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Impact of Acarbose on the Serum YKL-40 Concentrations of Coronary Heart Disease Patients with Impaired Glucose Tolerance

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Abstract

Background: YKL-40 is involved in inflammation and endothelial dysfunction, and associated with diabetes and atherosclerosis disease. In the present study we investigated the effect of an alpha-glucosidase inhibitor, acarbose, on coronary heart disease patients with impaired glucose tolerance (IGT) and the impact of acarbose on the serum YKL-40 concentrations of these patients.

Methods: This was a 24 weeks study in patients with established coronary artery disease (CAD) (50% stenosis on quantitative coronary angiography) who were newly diagnosed with IGT. After undergoing coronary angiography, CAD patients with IGT were randomly allocated to receive either acarbose 100 mg/d (C group) or no treatment group (B group) for 24 weeks. 30 patients with CAD and normal glucose tolerance were enrolled in control group (A group). Anthropometrical evaluation, fast blood glucose (FBG), postprandial blood glucose (PBG), serum fast insulin (FINS), lipid profile including triglycerides (TG), total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), HbA1c and serum YKL-40 were measured at baseline and 24 weeks end point.

Results: There were no significant differences among tree groups in terms of age, gender distributions, SBP, DBP, TGTC, HDL-C, LDL-C, FBG. The levels of WHR, BMI, FINS, HOMA-IR, YKL-40 in the B group were significantly higher than A group. After 24-weeks treatment of acarbose (100 mg/d), the levels of WHR, TG, YKL-40 FINS, PBG, HbA1c and HOMA-IR were significantly reduced ($p<0.05$).

Conclusions: After the treatment of acarbose 100 mg/d, the coronary heart disease patients with IGT had a beneficial effect in the glucose and lipid metabolism, the insulin resistance and serum YKL-40 concentrations were decreased.

Keywords: Acarbose; Coronary heart disease; Impaired glucose tolerance (IGT); YKL-40

Abbreviations CAD: Coronary Artery Disease; IGT: Impaired Glucose Tolerance; T2DM: Type 2 Diabetes Mellitus; WHO: World Health Organization; OGTT: Oral Glucose Tolerance Test; SBP: Systolic Blood Pressure; DBP: Diastolic Blood Pressure; WHR: Waist Circumference/Hip Circumference; BMI: Body Mass Index; FBS: Fasting Blood Sugar (FBS);FINS: Fasting Insulin; TG: Triglycerides; TC: Total Cholesterol; HDL-C: High-density Lipoprotein Cholesterol; LDL-C: Low-density Lipoprotein Cholesterol; HOMA-IR: Homeostasis Model Assessment of Insulin Resistance

Background

Insulin resistance is an important factor that substantially increases the risk for atherosclerotic cardiovascular disease and diabetes [1,2]. Impaired glucose tolerance (IGT) is considered a pre stage of the onset of T2DM and this stage has the typical characteristics of insulin resistance. Several clinical studies had confirmed the increased risk of coronary artery disease (CAD) in patients with IGT [3,4]. Insulin resistance could explain the increased risk for CAD in patients with IGT because insulin resistance is associated with IGT and postprandial hyperglycemia [5]. To investigate the pathogenesis of IGT and CAD, seek the effective control measures to improve the insulin resistance is beneficial for the treatment of CAD patients. YKL-40 is a 40 kDa heparin-and chitin-binding glycoprotein. It is secreted *in vitro* by several cell-types with relation to the innate immune system, e.g. activated macrophages and vascular smooth muscle cells [6,7]. YKL-40 is a potent angiogenic factor and is thought to facilitate the formation of atherosclerotic plaques [8]. In addition, elevated YKL- 40 levels have been found in cardiovascular disease, diabetes (T2DM), and several types of cancer [9,10,11]. In this study we aimed to investigate the effect of an alpha-glucosidase inhibitor, acarbose, on coronary heart disease patients with impaired glucose tolerance (IGT) and the impact of acarbose on the serum YKL-40 concentrations of these patients.

Materials and Methods

Subjects and methods

Participants were recruited from the Department of Cardiology and Endocrinology at the Second Hospital of Shandong University (Jinan, China) for elective coronary angiography between January 2016 and August 2016. According to the coronary angiography outcome, patients should have 50% stenosis on quantitative coronary

angiography and be diagnosed CAD. At the same time, all of the subjects exhibited a normal oral glucose tolerance test (75 g glucose) according to World Health Organization (WHO) 1999 criteria [12]. IGT was defined as a fasting plasma glucose concentration <126 mg/dL and a 2 h plasma glucose concentration on the 75-g oral glucose tolerance test (OGTT) of 140 to 199 mg/dL. The patients enrolled must meet with the IGT criteria. Exclusion criteria were age>70 years, history of unstable angina, myocardial infarction, heart failure, cerebrovascular accident or major surgery within the 6 months preceding the study. Patients with acute or chronic inflammatory disease, history of kidney, respiratory, hypertension, DM disease, tumor diseases, rheumatic immune diseases, and any disease that might affect absorption of medications were excluded. None of the patients had previously received acarbose therapy. All patients didn't have the medication history of any non-steroidal anti-inflammatory drugs, -blockers, anticoagulants and antipsychotics drugs. Tea and coffee were forbid before 12 h of the test. A total of 52 subjects met with the enroll criteria and they were then randomly allocated to either the acarbose (Bayer Healthcare Pharmaceuticals Inc) 100-mg/d group for 24 weeks (C group, 26 cases) or the control group (no treatment B group, 26 cases). We chose another 30 subjects (A group, 30 cases) with simple CAD and normal glucose tolerance as control group. One patient in C group withdrew because of gastrointestinal side effects during the first month. This study was approved by the human research ethics committee of the hospital, and informed consent was obtained from each patient.

Clinical and biochemical measurements

All subjects underwent anthropometrical evaluation. Height, weight, waist circumference, and hip circumference were measured by a trained nurse. Systolic blood pressure (SBP) and diastolic blood pressure (DBP) were also measured. Biochemical parameters including fast blood glucose (FBG), postprandial blood glucose (PBG), serum fast insulin (FINS), lipid profile including triglycerides (TG), total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), HbA1c and serum YKL-40 were performed at baseline and at the end of the study. Venous blood was collected after overnight fasting, centrifuged, and the separated serum was frozen immediately at -80°C. FBG was measured by the glucose-oxidase method. Fasting insulin was assessed using a commercially available radioimmuno assay kit (Linco Research, St. Louis, MO, USA). Serum total cholesterol, HDL cholesterol, and triglycerides were measured using the Beckman DXC 800 analyzer (USA). LDL cholesterol was calculated from these results. YKL-40 (Quidel, San Diego, CA, USA) was measured by using commercially available enzyme-linked immunosorbent assays (ELISA) according to the manufacturer's protocol. The intra-assay coefficients of variation were 9% and inter-assay coefficients of variation were 11%. Insulin resistance was estimated using the homeostasis model assessment equation (homeostasis model assessment of insulin resistance (HOMAIR)=fasting insulin (mU/ml) *fasting glucose (mmol/L)/22.5. BMI=body weight/ body height [2]. After 24 weeks, the 25 patients with severe CAD repeated the same clinical and biochemical measurements.

Statistics analysis

Data were expressed as mean ± standard deviation (M ± SD), median (interquartile range). Before analysis, data were tested for normality of distribution using the Shapiro-Wilk test. The t-test was applied to compare the differences of the measurement data between the groups. Pearson's correlation coefficient univariate and stepwise multivariate linear regression analyses were performed for calculation of associations between serum YKL-40 and other variables. SPSS 19.0 software was used for statistical analysis. P<0.05 was considered statistically significant.

Results

The characteristics of the participants are shown in Table 1 and Table 2

The study enrolled 82 patients including 30 cases of CAD without IGT in A group and 26 untreated cases of CAD with IGT in B group and 26 treated cases of CAD with IGT in C group. One patient in C group withdrew because of gastrointestinal side effects during the first month. There was no cardiovascular event during 24 weeks. The baseline characteristics of the patients with complete follow-up data are summarized in Table 1. As can be seen, there were no significant differences among tree groups in terms of age, gender distributions, SBP, DBP, TGTC, HDL-C, LDL-C, FBG. The levels of WHR, BMI, FINS, HOMA-IR, YKL-40 in the B group were significantly higher than A group. After 24 weeks treatment of acarbose (100 mg/d), we got the same indexes of 25 patients with CAD and IGT. As showed in table 2, the levels of WHR, TG, YKL-40, FINS, PBG, HbA1c and HOMA-IR in C group were significantly reduced comparing to B group (p<0.05).

Metabolic parameters and their correlations with serum YKL-40 levels

Next, we evaluated the correlation between serum YKL-40 levels and various metabolic parameters (Table 2). Pearson's correlation analysis indicated that serum YKL-40 was positively correlated with WHR (r=0.303, p=0.01), HOMA-IR (r=0.425, p=0.004), FINS (r=0.462, p=0.002), TG (r=0.337, p=0.009), HbA1C (r=0.382, p=0.006) significantly. There was a negative correlation between YKL-40 and HDL-C but not significantly (Table 3).

Logistic regression analysis was performed using CAD as a dependent variable

YKL-40 was selected as an independent variable together with age, BMI, WHR TC, TG, HDL-C, LDL-C, and HOMA-IR in all subjects. Homeostasis model assessment for PBG (OR 1.392, 95% CI 1.072 to 1.451; P=0.012), HOMA-IR (OR 1.308, 95% CI 1.069 to 1.370; P=0.008) and YKL-40 (OR 1.208, 95% CI 1.034 to 1.217; P=0.005) were independent variables associated with CAD.

	A group	B group	C group
Cases (n)	30	26	25
Male/female (M/F)	16/14	12/14	13/12
Age	58 ± 9	56 ± 7	59 ± 10
SBP (mmHg)	132 ± 14	135 ± 16	134 ± 13
DBP (mmHg)	80 ± 12	81 ± 14	84 ± 11
WHR (cm)	0.83 ± 0.18	0.92 ± 0.15*	0.89 ± 0.25*
BMI (Kg/m2)	23.12 ± 2.38	25.09 ± 1.52*	25.16 ± 1.23*
FBG (mmol/L)	4.68 ± 0.77	4.98 ± 0.51	5.10 ± 0.63

PBG (mmol/L, 2h)	6.43 ± 1.30	8.98 ± 1.10*	8.36 ± 0.84*
HbA1C (%)	5.0 ± 0.5	5.8 ± 0.6*	6.0 ± 0.38*
FINS (mU/L)	9.48 ± 1.71	12.20 ± 1.02*	12.94 ± 1.73*
TG (mmol/L)	1.75 ± 0.62	1.82 ± 0.63	1.79 ± 0.37
TC (mmol/L)	5.27 ± 1.38	5.43 ± 1.20	5.31 ± 0.84
HDL-C (mmol/L)	1.35 ± 0.31	1.30 ± 0.43	1.35 ± 0.21
LDL-C (mmol/L)	3.25 ± 0.83	3.31 ± 1.14	3.20 ± 0.72
HOMA-IR	1.97 ± 0.49	2.72 ± 0.37*	2.80 ± 0.35*
YKL-40 (μg/L)	85.93 ± 15.41	122.3 ± 20.35 *	125.2 ± 15.32*

Table 1: Baseline demographic and clinical characteristics of study patients, A group: Patients with simple CAD and normal glucose tolerances; B group: Patients with CAD and impaired glucose tolerance; C group: Patients with CAD and impaired glucose tolerance and 100-mg/d acarbose treatment.

	B group	C group
SBP (mmHg)	130 ± 12	132 ± 15
DBP (mmHg)	84 ± 11	81 ± 17
WHR (cm)	0.91 ± 0.13	0.88 ± 0.12#
BMI (Kg/m2)	25.29 ± 1.56	23.35 ± 2.20#
FBG (mmol/L)	4.88 ± 0.66	4.70 ± 0.63
PBG (mmol/L,2h)	9.12 ± 1.08	6.24 ± 0.96#
HbA1C (%)	5.9 ± 0.5	5.2 ± 0.66#
FINS (mU/L)	13.16 ± 1.37	10.35 ± 1.56#
TG (mmol/L)	1.90 ± 0.49	1.69 ± 0.49#
TC (mmol/L)	5.33 ± 1.38	5.20 ± 0.96
HDL-C (mmol/L)	1.32 ± 0.81	1.36 ± 0.29
LDL-C (mmol/L)	3.28 ± 1.21	3.22 ± 0.77
HOMA-IR	2.85 ± 0.37	2.16 ± 0.44#
YKL-40 (μg/L)	129.3 ± 15.76	101.8 ± 10.26#

Table 2: Metabolic index after 24 weeks in B group and C group. Note: Compared with B group #P<0.05. B group: Patients with CAD and impaired glucose tolerance; C groupPatients with CAD and impaired glucose tolerance and 100-mg/d acarbose treatment.

	YKL-40 (r)	p values
WHR	0.303	0.01*
HOMA-IR	0.425	0.004*
PBG	0.485	0.001
FINS	0.462	0.002*
TG	0.337	0.009*
HbA1C	0.382	0.006*

Table 3: Correlation coefficients (r) between YKL-40 and selected variables. Note: *P<0.05.

Discussion

Coronary artery disease (CAD) is the leading cause of mortality worldwide, accounting for 17.1 million deaths [13]. The Euro Heart Survey (Germany) found that more than one third of the patients with CAD who underwent an OGTT had an impaired glucose tolerance [14]. Prospective studies have shown that hyperglycemia itself is clearly involved in predicting CAD [15]. A graded relationship has been demonstrated in non-diabetic subjects between fasting and postprandial glucose levels and subsequent cardiovascular event risk, indicating that the relationship between blood glucose levels and increased cardiovascular risk starts below the diabetic threshold. The Honolulu Heart Study was the first epidemiological investigation to describe the association between the plasma glucose 1 h post-glucose load and incidence of CAD [16]. Blood glucose levels, even below the diabetic range, are a significant risk marker for future CAD. With respect to fasting plasma glucose (FPG), postprandial glucose is a more important risk factor to vascular damage and CAD. As data continue to emerge, highlighting the importance of postprandial hyperglycaemia (PPHG) in predicting CAD risk, several professional bodies including the IDF have issued guidelines on the management of PPHG in type 2 diabetes.

Insulin resistance, a key feature of type 2 diabetes, is an independent risk factor for developing cardiovascular diseases (CAD). Insulin resistance in the absence of overt diabetes has been associated with endothelial dysfunction, a surrogate marker of atherosclerosis [17,18]. Insulin resistance-associated postprandial hyper-glycemia may play a role in the development and progression of CAD in patients with recently diagnosed diabetes. Study showed that individuals with elevated HOMA-IR index have the twofold risk of cardiovascular disease [19]. Quebec cardiovascular study showed that high fasting insulin is the predictor of coronary heart disease and the level of insulin is an important independent risk factor of CAD. In our study the CAD patients with IGT had higher level of FINS, HOMA-IR than the patients with simple CAD. Logistic regression analysis also showed that HOMA-IR was independent risk factor of CAD that consistent with previous findings [20]. It indicates that improvement of hyperinsulinemia and insulin resistance is important to CAD treatment.

In IGT, sustained hyperglycemia causes increased intracellular concentrations of glucose metabolites in endothelial cells and increased secretion of proinflammatory cytokines such as IL-6, TNF-α. Moreover, postprandial hyperglycemia elicited oxidative stress generation induces platelet activation and thrombin generation and aggravated the progression of atherosclerosis [21,22]. YKL-40, also known as human cartilage glycoprotein-39 (HCgp-39) or chitinase-3-like protein 1 (CHI3L1), is a heparin and chitin-binding lectin without any enzymatic activity. It is secreted *in vitro* by several cell-types with relation to the innate immune system, e.g. activated macrophages and vascular smooth muscle cells [23]. YKL-40 is found to be a potent angiogenic factor [24] and is thought to facilitate the formation of atherosclerotic plaques [25]. Studies found that the serum YKL-40 levels were elevated in cardiovascular disease [26,27], Elevated circulating levels of YKL-40 has been considered as marker of

atherosclerosis. Recent studies reported that in T2DM subjects the levels of YKL-40 were elevated significantly and the index is proportional with the HOMA-IR. High level of YKL-40 also appeared in adult subjects who did not report a medical history of T2D and CAD comorbidities [28,29], even at the childhood stage [30]. Stine B found that in a Danish sample of non-diabetic relatives to T2DM patients fasting serum level of YKL-40 was positively associated with waist-hip-ratio, and fasting plasma triglyceride levels. None of the insulin sensitivity indexes were significantly associated with YKL-40. They suggested a role of serum YKL-40 in obesity-related low grade inflammation, but do not indicate that YKL-40 is directly involved in the development of T2DM [31]. Our study showed that the level of fasting serum YKL-40 in CAD patients with IGT was significantly higher than CAD patients. Furthermore, YKL-40 was correlated positively with HOMA-IR. It indicates that the level of YKL-40 maybe elevates form the state of IGT. As a marker of inflammation, YKL-40 should play a role in the development of insulin resistance and T2DM.

Aimed at reducing overall cardiovascular risk, the management of blood glucose levels should be as important as cardiovascular treatment. Studies have proved that effective PPHG management in individuals with IGT could reduce the risk of CAD endpoints. Acarbose is an effective drug for controlling PPHG excursion and HbA1c as cardiovascular risk factors in patients with T2DM. Post-marketing surveillance of acarbose treatment in patients with type 2 diabetes and people with IGT in China HbA1c was reduced by 1.4% and 0.9% respectively [32]. This is in accordance with data from a large 5 year follow-up study in Germany [33]. The effect of acarbose on the glucose was reliable in our study. Moreover, treatment of 24 weeks of acarbose in the study improved the FINS and HOMA-IR in the patients of CAD with IGT. This may mainly be due to reduction of PPHG. Prevention of rapid rise of PPHG and fluctuations may also protect β-cells from glucotoxicity. The effect of acarbose treatment on CAD events was first shown in the STOP-NIDDM study [34]. The STOP-NIDDM Trial investigated the effects of acarbose on the incidence of type2 diabetes and the development of cardiovascular events. It demonstrated that early intervention with acarbose in individuals with IGT significantly reduces the occurrence of newly diagnosed diabetes. The STOP-NIDDM Trial also showed that treatment of acarbose is associated with a significant reduction in cardiovascular endpoints. Other *vivo* and *vitro* experiments provided proof for the conclusion. Administration of acarbose for 12 weeks in non-obese type 2 diabetic rats improved postprandial hyperglycemia, triglyceride, and fatty acid levels. Oral administration of acarbose decreased serum levels of MCP-1 and its expression in aorta in fructose-fed rats. Furthermore, acarbose efficiently reduced the number of monocytes adherent to aortic endothelial layer, improved acethychol independent vasodilation and reduced intimal thickening of the aorta. These findings suggested that acarbose could exert athero protective properties. In our study the PPHG, TG and LDL-C of the patients with CAD and IGT got significantly decrease after 24 weeks treatment of acarbose. The improvement of glucose and lipid metabolism will be beneficial to cardiovascular disease. At the same time, the reduction of FINS and HOMA-IR comparing to baseline indicated that the improvement of insulin resistance. The serum YKL-40 level of patients who received acarbose treatment was decreased significantly. In the light of closed relationship of YKL-40 with insulin resistance and atherosclerosis, the decrease of YKL-40 should reduce the inflammation and has a protective effect on artery plaque.

Conclusion

In conclusion the patients of CAD with IGT got the improvement of glucose, lipid metabolism and insulin resistance after 24 weeks acarbose treatment. Serum YKL-40 level was also decreased significantly. The 24 weeks of acarbose treatment had a beneficial effect on the patients of CAD with IGT. The major limitation of this study is the relatively small sample size. The present study population might not represent ordinal non-diabetic subjects and thus further studies in a large number of general subjects are required to confirm our results.

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Ethics Approval and Consent to Participate

All procedures performed in studies involving human participants were in accordance with the ethical standards of the Second Hospital of Shandong University and national research committee and with the 1964 Helsinki declaration and its later amendments ethical standards. Informed consent was obtained from all individual participants included in the study.

Author's Contributions

Xianghua Zhuang, Dianhui Wang and Dongqing Jiang participated in the data acquisition. Yihong Ni participated in the design of the study. Xiaobo Li and Fufang Wang participated in the statistical analysis. All authors read and approved the final manuscript.

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