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Brief communication (Original)

Higher plasma C-reactive protein and lower plasma adiponectin are associated with increased carotid artery intima-media thickness in patients with impaired glucose regulation

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Background: Impaired Glucose Regulation (IGR) is a term that refers to blood glucose levels that are higher than the normal range, but lower than Type 2 diabetes mellitus (T2DM).
Objective: We aimed to test the role of plasma adiponectin (APN) and plasma C-reactive protein (CRP) in predicting the risk of cardiovascular disease in patients with different degrees of impaired glucose regulation (IGR).
Methods: A total of 210 outpatients for physical examination were divided into 4 groups: 42 cases of normal glucose tolerance (NGT), 36 cases of impaired fasting glucose (IFG), 92 cases of impaired glucose tolerance (IGT) and 40 cases of IFG+IGT. Body mass index (BMI), blood pressure, lipids, insulin resistance (homeostasis model assessment, HOMA-IR), APN, CRP and carotid intima-media thickness (CIMT) were measured.
Results: In IGT and IFG+ IGT groups, CIMT and CRP were significantly higher, whereas APN was significantly lower compared with IFG and NGT groups ($p < 0.05$). BMI and HOMA-IR were significantly higher in IGR patients compared with control subjects ($p < 0.05$). CIMT was positively related to CRP and HOMA-IR and negatively to APN ($p < 0.05$). Multiple stepwise regression analysis using CIMT as a dependent variable showed that APN and 2hPG were independently risk factors associated with CIMT.
Conclusion: Increased CIMT in prediabetes state may in part be explained by lower plasma adiponectin and higher C-reactive protein levels.

Keywords: Adiponectin, carotid intima-media thickness, C-reactive protein, fasting plasma glucose, impaired glucose regulation, impaired glucose tolerance

Abbreviations
APN = Adiponectin
CIMT = Carotid artery intima-media thickness
CRP = C-reactive protein
DBP = Diastolic blood pressure
FIN = Fasting insulin
FPG = Fasting plasma glucose
HDL-c = High density lipoprotein cholesterol
HOMA-IR = Homeostasis model assessment of insulin resistance
IFG = Impaired fasting glucose
IGR = Impaired glucose regulation
IGT = Impaired glucose tolerance
LDL-c = Low density lipoprotein cholesterol
Lpa = Lipoprotein
NGT = Normal glucose tolerance
SBP = Systolic blood pressure
TC = Total cholesterol
TG = Triglyceride
T2DM = Type 2 diabetes mellitus
2hPG = 2 hours postprandial blood glucose;

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Impaired Glucose Regulation (IGR) is a term that refers to blood glucose levels that are higher than the normal range, but lower than Type 2 diabetes mellitus (T2DM) [1]. It is the name given to the two conditions called impaired fasting glucose (IFG) and impaired glucose tolerance (IGT), which are intermediate states of abnormal glucose regulation that exist between normal blood glucose levels and T2DM [2]. IFG and IGT can occur as mutually exclusive conditions (isolated IFG or isolated IGT) or they can occur in combination (combined IFG and IGT) [3]. Epidemiological studies in North America, Europe, and Asia show that approximately 15 percent of adults have either IFG or IGT based on the World Health Organization criteria [4, 5], of which an estimated 5 to 12 percent develop Type 2 diabetes annually [6].

The etiological role of adiponectin (APN) in insulin resistance (IR), low grade and cardiovascular disease

(CVD) is increasingly recognized. APN is a novel hormone made by fat tissue, which regulates energy metabolism and endothelial activation [7]. APN has been suggested to play anti-inflammatory and antiatherogenic roles in the development of low grade inflammation and atherosclerosis, with potential as a new pharmacological treatment modality for the metabolic syndrome and T2DM [8]. Plasma APN levels are inversely related to insulin resistance, and to plasma C-reactive protein (CRP) [9, 10]. It is noted that the risk of cardiovascular disease is no longer limited to T2DM, but extends to the prediabetes stage. Individuals with IGR have shown evidence of microvascular and macrovascular complications [11-13]. They have an unfavorable cardiovascular risk profile compared with healthy people and therefore have a higher rate of cardiovascular disease and mortality [14-16]. However, limited literature data investigate the role of APN in predicting the risk of CVD.

The carotid intima-media thickness (CIMT) is an established predictor of CVD and stroke in older subjects [17] and has been widely used to reflect the cardiovascular risk in T2DM [18-20]. The present study was conducted to investigate the role of APN and CRP in predicting macrovascular complications by measuring the levels of APN, CRP, and CIMT in patients with different degrees of IGR.

Materials and methods

Clinical materials

This study was approved by the Hospital Ethics Committees and all participants provided written informed consent. A total of 210 outpatients were recruited for physical examination and performed an oral glucose tolerance test (OGTT). The subjects were divided into 4 groups using glucose cut-off values as defined by the World Health Organization in 1999: 42 cases of NGT (FPG < 6.1 mmol/l and 2hPG < 7.8 mmol/l), 36 cases of IFG (6.1mmol/l ≤ FPG ≤ 6.9 mmol/l and 2hPG < 7.8mmol/l), 92 cases of IGT (FPG < 7mmol/l and 7.8mmol/l ≤ 2hPG < 11.1 mmol/l), and 40 cases of IFG+IGT (6.1mmol/l ≤ FPG ≤ 6.9 mmol/l and 7.8mmol/l ≤ 2hPG < 11.1 mmol/l). The IGT group was further divided into IGT1 (7.8mmol/L ≤ 2hPG < 10.0mmol/L, 44 cases) and IGT2 (10.0mmol/L ≤ 2hPG < 11.1mmol/L, 48 cases). Clinically manifest cardiac, liver or renal function abnormalities, thyroid disorders, cardiovascular disease, acute metabolic disorder, heart failure, infection, autoimmune diseases, connective tissue disease and tumor were exclusion criteria. Patients using drugs that influence insulin secretion or insulin resistance were also excluded.

Methods

All participants were tested using the OGTT at 8 AM after an overnight fast, using a glucose oxidase method on an automatic biochemistry analyzer (Beckman, USA). Fasting triglyceride (TG), total cholesterol (TC), high density lipoprotein cholesterol (HDL-c), low density lipoprotein cholesterol (LDL-c) and lipoprotein (Lpa) were measured simultaneously. Plasma total APN was assayed using radioimmunoassay with commercially available kits, according to the manufacturer's instructions (Linco Research, USA). Fasting insulin (FIN) and CRP were determined by an ELISA method (BioCheck, USA). Systolic and diastolic blood pressure were measured after 15 min rest using a sphygmomanometer in a sitting position. Body mass index (BMI) was calculated as weight divided by height squared (kg/m^2). Homeostasis model assessment was taken as a measure of insulin resistance (homeostasis model assessment; HOMA-IR) using the equation: fasting plasma insulin × glucose/22.5 [21].

Carotid intima-media thickness measurement

CIMT was measured by ultrasonography in the supine position. The CIMT was defined as the distance between the outer edges of calcification (actually this leaves out most of the media) and the outer edges of an angiographic dye column within the artery lumen. Left and right common carotid artery, internal and external carotid artery were scanned. Three arterial wall segments in each carotid artery were imaged: the segment 1 cm distal to the flow divider (common carotid artery), the segment of the initiating terminal of internal carotid artery and the segment between the carotid dilatation and carotid flow divider (carotid bulb). Each segment was measured 3 times and the averaged value was designated as CIMT. This measurement was conducted by a well-trained sonographer.

Statistical analysis

Data were analyzed using SPSS version 11.0 software and the results were expressed as mean value ± standard deviations. Pair-wise comparison was performed using one-way ANOVA and Student's

t test. Differences in proportions of variables were determined by a χ^2 analysis. Multiple stepwise regression analysis and a Pearson correlation test were used to disclose relationships between variables. Two-sided *p* values < 0.05 were considered significant.

Results

Pair-wise comparison among patients with IGR and control subjects

As shown in **Table 1**, age, gender, TC, TG, HDL-c, LDL-c, Lpa, FIN, positive rate of hypertension, and smoking rate were not statistically significant different among the groups ($p > 0.05$). BMI was higher in IGT and IFG+IGT groups compared with the NGT and IFG groups ($p < 0.05$). FPG and 2hPG levels in the NGT group was significantly lower than those in other groups ($p = 0.000$). FPG level in the IFG group was higher than that in the IGT group ($p = 0.000$), while not statistically different from that in the IFG+IGT group ($p = 0.511$). The 2hPG level in the IFG group was significantly lower than that in the IGT and IFG+IGT groups ($p = 0.000$). The IGT group and IGT+IFG group were significantly different on FPG level ($p = 0.000$), while not significantly different on the 2hPG level ($p = 0.327$). HOMA-IR in the NGT group was significantly lower than that in the IGR groups ($p = 0.000$), while not statistically different among these three groups ($p > 0.05$). Plasma APN levels in the IGT and IFG+ IGT groups were significantly lower than that in the IFG group ($p = 0.013$ and $p = 0.002$, respectively) and NGT group ($p = 0.004$ and $p = 0.000$, respectively); however, there was no statistical difference between the IGT and IFG+IGT groups ($p = 0.419$). Although the plasma APN level in the NGT group were higher than that in the IFG group, there was no statistical difference ($p = 0.779$). Plasma CRP levels in the IGT and IFG+IGT groups were significantly higher than that in the IFG group ($p = 0.037$ and $p = 0.011$, respectively) and NGT group ($p = 0.000$). CRP level in the IFG group was significantly higher than that in the NGT group ($p = 0.037$) and not statistically different between the IGT group and IFG+IGT groups ($p = 0.583$).

Table 1. Clinical characteristics, mean carotid artery intima-media thickness (CIMT), adiponectin (APN), and C-reactive protein (CRP) in impaired glucose regulation (IGR) patients and control subjects

	NGT	IFG	IGT	IFG+IGT
Patients	n = 42	n = 36	n = 92	n = 40
Age (years)	60.3 ± 10.9	62.8 ± 8.2	61.5 ± 9.9	61.0 ± 9.5
Gender (M/F)	23/21	20/16	54/38	25/15
BMI (kg/m^2)[a]	22.1 ± 1.6	22.8 ± 1.3	24.3 ± 1.8**#	24.0 ± 1.9**#
SBP (mmHg)	131.3 ± 7.6	134.6 ± 7.1	136.4 ± 6.4	138.6 ± 6.7
DBP (mmHg)	73.2 ± 8.0	73.9 ± 6.7	75.1 ± 6.8	76.9 ± 7.6
Smoking (%)[b]	35.6	37.8	37.5	42.2
Hypertension (%)[b]	47.5	48.9	50.3	52.0
TG(mmol□L^{-1})[a]	1.78 ± 1.25	1.90 ± 1.86	1.70 ± 1.38	1.96 ± 1.29
TC(mmol□L^{-1})[a]	4.85 ± 1.04	4.60 ± 1.14	4.45 ± 0.99	4.89 ± 1.02
HDL-c (mmol L^{-1})[a]	1.08 ± 0.26	1.12 ± 0.37	1.01 ± 0.23	1.27 ± 0.86
LDL-c(mmol□L^{-1})[a]	2.94 ± 0.81	2.69 ± 0.92	2.63 ± 0.73	2.93 ± 0.78
Lpa(mmol□L^{-1})[a]	20.24 ± 6.48	20.00 ± 4.80	26.43 ± 8.58	19.23 ± 5.95
FPG(mmol□L^{-1})[a]	5.02 ± 0.47	6.39 ± 0.29**	5.35 ± 0.42**#	6.33 ± 0.22**
2hPG(mmol□L^{-1})[a]	6.65 ± 0.71	7.48 ± 0.61**	9.53 ± 0.79**##	9.48 ± 0.73**##
FIN(mU□L^{-1})[a]	12.65 ± 1.97	12.06 ± 1.63	15.20 ± 3.71	13.21 ± 2.67
HOMA-IR[a]	2.83 ± 0.58	3.42 ± 0.46**	3.60 ± 0.85**	3.73 ± 0.82**
APN(ng□ml^{-1})[a]	12.15 ± 3.85	11.92 ± 2.94	9.95 ± 3.58*#	9.33 ± 3.57**#
CRP(mg□L^{-1})[a]	5.78 ± 1.69	6.51 ± 1.27*	7.23 ± 1.37**#	7.41 ± 1.73**#
CIMT	0.76 ± 0.09	0.79 ± 0.13	0.84 ± 0.11*	0.88 ± 0.10**#

Data are expressed as mean value ± standard deviations. NGT, normal glucose tolerance; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; BMI, body mass index; SBP, systolic blood pressure; DBP , diastolic blood pressure; TG, triglyceride; TC, total cholesterol; HDL-c, high density lipoprotein cholesterol; LDL-c, low density lipoprotein cholesterol; Lpa, lipoprotein; FPG, fasting plasma glucose; 2hPG, 2 hours postprandial blood glucose; FIN, fasting insulin; HOMA-IR, homeostasis model assessment of insulin resistance; APN, adiponectin; CRP, C-reactive protein; CIMT, carotid intima-media thickness. a: ANOVA analysis; b: χ^2 analysis; $^{*}p < 0.05$, $^{**}p < 0.01$ compared with the NGT group, $^{\#}p < 0.05$, $^{\#\#}p < 0.01$ compared with the IFG group

When comparing CIMT, the NGT group was significantly lower than the IGT and IFG+IGT groups (p = 0.001 and p = 0.000) and the IFG group was also significantly lower than IFG+IGT group (p = 0.000), while not statistically different from the IGT group (p = 0.071). Besides, there was no significant difference between the IGT and IFG+IGT groups (p = 0.419) or the IFG and NGT groups (p = 0.181).

Further investigation in IGT patients

To further investigate the role of APN and CRP in predicting the risk of CVD, we divided the IGT into two groups. As shown in **Table 2**, there were no statistical differences between the IGT1 and IGT2 groups on FPG, TC, TG, HDL-c, LDL-c, Lpa, FIN, BMI, HOMA-IR, or CRP levels ($p > 0.05$). The two groups were only significantly different on 2hPG, CIMT, and APN levels (p = 0.000, p = 0.008 and p = 0.015).

Correlation analysis

CIMT was positively related to BMI (r = 0.472, p = 0.000), HOMA-IR (r = 0.364, p = 0.000) and CRP (r = 0.339, p = 0.000), but inversely with plasma APN (r = –0.344, p = 0.000). Plasma APN was inversely associated with CRP (r = –0.576, p = 0.000), HOMA-IR (r = –0.560, p = 0.000), 2hPG (r = –0.454, p = 0.000) and CIMT (r = –0.344, p = 0.000). CRP was positively related to BMI (r = 0.591, p = 0.000), HOMA-IR (r = 0.591, p = 0.000) and CIMT (r = 0.339, p = 0.000), but inversely with plasma APN (r = –0.576, p = 0.000).

Multiple stepwise regression analysis

To disclose which variables could explain the higher CIMT in IGR patients, we performed multiple stepwise regression analysis using the combining data from IGR patients and the control subjects. In the first analysis, CIMT was defined as a dependent variable, APN, CRP, BMI, HOMA-IR, TG, TC, HDL-c, LDL-c, FPG, FIN, 2hPG, blood pressure, and smoking were defined as continuous variables. An F test showed the regression equation was statistically significant (F = 23.681, p = 0.000). This analysis suggested that the independent risk factors associated with CIMT were APN and 2hPG. In the second analysis, APN was defined as a dependent variable, CRP, BMI, HOMA-IR, TG, TC, HDL-c, LDL-c, FPG, FIN, 2hPG, blood pressure and smoking were continuous variables. The F test showed that the regression equation was also statistically significant (F = 145.185, p = 0.000). This analysis showed that APN was independent associated with BMI and CRP. Finally, CRP was defined as a dependent variable, APN, BMI, HOMA-IR, TG, TC, HDL-c, LDL-c, FPG, FIN, 2hPG, Lpa, blood pressure and smoking were defined as continuous variables. The regression equation was statistically significant (F = 49.399, p = 0.000) and result showed that CRP was independent associated with BMI and APN.

Table 2. Clinical characteristics, mean carotid artery intima-media thickness (CIMT), adiponectin (APN), and C-reactive protein (CRP) in impaired glucose tolerance patients

Clinical indicator	IGT1 (n = 44)	IGT2 (n = 48)
BMI (kg/m^2)	23.57 ± 1.48	24.22 ± 2.02
FPG(mmol□L^{-1})	5.38 ± 0.38	5.33 ± 0.46
2hPG(mmol□L^{-1})	8.71 ± 0.49	10.35 ± 0.33**
TG(mmol□L^{-1})	1.84 ± 1.08	1.61 ± 0.58
TC(mmol□L^{-1})	4.49 ± 0.70	4.41 ± 1.16
HDL(mmol□L^{-1})	1.01 ± 0.22	1.01 ± 0.23
LDL(mmol□L^{-1})	2.52 ± 0.67	2.70 ± 0.78
Lpa(mmol□L^{-1})	33.40 ± 7.13	21.78 ± 8.26
FIN(mU□L^{-1})	14.24 ± 2.50	15.84 ± 4.26
HOMA-IR	3.41 ± 0.64	3.73 ± 0.96
APN(ng□ml^{-1})	11.51 ± 3.69	8.91 ± 3.15*
CRP(mg□L^{-1})[a]	7.10 ± 1.54	7.31 ± 1.27
CIMT	0.80 ± 0.10	0.89 ± 0.11*

Data are expressed as mean value ± standard deviations. a: ANOVA analysis; b: χ^2 analysis; $^{*}p < 0.05$, $^{**}p < 0.01$ compared to NGT group; $^{\#}p < 0.05$, $^{\#\#}p < 0.01$ compared with the IFG group

Discussion

Impaired Glucose Regulation (IGR) is the intermediate state of abnormal glucose regulation that exists between normal blood glucose levels and T2DM [2] and has been regarded as a risk factor for cardiovascular disease (CVD). It has been demonstrated that insulin resistance and impaired insulin secretion in pancreatic β cells exist in IGR patients, especially in IGT patients. Aydin et al. suggest that IGT is more sensitive than IFG for identifying people who will develop CVD [22]. IFG and IGT are both strong risk markers for the development of CVD, with the highest risk in people with combined IFG and IGT.

CIMT is an established predictor of CVD. Previous studies have demonstrated that increases in the thickness of CIMT are directly associated with an increased risk of CVD [17, 23]. In this study, we found that CIMT increases gradually from NGT to IFG+ IGT, with IFG and IGT between them. Our result was consistent with previous studies. Further, we divided IGT patients into two groups using cut-off value of 10 mmol/l of 2hPG and found that CIMT was significantly increased when 2hPG ≥ 10 mmol/l. This result confirmed that IGT, not IFG, may be an independent risk factor for CVD throughout the glucose intolerance continuum. Moreover, our result suggested that the risk of developing CVD would be significantly reduced if we kept the 2hPG below 10mmol/l. Similarly, Karasik et al. suggest postprandial hyperglycemia is particularly deleterious to vascular function and pharmacological intervention to deduce postprandial hyperglycemia can significantly decrease the risk of cardiovascular events in individuals with IGT or T2DM [24].

IR typically characterizes type 2 diabetes and prediabetic states and is a prominent feature of metabolic syndrome. APN is specifically expressed and produced in adipocytes and plays an important part in glucose metabolism and insulin resistance [25]. Previous studies have demonstrated that APN levels are inversely related to IR [9, 26]. There is worsening IR as well as progressive impairment of insulin secretion (or β-cell dysfunction) in people with IFG, IGT and T2DM [27]. In our study, the HOMA-IR increased in the progression NGT – IFG – IGT – IFG+IGT. Pair-wise comparison showed that HOMA-IR was higher in IGR patients than that in NGT subjects and no statistical difference was found among the three IGR groups. This result was partly inconsistent with the study of Ferrannini et al. which reports that IR is higher in IGT patients than that in IFG patients and the difference between IGT and IFG+IGT was not statistical significance using the hyperglycemic clamp technique (HGCT) [28]. As HOMA-IR is a measurement of insulin sensitivity in a fasting state, we think it may be unsuited to assess the extent of IR in IGR patients. In addition, we found that the plasma APN level was inversely associated with HOMA-IR and the APN was decreased gradually in the progression NGT – IFG – IGT – IFG+IGT. Pair-wise comparison showed that plasma APN levels in IGT and IFG+ IGT groups were significantly lower than that in the IFG group and NGT group, and there was no statistically difference between the IGT and IFG+IGT groups. Further investigation in IGT found that the plasma APN level in IGT2 group was lower than that in the IGT1 group, while HOMA-IR showing no statistical difference between these groups. The APN level seems more consistent with the criterion of HGCT to assess the extent of IR in IGR patients. Besides, the decline of APN exists in the early stage of IR, and the downtrend is parallel to the disease progression. Therefore, some researchers suggest plasma APN level as the indicator of the extent of IR in IGR patients. Our study showed that a low level of plasma APN may predict the extent of IGR and IR. Moreover, the predictive role of APN for CVD was even more significant than CRP when 2hPG ≥ 10 mmol/l. It may be necessary to refocus therapy to improve plasma APN levels to effectively reduce cardiovascular risk in the IGT population.

A correlation analysis showed that plasma APN level was inversely associated with CRP, 2hPG and CIMT. This result indicated that APN was associated with CVD risk factors, such as inflammatory mediators, and dyslipidemia. That is, plasma APN level was closely related to the initiation and progression of IGR and CVD. Further, regression analysis showed that plasma APN level was an independent risk factor associated with CIMT, which consistent with previous findings [29]. The IGT1 and IGT2 groups were only different on CIMT, APN level and 2hPG level. These results further confirm that low plasma APN level may be more sensitive for predicting the CVD risk and progression. Therefore, we propose a hypothesis that APN level is linked to T2DM, CVD, hypertension, adiposity, and IR.

CRP is protein found in the blood, the levels of which rise in response to inflammation. Previous

research suggests that patients with elevated basal levels of CRP are at an increased risk of T2DM [30, 31]. A recent study conducted by Shahid et al. shows that highly-sensitive CRP is associated with coronary artery disease in T2DM [32]. In this study, the CRP level was increasing as the risk for CVD increased (NGT – IFG – IGT – IFG+IGT). Statistical analysis showed that the CRP level was significantly different between the NGT group and the other groups, and that furthermore, the CRP level in IFG group was significantly different from the IGT and IFG+IGT groups. This result indicates that CRP is more sensitive than APN in IFG patients. However, further investigation in IGT patients found that there was no statistical difference between the IGT1 group and IGT2 group, although CRP level was increased. A correlation analysis showed that CRP is positively related to CIMT and inversely with APN. However, CRP is not an independent risk factor associated with CIMT. These results suggested that the role of the CRP level to predict the risk of CVD is weaker than APN, although it is probably involved in the progression of CVD.

In conclusion, increased CIMT in a prediabetes state was associated with lower plasma adiponectin and higher C-reactive protein levels. CRP and APN may be considered optional markers for better prediction of cardiovascular risk in IGR patients. Intervention to deduce postprandial hyperglycemia below 10mmol/l can significantly decrease the risk of cardiovascular events in patients with IGR.

The authors have no conflicts of interest to report in this study.

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