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Original article

Correlations of insulin function with levels of adipocyte fatty acid-binding protein and serum uric acid in patients with newly diagnosed type 2 diabetes mellitus and abdominal obesity

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Abstract. *Aim:* To explore the correlations of insulin function with the levels of adipocyte fatty acid-binding protein (A-FABP) and serum uric acid (SUA) in patients with newly diagnosed type 2 diabetes mellitus (T2DM) with abdominal obesity. *Methods:* A total of 218 newly diagnosed T2DM patients were divided into abdominal obesity (n=98) and non-abdominal obesity groups (n=120) according to waist circumference. Their baseline clinical data, laboratory indices, A-FABP and SUA levels, homeostasis model assessment of insulin resistance (HOMA-IR) and HOMA-β were compared. The correlations of HOMA-IR with A-FABP, SUA levels and HOMA-β were subjected to Pearson's analysis. The risk factors for IR were explored by logistic regression analysis. *Results:* The abdominal obesity group had significantly higher body mass index (BMI), waist circumference, waist-to-hip ratio, diastolic blood pressure and systolic blood pressure than those of non-abdominal obesity group (P<0.05). Compared with non-abdominal obesity group, the abdominal obesity group had higher levels of very low-density lipoprotein-cholesterol, low-density lipoprotein-cholesterol, triglyceride (TG), total cholesterol, aspartate aminotransferase, alanine aminotransferase and fasting serum insulin (P<0.05), and lower high-density lipoprotein-cholesterol level (P<0.05). The abdominal obesity group had higher HOMA-IR, HOMA-β and A-FABP, SUA levels than those of non-abdominal obesity group (P<0.05). HOMA-IR was positively correlated with A-FABP, SUA levels and HOMA-β (P<0.0001). BMI, waist circumference, as well as TG, A-FABP and SUA levels were risk factors for IR (P<0.05). *Conclusion:* In newly diagnosed T2DM patients with abdominal obesity, A-FABP and SUA levels significantly rise, being positively correlated with IR. Therefore, reducing lipids and weight together with controlling A-FABP and SUA levels may be important strategies for relieving IR and preventing T2DM complicated with abdominal obesity.

Keywords: type 2 diabetes mellitus; insulin resistance; adipocyte fatty acid-binding protein; serum uric acid; correlation

Introduction

The morbidity rate of type 2 diabetes mellitus (T2DM), a chronic metabolic disease, keeps increasing. Abdominal fat accumulation, also known as abdominal obesity, is considered as a risk factor for T2DM (1, 2). Insulin resistance (IR) refers that the sensitivity of target organs (e.g. fat, muscle and liver) to insulin declines, reducing insulin-mediated biological effects (3). In the case of obesity, a large amount of insulin is secreted to keep a normal blood glucose level, thereby aggravating IR and causing damage or dysfunction of islet β cells.

Ultimately, T2DM occurs (4). It has been found in recent years that adipocyte fatty acid-binding protein (A-FABP) binds fatty acid ligand with high affinity after being released into the blood, thus playing a crucial regulatory role in insulin sensitivity and glucolipid metabolism (5). In diabetic patients, abnormal increase of purine catabolite, i.e. serum uric acid (SUA), can lead to islet dysfunction, which has been closely related to IR (6). At present, the correlations of insulin function with the levels of A-FABP and SUA in newly diagnosed T2DM patients with abdominal obesity have been rarely reported. In this study, IR was evaluated and the levels of A-FABP and SUA were detected in these patients, and the correlations of IR with A-FABP and SUA were analyzed, aiming to provide valuable evidence for the treatment of T2DM and abdominal obesity.

Methods

Subjects

A total of 218 newly diagnosed T2DM patients admitted to our hospital from October 2018 to November 2019 were selected, who all met the WHO diagnostic criteria for T2DM in 1999 (7): without typical symptoms; 2 h postprandial blood glucose or random blood glucose level of ≥11.1 mmol/L (200 mg/dL), or fasting blood glucose of ≥7.0 mmol/L (126 mg/dL) after repeated measurement; with the same values as above and diabetic symptoms. According to the 2016 Chinese Guideline for the Management of Dyslipidemia in Adults (8), the patients were divided into an abdominal obesity group (n=98, waist circumference ≥90 cm in males and ≥85 cm in females) and a non-abdominal obesity group (n=120, waist circumference <90 cm in males and <85 cm in females). Inclusion criteria: 1) Patients diagnosed as T2DM, 2) those receiving no hypolipidemic, hypoglycemic or SUA-lowering therapies in any types, 3) those without other endocrine diseases, immune diseases, diseases and tumors in vital organs, hypertension and mental diseases, fracture or trauma recently, and 4) those who and whose families were informed and actively cooperated in this study. Exclusion criteria: 1) Patients with secondary diabetes or a history of diabetes, secondary hyperuricemia, severe acute and chronic complications of diabetes, or 2) pregnant and lactating women. This study was reviewed and approved by the Medical Ethics Committee of our hospital. Informed written consents haven been obtained from all patients.

Physical examinations

Physical examinations were performed by the same personnel in the same way. The diastolic blood pressure (DBP), systolic blood pressure (SBP), waist circumference, hip circumference, height and weight were measured, and the waist-to-hip ratio (waist circumference/hip circumference) and body mass index (BMI) [weight (kg)/height^2 (m^2)] were calculated. The height and weight were measured in a fasting state of patients with light clothes and without hat or shoes. To measure the waist circumference, the patient was required to stand upright with two feet apart by 25-30 cm. It was measured horizontally through the midpoint that linked the iliac crest and the lower margin of the 12th rib (a measurement tape was placed close to the skin, without oppressing the skin) (9). To measure the hip circumference, the patient was required to stand upright with two arms sagging naturally and feet together. It was measured from the most convex part of gluteus maximus to the pubic symphysis using an inelastic tape. The above indices were measured 3 times, and the average was recorded.

Detection of laboratory indices

All patients were deprived of water and food for 12 h. On the next day, the fasting venous blood was collected in the early morning to measure the levels of fasting plasma glucose (FPG), very low-density lipoprotein-cholesterol (VLDL-C), low-density lipoprotein-cholesterol (LDL-C), high-density lipoprotein-cholesterol (HDL-C), triglyceride (TG), total cholesterol (TC), SUA, serum creatinine (Scr), aspartate aminotransferase (AST), alanine aminotransferase (ALT) and homocysteine (HCY) by 7600 automatic biochemical analyzer (Hitachi, Japan).The level of

hemoglobin A1c (HbA1c) was measured with Variant II hemoglobin testing system (Bio-Rad, USA). The level of fasting serum insulin (FINS) was detected using Cobas-601 electrochemiluminescence analyzer (Roche, Switzerland).Serum A-FABP level was measured by ELISA. All experiments were carried out strictly according to manufacturers' instructions.

Assessment of insulin function

IR and the secretion function of islet β cells were evaluated using homeostasis model assessment (HOMA) (10). HOMA-IR = FPG (mmol/L) × FINS (mU/L) / 22.5. HOMA-β = FINS (mU/L) × 20 / [FPG (mmol/L) - 3.5].

Statistical analysis

All data were statistically analyzed by SPSS 20.0 software. The measurement data were expressed as mean ± standard deviation (`x ± s), and intergroup comparisons were performed by the independent t test. The numerical data were represented as percentage (%), and intergroup comparisons were conducted with the χ^2 test. The correlations of HOMA-IR with A-FABP, SUA levels and HOMA-β were explored by Pearson's analysis. The risk factors for IR were explored using logistic regression analysis. P<0.05 was considered statistically significant.

Results

Baseline clinical data

The two groups had similar gender ratio and age (P>0.05). The abdominal obesity group had significantly higher BMI, waist circumference, waist-to-hip ratio, DBP and SBP than those of the non-abdominal obesity group (P<0.05) (Table 1).

Laboratory indices

The two groups had similar levels of FPG, Scr, HCY and HbA1c (P>0.05).Compared with the non-abdominal obesity group, the abdominal obesity group had higher levels of VLDL-C, LDL-C, TG, TC, AST, ALT and FINS (P<0.05), and lower level of HDL-C (P<0.05) (Table 2).

HOMA-IR and HOMA-β

The abdominal obesity group had higher HOMA-IR and HOMA-β than those of the non-abdominal obesity group (P<0.05) (Table 3).

A-FABP and SUA levels

The abdominal obesity group had higher A-FABP and SUA levels than those of the non-abdominal obesity group (P<0.05) (Table 4).

Table 1. Baseline clinical data [case (%)] (x ± s)

Item	Abdominal obesity group (n=98)	Non-abdominal obesity group (n=120)	χ^2/t	P
Gender			0.012	0.913
Male	63	78		
Female	35	42		
Age (year)	46.73±4.58	47.12±4.65	0.620	0.536
BMI (kg/m^2)	26.85±2.59	22.36±2.17	13.927	0.000
Waist circumference (cm)	94.91±6.74	81.45±5.73	15.935	0.000
Waist-to-hip ratio	0.95±0.07	0.84±0.05	13.507	0.000
DBP (mmHg)	84.61±8.83	73.39±7.21	10.329	0.000
SBP (mmHg)	145.38±14.16	128.57±12.48	9.311	0.000

BMI: Body mass index; DBP: diastolic blood pressure; SBP: systolic blood pressure.

Table 2. Laboratory indices (x ± s)

Item	Abdominal obesity group (n=98)	Non-abdominal obesity group (n=120)	t	P
FPG (mmol/L)	10.41±0.92	10.25±0.97	1.240	0.216
VLDL-C (mmol/L)	1.07±0.35	0.86±0.21	5.477	0.000
LDL-C (mmol/L)	3.68±0.74	2.79±0.53	10.327	0.000
HDL-C (mmol/L)	1.05±0.29	1.48±0.36	9.559	0.000
TG (mmol/L)	2.59±1.56	1.37±0.65	7.783	0.000
TC (mmol/L)	5.32±0.68	4.24±0.43	14.258	0.000
Scr (μmol/L)	67.47±12.35	68.13±13.22	0.378	0.706
AST (IU/L)	43.56±30.27	31.52±20.16	3.508	0.001
ALT (IU/L)	32.74±19.38	26.43±13.51	2.825	0.005
HCY (μmol/L)	14.69±3.52	15.07±3.64	0.778	0.437
HbA1c (%)	9.83±1.04	9.67±0.95	1.185	0.237
FINS (mU/L)	46.72±4.58	25.37±2.61	43.205	0.000

ALT: Alanine aminotransferase; AST: aspartate aminotransferase; FINS: fasting serum insulin; FPG: fasting plasma glucose; HbA1c: hemoglobin A1c; HCY: homocysteine; HDL-C: high-density lipoprotein-cholesterol; LDL-C: low-density lipoprotein-cholesterol; Scr: serum creatinine; TC: total cholesterol; TG: triglyceride; VLDL-C: very low-density lipoprotein-cholesterol.

Table 3. HOMA-IR and HOMA-β (x ± s)

Item	Abdominal obesity group (n=98)	Non-abdominal obesity group (n=120)	t	P
HOMA-IR	5.83±1.06	3.71±0.82	16.646	0.000
HOMA-β	79.54±7.87	58.45±5.69	22.926	0.000

HOMA-β: Homeostasis model assessment-β; HOMA-IR: homeostasis model assessment-insulin resistance.

Table 4. A-FABP and SUA levels (x ± s)

Item	Abdominal obesity group (n=98)	Non-abdominal obesity group (n=120)	t	P
A-FABP (μg/L)	15.36±3.27	9.85±2.04	15.194	0.000
SUA (μmol/L)	312.45±30.69	257.51±26.93	14.070	0.000

A-FABP: Adipocyte fatty acid-binding protein; SUA: serum uric acid.

Correlations between A-FABP, SUA, HOMA-β and HOMA-IR

HOMA-IR was significantly positively correlated with A-FABP, SUA levels and HOMA-β (P<0.0001) (Figure 1).

Risk factors for IR

BMI, waist circumference, as well as levels of TG, A-FABP and SUA were risk factors for IR in newly diagnosed T2DM patients with abdominal obesity (P<0.05) (Table 5).

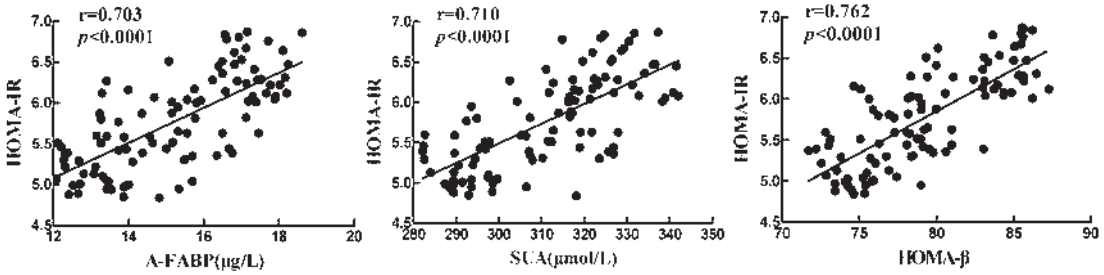

Figure 1. Correlations between A-FABP, SUA, HOMA-β and HOMA-IR. A-FABP: Adipocyte fatty acid-binding protein; HOMA-β: homeostasis model assessment-β; HOMA-IR: homeostasis model assessment-insulin resistance; SUA: serum uric acid.

Table 5. Risk factors for IR

Factor	β	SE	Wald	P	OR (95%CI)
BMI	1.964	0.837	3.153	0.001	1.798 (1.103~2.379)
TG	0.587	0.659	1.748	0.006	3.124 (2.267~5.438)
Waist circumference	0.841	0.718	1.962	0.010	3.261 (1.529~4.756)
A-FABP	1.225	0.956	2.371	0.005	2.543 (1.435~3.982)
SUA	2.136	0.742	4.285	0.004	4.876 (3.217~6.541)

Independent variable assignment: BMI: ≥25 kg/m^2 = yes, <25 kg/m^2 = no; TG: ≥1.7 mmol/L = yes, <1.7 mmol/L = no; waist circumference: male ≥90 cm and female ≥85 cm = yes, male <90 cm and female <85 cm = no; A-FABP: ≥12.5 μg/L = yes, <12.5 μg/L = no; SUA: ≥280 μmol/L = yeas, <280 μmol/L = no. A-FABP: Adipocyte fatty acid-binding protein; BMI: body mass index; IR: insulin resistance; OR: odds ratio; SE: standard error; SUA: serum uric acid; TG: triglyceride.

Discussion

As we all know, abdominal obesity is caused by the accumulation of fats around the visceral organs, the aortas and the intraperitoneal mesenteries. The abdominal fat cells of patients with abdominal obesity can store energy, and abundant inflammatory substances secreted by them can be involved in the inflammatory response, inducing metabolic syndrome (11). In addition, the increase of waist circumference caused by abdominal fat accumulation is a high risk factor for T2DM (12). At present, waist circumference is widely recognized as the most simple, economical and practical parameter reflecting the degree of abdominal visceral fat accumulation for the diagnosis of abdominal obesity (13). In this study, according to the 2016 Chinese Guideline for the Management of Dyslipidemia in Adults (7), the selected patients with T2DM were divided into abdominal obesity group (male waist circumference ≥90 cm, female waist circumference ≥85 cm) and non-abdominal obesity group (male waist circumference <90 cm, female waist circumference <85 cm). Compared with those of non-abdominal obesity group, BMI, waist circumference, waist-to-hip ratio, DBP and SBP of abdominal obesity group were all significantly increased (P<0.05), indicating that the above parameters can be employed to evaluate the obesity degree. Moreover, compared with non-abdominal obesity group, abdominal obesity group had obviously increased levels of VLDL-C, LDL-C, TG, TC, AST, ALT and FINS (P<0.05), but an obviously decreased level of HDL-C (P<0.05).

Thus, both groups had various degrees of disturbance of lipid metabolism, more serious in abdominal obesity group.

Insulin resistance is an important link of abdominal obesity-induced T2DM. Abdominal fat storage is increased in the case of excessive body fat and insufficient subcutaneous storage space, which can lead to abdominal obesity. However, in order to maintain the normal blood glucose concentration, the body must secrete a large amount of insulin, which can lead to IR under the action of a variety of mechanisms, thereby causing the dysfunction or even apoptosis of islet β cells, and finally developing into T2DM (4). In this study, IR and islet β cell function were evaluated via homeostasis model assessment. HOMA-IR and HOMA-β in abdominal obesity group were all higher than those in non-abdominal obesity group, and there were statistically significant differences ($P<0.05$). Accordingly, abdominal obesity is an important cause of IR, whose compensatory response can enhance the secretion of islet β cells, eventually damaging islet β cells. A-FABP, a molecular chaperone of fatty acids, widely exists in various normal tissues and cells of mammals, which is mainly involved in the absorption and transport of fatty acids, and promotes the storage of energy *in vivo* (14). In general, SUA mainly originates from purine nucleotides in human body and the metabolites of animal and plant purine nucleotides taken from food. Uric acid is a main antioxidant substance in the blood, and it can not only effectively remove the oxygen radicals *in vivo* to exert an antioxidant effect, but also increase the active oxygen clusters through the prooxidant effect (15). Herein, compared with those in non-abdominal obesity group, the levels of A-FABP and SUA in abdominal obesity group were significantly increased, and there were statistically significant differences ($P<0.05$). The reason for the higher level of A-FABP in the abdominal obesity group is that it participates in the absorption and transport of fatty acids and benefits the energy storage *in vivo*. In the abdominal obesity group, the reasons why the SUA level rose may be as follows: the abdominal fats accumulate due to the absorption of large amounts of energy when taking too much high purine food. The aggravation of IR induces hyperinsulinemia, and directly affects renal proximal convoluted tubular cells, promoting the reabsorption and reducing the excretion of uric acid.

After knockout of A-FABP gene, the insulin sensitivity of rats is enhanced, the function of islet β cells is recovered, and the insulin concentration is decreased, suggesting that A-FABP is closely bound up with IR (16). The islets, insulin content and islet β cell activity of hyperuricemic rats are significantly reduced, confirming that the uric acids can damage the function of islets (17). As the serum uric acid level increases, the islet β cells in patients with T2DM have compensatory responses due to IR, which improves the secretion function, and then maintains the homeostasis of blood glucose (18). The correlation analysis in this study exhibited that HOMA-IR had a significant positive correlation with A-FABP, SUA and HOMA-β ($P<0.0001$). Hence, A-FABP and SUA play an irreplaceable role during the IR and glucose metabolism disorders. HOMA-IR was positively correlated with HOMA-β, but we still attributed the increase of HOMA-β to the compensatory response of IR. Multiple regression analysis showed that BMI, TG, waist circumference, A-FABP and SUA were the risk factors of IR in newly diagnosed T2DM patients with abdominal obesity ($P<0.05$).

Conclusion

In summary, the levels of A-FABP and SUA in newly diagnosed T2DM patients with abdominal obesity are significantly increased, and they are positively correlated with IR. Therefore, reducing lipid and weight and controlling A-FABP and SUA levels may improve IR and prevent T2DM with abdominal obesity. In the future, we will enlarge the sample size, and conduct in-depth research on the pathogenesis, aiming to provide guidance for clinical practice.

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