokines or inflammatory cytokines had any significant correlation to glycemic measures, except negative correlation in AGT with leptin (FPG: r=-0.405, p=0.010; 2hPG: r=-0.431, p=0.006; HbA1c: r=-0.399, p=0.011) and CRP (2hPG; r=-0.490, p=0.021). Fasting insulin or IR had a positive correlation with leptin (in AGT: insulin r=0.545, p<0.001 & IR r=0.337, p=0.034) and CRP (in NGT r=0.318, p=0.045 & r=0.323, p=0.042), negative correlation with adiponectin (in NGT insulin r=-0.350, p=0.027 & IR r=-0.352, p=0.026) and resistin (IR in NGT: r=-0.340, p=0.032) while no significant correlations with TNF-á. None of the cytokines or inflammatory markers were independent predictors of AGT in youth.

Conclusions: The serum levels of cytokines do not differ significantly between AGT and NGT subgroups of young subjects and none of the cytokines was observed to be independent predictor over AGT in young.

Keywords: Adipokine, Inflammatory cytokine, abnormal glucose tolerance, diabetes in young

Introduction

The prevalence of diabetes is increasing worldwide, and it is estimated that onset in young adulthood comprises 16% of the adult type 2 diabetes (T2D) population globally.[1] This is mostly because of the rising obesity and sedentary lifestyle contributing to more T2D in young.[2] In the registry of diabetes in the young in India, 25.3% of individuals developing diabetes under the age of 25 years had a diagnosis of T2D.[3] Among Bangladeshi children, the prevalence of impaired fasting glucose (IFG) and diabetes were high, 3.4% and 1.8% respectively, and more associated with urban living and high family income.[4] In Bangladeshi overweight and obese children, metabolic syndrome was present in more than 50%, while 60% had evidence of insulin resistance assessed by homeostasis model assessment (HOMA-IR), and 8% had impaired glucose tolerance (IGT).[5] The onset of T2D at a young age is a more aggressive condition than when develops in older age and the chance of significant morbidity and early mortality is higher.[6,7] Therefore, early prediction of DM in young and subsequent steps to prevent it is worthwhile.

Recent studies have shown that several cytokines released from adipose tissue, liver, muscle, and skeleton for inter-organ communication are associated with abnormal glucose and lipid metabolism and they can predict the future development of diabetes.[8] Instead of

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being an inactive energy reserve, adipose tissue has been recognized as an endocrine organ that secretes adipokines (adiponectin, leptin, resistin, asprosin, chemerin, omentin1etc.) and there is a possible link of these adipokines with obesity, insulin resistance, and metabolic syndrome.[9,10] Among the adipokines, serum adiponectin is beneficial and it has got powerful insulin sensitizing role, and it increases free fatty acid (FFA) oxidation, reduces FFA influx, de novo lipogenesis and gluconeogenesis.[11] Despite being produced mainly by adipose tissue, adiponectin secretion is paradoxically decreased in obesity and thereby associated with decreased insulin sensitivity.[12] Decreased serum level of adiponectin is considered as a biochemical predictor of diabetes.[11] Leptin is another adipocyte-derived hormone that promotes the oxidation of fatty acids, enhances insulin sensitivity, stimulates the uptake of glucose, and controls feeding.[13,14] Notably, leptin levels are markedly elevated in obesity and T2D, and they are positively linked with adipose mass, but there is presence of leptin resistance.[15] Another adipocytokine, resistin is predominantly produced in human by macrophages infiltrating adipose tissue and peripheral blood mononuclear cells, and it is not detectable in adipocytes. Resistin expression is found increased in subjects with central obesity, T2D and metabolic fatty liver disease.[16] Although studies in animal models consistently show that resistin promotes insulin resistance, evidence for this effect in humans is unclear.

Some pro-inflammatory cytokines, such as tumor necrosis factor alpha (TNF-α) and C-reactive protein (CRP), take part in disrupting the insulin and lipid signaling pathways, thereby influencing insulin sensitivity and lipid metabolism and thus playing a crucial role in the pathophysiology of diabetes.[17] In humans, the circulating concentration of TNF-α which is released from adipocytes and inflammatory cells is elevated in T2D, and this alteration is strongly associated with IGT and enhanced insulin resistance, islet dysfunction, and increased T2D risk.[18] Increased CRP levels have also been found in people with T2D and metabolic syndrome.[19] If the individuals at risk for developing T2D have raised inflammatory markers like TNF-α and CRP before, they are more likely to develop diabetes in future.[20]

As mentioned above, a number of studies have reported that altered levels of inflammatory cytokines and adipokines are associated with insulin resistance and future onset of diabetes mellitus although this issue has not been settled yet. In the era of the rising trend of diabetes in young across the globe and also in the South Asian region, we intended to see the impact of adipokines and inflammatory markers on glucose intolerance and diabetes.

Materials and Methods

This case-control study was conducted in the Department of Endocrinology of Bangabandhu Sheikh Mujib Medical University (BSMMU) from January to December 2021. The study included 40 young participants (age range: 14-29 years) of both sexes with abnormal glucose tolerance (AGT) comprising both prediabetes and diabetes along with an equal number of age-matched control with normal glucose tolerance (NGT). Cases were defined as having AGT (i.e. pre-diabetes and diabetes) following American Diabetes Association (ADA) 2021 diagnostic criteria.[21] All participants with DM had phenotypically T2DM. They were included by non-probability purposive sampling after matching inclusion and exclusion criteria. Subjects with gestational diabetes, diabetes due to a specific medical condition, drug-induced diabetes and any condition affecting acute phase protein were excluded from the study.

After enrollment, a comprehensive history was taken and each subject underwent a thorough examination. Height was measured using a stadiometer and weight by a calibrated scale to calculate body mass index (BMI). Waist-hip ratio (WHR) and waist circumference (WC) were determined following standard procedure. All the data including demographic, clinical, and laboratory information were recorded in a semi-structured data sheet. Then fasting blood sample (10 ml) was collected, oral glucose tolerance test (OGTT) was performed and hemoglobin A1c (HbA1c) was measured to assign the glycemic status. When the desired number of participants were recruited in one group, recruitment of only the other group was continued. Serum was stored at a temperature of -70^0 C until assay of adiponectin, leptin, resistin, insulin, CRP and TNF-α. Insulin resistance was calculated by homeostasis model assessment (HOMA).

Plasma glucose was estimated by colorimetric assay of the glucose-oxidase method using an automated analyzer (Dimension RxL Max) and HbA1C was analyzed by the NGSP-certified Bio-Rad D-10TM Hemoglobin A1c Program 220-0101, USA. For the assay of fasting Insulin chemiluminescent immunoassay was used (Architect/Beckman coulter).

The measurement of serum adiponectin, leptin, TNF-α and resistin was done by ELISA whereas CRP was by Chemiluminescent test. The lower limits of detection were 3.12 mg/L for CRP and 0.01 pg/ml for resistin whereas other variables could be quantified to their extreme values.

All data were processed by using IBM SPSS Statistics for Windows, Version 25.0 (IBM Corp, Armonk, NY, USA). Results were described in frequencies or percentages for qualitative values and mean (±standard deviation, SD) for quantitative values with normal distribution whereas median and interquartile range (IQR) for skewed distribution. Variables were compared by Chi-square test and unpaired Student's t-test or Mann-Whitney U test as applicable. Adiponectin, leptin and TNF-α were analyzed as numerical values. However, CRP and resistin values were dichotomized using cut-offs of 3.12 and 5.9 pg/ml respectively (Reference). Correlation among variables was analyzed by Spearman or Pearson correlation as appropriate. Multivariate logistic regression analysis was done to adjust the effect of the covariates over prediction of AGT. P-value ≤0.05 was considered statistically significant.

Before the commencement, the study protocol was approved by the Institutional Review Board, BSMMU, and informed written consent/assent was obtained from the participants or their guardians.

Results

The median age of the participants was 26 years (IQR 23-28) and 42 (52.5%) were female. There was no significant difference between the AGT and NGT group in respect of age, gender, BMI, BP, or family history of DM (n=ns for all). AGT group had significantly higher WHR in comparison to the NGT group (AGT vs. NGT 0.94±0.09 vs. 0.89±0.08, p=0.013). WC was also elevated in the AGT group (p=0.051) (table I).

The median TNF-α, leptin, and adiponectin were similar in both groups (p=0.142, p=0.655, and p=0.246 respectively). The frequency of participants with elevated resistin and CRP was similar in both groups (p=0.820 for both) (table II).

TNF-α positively correlated with BMI in AGT (r=0.354, p=0.025) but not in NGT (p=0.301). There was no significant correlation of TNF-α with WC and WHR in any groups (p=NS for all). Leptin showed positive correlations with BMI (AGT r=0.760, p<0.001, NGT 0.675, p<0.001) and WC (AGT r=0.675, p<0.001, NGT 0.493, p=0.001) but not with WHR in any of the groups (p=NS for both). Adiponectin had no correlation with BMI or WC in any groups or with WHR in the AGT group (p=NS for all). But it had a significant negative correlation with WHR in the NGT group (r=-413, p=0.008). CRP had a significant positive correlation with BMI and WC in the NGT group (BMI: 0.579, p<0.001; WC: 0.553, p<0.001) but not in AGT (p=NS for all). There was no significant correlation of CRP with WHR in any of the groups (p=NS for all). Resistin had no significant correlation with BMI or WC in any of the groups or with WHR in the NGT group (p=NS for all). But there was a significant negative correlation of WHR with resistin in the AGT group (r=-0.607, p=0.003) (table III).

Table I: Characteristics of the study subjects (n=80)

Variables	All subjects	AGT	NGT	P
n	80	40	40	
Age (years, median and IQR)	26 (23-28)	26 (24-29)	25 (22-28)	0.241
Gender				
Male	38 (47.5)	16 (40.0)	22 (55.0)	0.179
Female	42 (52.5)	24 (60.0)	18 (44.0)	
BMI (kg/m^2, mean±SD)	26.8±5.6	27.7±5.5	25.8±5.5	0.124
WC (cm, mean±SD)	91.1±13.4	94.1±13.1	88.1±14.4	0.051
WHR (mean±SD)	0.92±0.09	0.94±0.09	0.89±0.08	0.013
SBP (mmHg, median & IQR)	110 (110-130)	110 (110-120)	120 (110-130)	0.463
DBP (mmHg, median & IQR)	80 (80-90)	80 (80-90)	80 (72-90)	0.877
Family history of DM in 1st degree relatives	46 (57.5)	24 (60.0)	16 (40.0)	0.499

Data were expressed as frequency and percentage over column total if not mentioned otherwise
p-values stand for comparison between AGT and NGT groups by Student's t-test, Mann Whitney U test or ÷2-test as applicable
AGT: abnormal glucose tolerance; NGT: normal glucose tolerance; BMI: body mass index; WC: waist circumference; WHR: waist hip ratio; SBP: systolic blood pressure; DBP: diastolic blood pressure

Table II: Adipokines and inflammatory markers in AGT and NGT

Variables	AGT(n=40)	NGT(n=40)	P
TNF-α (pg/ml)	14.85 (12.20-19.15)	13.25 (10.90-17.18)	0.142
Leptin (ng/ml)	10.75 (5.06-15.05)	8.14 (2.96-17.00)	0.655
Adiponectin (ng/ml)	7.40 (5.93-10.60)	8.32 (6.76-10.44)	0.246
Resistin (pg/ml)			
<5.9	24 (60.0)	23 (57.5)	0.820
≥5.9	16 (40.0)	17 (42.5)	
CRP (mg/L)			
<3.12	23 (57.5)	24 (60.0)	0.820
≥3.12	17 (42.5)	16 (40.0)	

Data were expressed as mean±SD (if normally distributed) or median followed by interquartile range in parentheses (if skewed)
‡Comparison between groups done by Mann-Whitney U test
DM: diabetes mellitus; NGT: normal glucose tolerance; TNF-α: tumor necrosis factor-á; CRP: C-reactive protein

Table III: Correlations of cytokines and inflammatory markers with BMI, WC, and WHR

Determinants of 'r'	AGT		NGT	
	r	p	r	p
TNF-α vs. BMI	0.354	0.025	0.168	0.301
TNF-α vs. WC	0.236	0.143	0.127	0.434
TNF-α vs. WHR	-0.006	0.972	0.104	0.521
Leptin vs. BMI	0.760	<0.001	0.675	<0.001
Leptin vs. WC	0.675	<0.001	0.493	0.001
Leptin vs. WHR	0.176	0.278	0.051	0.753
Adiponectin vs. BMI	0.066	0.686	0.011	0.948
Adiponectin vs. WC	0.163	0.315	-0.174	0.283
Adiponectin vs. WHR	0.090	0.580	-0.413	0.008
CRP vs. BMI	0.357	0.103	0.579	<0.001
CRP vs. WC	0.212	0.345	0.553	<0.001
CRP vs. WHR	-0.022	0.923	0.252	0.117
Resistin vs. BMI	-0.043	0.850	-0.156	0.338
Resistin vs. WC	-0.385	0.077	-0.180	0.267
Resistin vs. WHR	-0.607	0.003	-0.024	0.883

by Pearson's and Spearman correlation coefficient test as applicable
AGT: abnormal glucose tolerance; NGT: normal glucose tolerance; BMI: body mass index; WC: waist circumference; WHR: waist-hip ratio; TNF-α: tumor necrosis factor-á; CRP: C-reactive protein

No adipokines or inflammatory cytokines assessed in the study had any significant correlation to any of the glycemic parameters in NGT group (p=NS for all). In AGT group, TNF-á, adiponectin or resistin had no significant correlation (p=NS for all); but leptin was negatively correlated to all the glycemic parameters (FPG: r=-0.405, p=0.010; 2hPG: r=-0.431, p=0.006; HbA1c: r=-0.399, p=0.011) and CRP with only 2hPG (r=-0.490, p=0.021) (table IV).

There was no significant correlation of TNF-á with either fasting insulin or IR in any of the groups (p=NS for all). Leptin was positively correlated to both fasting insulin and IR in AGT (r=0.545, p<0.001 & r=0.337, p=0.034 respectively) but not in NGT (p=NS for both). Conversely, Adiponectin was negatively correlated and CRP was positively correlated to both fasting insulin and IR in NGT (Adiponectin: r=-0.350, p=0.027 & r=-0.352, p=0.026 respectively; CRP r=0.318, p=0.045

& r=0.323, p=0.042) but not in AGT (p=NS for all). Resistin was negatively correlated with IR in NGT (r=-0.340, p=0.032). But relationship with fasting insulin in both groups and with fasting insulin in NGT was not significant (p=NS for all) (table V).

A binary logistic regression model adjusted for age, BMI, WC and WHR revealed none of the cytokines or inflammatory markers assessed in the study were independent predictor of AGT in youth (table VI).

Table IV: Correlations of cytokines and inflammatory markers with glucose profile during 75gm OGTT

Determinants of 'r'	AGT		NGT	
	r	p	r	p
TNF-α vs. FPG	0.132	0.416	-0.071	0.664
TNF-α vs. 2hPG	0.085	0.601	-0.237	0.140
TNF-α vs. HbA1c	0.123	0.451	0.177	0.274
Leptin vs. FPG	-0.405	0.010	-0.047	0.773
Leptin vs. 2hPG	-0.431	0.006	0.072	0.658
Leptin vs. HbA1c	-0.399	0.011	-0.066	0.684
Adiponectin vs. FPG	-0.210	0.193	0.068	0.677
Adiponectin vs. 2hPG	-0.274	0.088	-0.215	0.183
Adiponectin vs. HbA1c	-0.284	0.076	0.003	0.984
CRP vs. FPG	-0.139	0.536	-0.016	0.924
CRP vs. 2hPG	-0.490	0.021	0.066	0.684
CRP vs. HbA1c	-0.125	0.581	-0.011	0.946
Resistin vs. FPG	0.017	0.939	-0.291	0.069
Resistin vs. 2hPG	-0.172	0.445	-0.048	0.768
Resistin vs. HbA1c	-0.009	0.970	-0.199	0.219

by Pearson's and Spearman correlation coefficient test as applicable
OGTT: oral glucose tolerance test; DM: diabetes mellitus; NGT: normal glucose tolerance; FPG: fasting plasma glucose; 2hPG: plasma glucose 2-hour after OGTT; TNF-α: tumor necrosis factor-á; CRP: C-reactive protein

Table V:Correlations of cytokines and inflammatory markers with fasting insulin and IR

Determinants of 'r'	AGT		NGT	
	r	p	r	p
TNF-α vs. Fasting insulin	0.192	0.234	-0.121	0.459
TNF-α vs. IR	0.256	0.110	-0.110	0.500
Leptin vs. Fasting insulin	0.545	<0.001	0.213	0.188
Leptin vs. IR	0.337	0.034	0.209	0.195
Adiponectin vs. Fasting insulin	-0.108	0.506	-0.350	0.027
Adiponectin vs. IR	-0.229	0.155	-0.352	0.026
CRP vs. Fasting insulin	0.401	0.065	0.318	0.045
CRP vs. IR	0.342	0.119	0.323	0.042
Resistin vs. Fasting insulin	-0.009	0.970	-0.300	0.060
Resistin vs. IR	-0.009	0.970	-0.340	0.032

by Pearson's and Spearman correlation coefficient test as applicable
IR: insulin resistance (measured by Homeostasis Model Assessment – HOMA); DM: diabetes mellitus; NGT: normal glucose tolerance; TNF-α: tumor necrosis factor-α; CRP: C-reactive protein

Table VI: Binary multivariate logistic regression for prediction of AGT

Variables	OR (95% CI)	p
TNF-á (per unit increase)	0.98 (0.84-1.14)	0.795
Leptin (per unit increase)	1.00 (0.90-1.11)	0.989
Adiponectin (per unit increase)	1.11 (0.90-1.34)	0.322
Resistin (e”5.9 pg/ml)	0.85 (0.18-3.98)	0.839
CRP (e”3.12 mg/l)	0.69 (0.18-2.70)	0.591

AGT: abnormal glucose tolerance; TNF-α: tumor necrosis factor-α, CRP: C-reactive protein

Discussion

The present study investigated subjects with AGT and an equal number of NGT who were statistically similar in age and gender. BMI was found similar in two groups though the WHR was significantly high and WC was near significantly high in AGT group. When we tried to see the impact of inflammatory cytokines (TNF-alpha and CRP), and adipokines (leptin, adiponectin and resistin) over glucose intolerance, we could not find any significant difference in levels of these markers between AGT and NGT groups.

Hyperglycemia and obesity are believed to be associated with low-grade inflammation and raised inflammatory markers. Several studies have found higher levels of TNF-α and CRP in patients with glucose intolerance and/or obesity which are mostly associated with insulin resistance rather than insulin secretory defect. Some studies have also found a positive correlation of TNF-α and CRP with BMI, plasma glucose levels and HbA1c.[18,19,22] In our study, the inflammatory cytokine, TNF-α was not significantly different in the AGT group in comparison to NGT. We have previously observed similar findings in the young diabetic Bangladeshi population.[23] TNF-α positively correlated with BMI in AGT but not in NGT. We did not find any positive correlation of TNF-α with insulin resistance (IR) which may be attributable to the lack of a positive correlation with WC or WHR. It raises the possibility that TNF-α may be better associated with obesity after the onset of the process of AGT. The CRP was also found similar in AGT and NGT groups. But interestingly, CRP positively correlated with BMI, WC, WHR, and IR in NGT. It reflects a better association of inflammatory markers with obesity when glucose intolerance is yet to manifest.[24] In correlation of different points of OGTT with TNF-α and CRP, no significant positive correlations were found except finding of a significant negative correlation of 2-hr plasma glucose with CRP which is contradictory to other study reports.[25,26]

The study of leptin showed a statistically similar level in AGT and NGT. In both groups, it positively correlated with obesity and insulin, which is in agreement with other studies.[13-15] Leptin is generally known as an anti-obesity hormone but excessive adipose tissue is paradoxically associated with very high leptin levels and leptin resistance.[15] The association of leptin with glucose homeostasis is not well understood but it is thought to be independent of body weight. According to recent research, leptin is more effective at controlling blood glucose levels than it is in suppressing appetite.[27] This is reflected in our study, as we found all the glycemic parameters to be negatively correlated with leptin in AGT.

The available literatures on resistin have been shown to be associated with insulin resistance, defective insulin signaling, obesity, and T2DM.[16,28] This association is evident in an animal model but not clear in humans.[8] The present study found similar levels of resistin in AGT and NGT. Moreover, resistin showed no significant correlation either with metabolic parameters like BMI and WC or blood glucose levels in any of the groups. Although, in a systematic literature search done in 2019 resistin levels in those with hyper-resistinemia, but not in those with normal circulating resistin levels, were strongly linked with insulin resistance, T2DM, and obesity.[29] The negative correlation of resistin to IR and WHR in AGT only in present study may need further study with a larger sample.

Serum adiponectin is found lower in obesity despite being released from adipocytes and low adiponectin is associated with decreased insulin sensitivity and glucose intolerance.[30] In our study, adiponectin was found similar in AGT and NGT. There was no correlation of adiponectin with BMI, WC, and WHR in the AGT group. Interestingly, in the NGT group, a significant negative correlation was found with WHR.

Similarly, adiponectin was also negatively correlated to both fasting insulin and IR in NGT but not in AGT. A negative correlation of adiponectin with blood glucose levels is reported in literature.[11,30] Surprisingly, no significant correlation was found between glycemic values and adiponectin in any of the groups. As lower adiponectin is associated with insulin resistance, plasma glucose would have been expected to be related negatively.

Finally, Adipokines and inflammatory markers are reported to be associated with insulin resistance and the onset of DM.[8] In the present study, we observed some association of cytokines with obesity and insulin resistance but could not demonstrate any significant impact. However, it should be mentioned that the number of participants was a bit limited though statistically not too small; should it be increased to a satisfactory number of subjects, the results might have explored the outcome more cle,arly especially about relationships of positive or inverse trend.

Conclusions

The serum levels of cytokines were not significantly different and none of the circulating cytokines were observed to have an independent impact on the development of abnormal glucose tolerance in young.

Informed consent

Informed written consent was taken from the participant or their legal guardian (if required) before enrollment.

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