Association of polymorphisms of preptin, irisin and adropin genes with susceptibility to coronary artery disease and hypertension

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Abstract

Objectives: Preptin, irisin and adropin are 3 new players in energy regulation that are related body mass index, lipids, glucose and insulin levels which may affect incidence of cardiovascular diseases. The aim of the present study was to evaluate eight single nucleotide polymorphisms (SNPs) of preptin genes (rs1003483, rs1004446, rs2239681, rs680, and rs3741204), irisin (rs16835198 and rs3480) and adropin (rs2281997) gene in patients with coronary artery disease (CAD) and hypertension.

Methods: This case-control study was carried out on 372 volunteers, which were divided into 3 subgroups including: CAD patients with hypertension (CAD+H+), CAD patients with no hypertension (CAD+H−), and non-hypertensive non-CAD subjects as control group (CAD−H−) as health control. Genomic DNA from whole blood was extracted and eight SNPs were assessed using polymerase chain reaction- ligase detection reaction method.

Results: A significant difference was found in the genotype and allele frequency of preptin rs1003483 gene in CAD+H+ compared to CAD+H− groups (P = 0.019 and P = 0.018, respectively). Allele frequency of rs1003483 was significantly different between CAD+H+ groups and healthy control groups (P = .043). There also existed a significant difference the genotype frequency of rs1004446 gene in CAD+H+ compared to CAD+H− groups (P = .027).

Conclusions: The findings of present study revealed that the preptin rs1003483 and rs1004446 gene polymorphism might serve as predisposing factor in CAD and hypertension.

Abbreviations: CAD = coronary artery disease, PCR = polymerase chain reaction.

Keywords: adropin, coronary artery disease, hypertension, irisin, polymorphisms, preptin

1. Introduction

Cardiovascular disease is the most common, deadly, non-infectious disease in various countries.\textsuperscript{[1]} Coronary artery disease (CAD) accounts for the high morbidity and mortality rates of cardiovascular disease and annually causes more than 7 million deaths worldwide.\textsuperscript{[2]} With the aging population of China, CAD has become the most common and fatal disease in this country.\textsuperscript{[3]} As a primary principal health challenge worldwide, hypertension is associated with CAD development and other risk factors. Approximately 338 million Chinese are hypertensive, and this number exceeds the entire population of U.S.\textsuperscript{[4]}

Diabetes, obesity, and metabolic syndrome are important CAD risk factors, and hypertension and their incidences are closely related to energy metabolism.\textsuperscript{[5]} Preptin, irisin, and adropin, with 34, 43, and 112 amino acids at 3948, 4999, and 12587 Da, respectively, are associated with energy regulation. With the synthesis and secretion of these 3 peptides from different organs and body parts, their critical roles in energy regulation have been studied.\textsuperscript{[6]}

Preptin derivates, such as pro-insulin-like growth factor II, are the latest discovered member of the insulin family. Preptin can elevate insulin secretion and is associated with increased insulin resistance in obesity.\textsuperscript{[7,8]} Adropin is involved in lipid metabolism regulation and can affect insulin resistance.\textsuperscript{[9]} Irisin can convert white adipose tissue to brown ones that store triglycerides and fatty acids and can mediate insulin resistance.\textsuperscript{[10]} The relation between the levels of preptin, irisin, and adropin and cardiovascular diseases has been extensively investigated. For instance, it
was reported that serum adropin level was associated with the severity of coronary atherosclerosis, cardiac syndrome X and stable CAD.\textsuperscript{11,12} Irisin was also proposed as a possible marker of macrovascular disease, including CAD.\textsuperscript{12} Preptin levels were associated with hypertension but exhibited discrepant results for different races.\textsuperscript{13,14} However, possible association of preptin, irisin, and adropin gene polymorphism with susceptibility to cardiovascular diseases is poorly analyzed.

This study aims to evaluate eight single nucleotide polymorphisms (SNPs) within the genes that encode preptin, irisin, and adropin in patients with CAD and/or hypertension in a Chinese population.

## 2. Materials and methods

### 2.1. Subjects

All participants were recruited from the First Peoples’ Hospital of Jining between January 2016 and February 2018. A total of 263 Chinese Han patients with CAD and/or hypertension were enrolled. Diagnosis was performed by experienced cardiologists in accordance with the following significant standards: angiographic evidence of luminal diameter narrowing >50\% in at least one main coronary artery or previous history of coronary artery bypass graft surgery or a history of percutaneous coronary intervention. Patients with diastolic and systolic blood pressures ≥90 and/or ≥140 mm Hg, respectively, or were taking antihypertensive drugs were defined as hypertensive. Patients with renal failure, congenital heart disease, tumors, immune system disorders, malignancies congenital heart disease, and infectious heart disease were excluded. A total of 109 healthy sex- and age-matched controls were selected from the physical examination program through clinical examination and electrocardiogram at the same period. All volunteers were divided into three subgroups including: CAD patients with hypertension (CAD+H\+), CAD patients with no hypertension (CAD+H\−), and non-hypertensive non-CAD subjects as control group (CAD-H\−).

This study was designed in accordance with the Declaration of Helsinki and was approved by the ethics committee of First Peoples’ Hospital of Jining (approval number: JY2016009). All subjects provided written informed consents.

### 2.2. DNA isolation and genotyping

Approximately 1 mL of venous blood was collected and purified from the subjects by using SQ Blood DNA Kit II (D0714-250, Omega Bio-Tek, Norcross) in accordance with the manufacturer’s instructions. All DNA samples were genotyped using polymerase chain reaction (PCR)–ligase detection reaction (LDR). The PCR of the eight target SNPs from each participant was amplified using the primers listed in Table 1. A DNA sequencer was applied to detect the amplification products. More than 10\% of the samples were randomly selected and retested to verify the validity of this procedure, and the results from the retested samples were consistent with those from the original samples.

### 2.3. Statistical analysis

All genotyping results in the studied patients and controls were tested for Hardy–Weinberg Equilibrium by applying the Chi-square test ($\chi^2$ test). Demographic characteristics were compared between the case and control groups by using the Student $t$ test and Chi-square. Differences in genotype distributions and allele frequencies in the cases and controls were compared between the groups for statistical significance by Chi-square statistics ($\chi^2$ test). Binary logistic regression was also applied to evaluate the independent roles of the genotypes against CAD and hypertension risk, and the results were determined via the odds ratio with a 95\% confidence interval. A 2-sided $P$ value below .05 was considered statistically significant. All statistical analyses were performed with the SPSS 17.0 for Windows (SPSS Inc., Chicago, IL).

### Table 1

| Peptides       | SNP    | Ancestor allele | Primer sequence (Product size) |
|----------------|--------|-----------------|--------------------------------|
| Preptin        | rs1003483 | T               | F (5'-3'): ACCTGGATGAAAGTGACGGAGGTGTTG 117 |
|                | rs1004446 | G               | F (5'-3'): ACCTGGATGAGCTCAACCTCAGGATG 106 |
|                | rs2239681  | A               | F (5'-3'): ACCTGGATGTCCTCAAGCTGAAGGTC 99 |
|                | rs680     | T               | F (5'-3'): ACCTGGATGAAAGGCGCTGAAGGTC 110 |
|                | rs3741204  | T               | F (5'-3'): ACCTGGATGCTCCTGGCAAGAATCTC 89 |
| Irisin         | rs16835198 | G               | F (5'-3'): ACCTGGATGCTGAGGAAAGGACAC 98 |
|                | rs3480     | G               | F (5'-3'): ACCTGGATGCTTGGGAAGCGGAAAGG 98 |
| Adropin        | rs2281997  | C               | F (5'-3'): ACCTGGATGCTCCTGGCTGAC 113 |

SNP = single nucleotide polymorphism.
In this study, we investigated the association of eight gene polymorphisms (rs2281997, rs1003483, rs1004446, rs2239681, rs680, rs3741204, rs16835198, and rs3480) with the risk for coronary artery disease (CAD) and hypertension. The study population included 351 patients with CAD and hypertension (CAD+H+), 351 patients with CAD without hypertension (CAD+H-), and 351 control subjects (CAD-H-). The Hardy-Weinberg equilibrium was assessed in all three groups. No significant differences were observed in the genotype and allele frequencies of any of the eight genes among the three groups.

3.3. Results of binary regression models

To further explore the associations, binary regression models were applied. Table 3 presents the results of the regression analysis. The model included age, sex, body mass index (BMI), blood pressure, and glucose levels. Significant results were observed for the following associations: age (β = 0.002, P = 0.010), systolic blood pressure (SBP) (β = 0.001, P = 0.001), diastolic blood pressure (DBP) (β = 0.001, P = 0.001), fasting blood sugar (FBS) (β = 0.001, P = 0.001), triglyceride (TG) (β = 0.001, P = 0.001), total cholesterol (TC) (β = 0.001, P = 0.001), low-density lipoprotein cholesterol (LDL-c) (β = 0.001, P = 0.001), high-density lipoprotein cholesterol (HDL-c) (β = 0.001, P = 0.001), and very low-density lipoprotein cholesterol (VLDL-c) (β = 0.001, P = 0.001). These results suggest that the risk for CAD and hypertension is associated with certain metabolic factors.

4. Discussion

Maintaining energy balance over time is vital to achieve and sustain the health of an individual. Many peptide hormones of the endocrine system play a key role in maintaining energy balance. When energy input is greater than expenditure, the balance is positive; otherwise, the balance is negative. The physical indicator changes with energy imbalance. The main indicators, including body mass index (BMI), lipids, glucose, and insulin levels, can be affected by energy metabolisms and influence the incidence of hypertension and CAD. Preptin, adiponectin, and irisin are the three new players in energy regulation, and the association of their gene polymorphisms with susceptibility to CAD and hypertension was studied in this work. This association in the Chinese population has never been reported.

Adropin is a 4.9 kDa amino acid secreted peptide that is mainly expressed in the liver, brain, and many peripheral tissues. Adropin mainly ameliorates the regulation of lipid metabolism and glucose homeostasis and controls energy balance, insulin resistance, and endothelial functions, all of which are associated with obesity. Irisin is a 112 amino acid exercise-induced peptide that was first reported in 2012 by Bostrom in Harvard University. This peptide is secreted principally in the heart and skeletal muscles and other peripheral tissues, including salivary glands, kidney, and liver. Irisin regulates adipose tissue, can induce the browning adipose tissue, and plays a key protective role in the development of obesity-related diseases, such as insulin resistance, arteriosclerosis, and type 2 diabetes. Adropin and irisin are related to cardiovascular diseases. The former is a potential protective regulator of atherogenesis and cardiovascular diseases. Zhao et al. found that serum adropin level is inversely associated with the severity of coronary atherosclerosis and serum level of homocysteine. Celik et al. reported that the serum adropin level is decreased in patients with cardiac syndrome X and stable CAD. Plasma adropin level is an independent indicator of hypertension. Individuals at risk for cardiovascular disease exhibit some type of irisin resistance. Therefore, irisin may be a possible marker of...
macrovascular disease in people with T2DM because it is reduced in people with T2DM and macrovascular complications, such as CAD. Eugen Brailoiu et al reported that irisin evokes bradycardia by activating the cardiac-projecting neurons of nucleus ambiguous. In the present work, no association was found for irisin (rs16835198 and rs3480) and adropin (rs2281997) gene polymorphisms with susceptibility to CAD and hypertension. This finding may be ascribed to the small sample size or the limited coverage of the selected SNPs for the genomes coding irisin and adropin.

Table 3
Genotypic and allelic distribution of preptin (rs1003483, rs1004446, rs2239681, rs680, and rs3741204), irisin (rs16835198 and rs3480) and adropin (rs2281997) polymorphisms among the 3 studied groups.

| SNP        | CAD+H*(n = 135) | CAD'H*(n = 128) | CAD'H*(n = 109) | 1 vs 2 | 1 vs 3 | 2 vs 3 | 1and 2 and 3 |
|------------|-----------------|-----------------|-----------------|--------|--------|--------|--------------|
| Preptin    |                 |                 |                 |        |        |        |              |
| rs1003483  |                 |                 |                 |        |        |        |              |
| TT         | 65 (48.2)       | 40 (31.3)       | 45 (41.3)       | .019   | .136   | .092   | .054         |
| TG         | 52 (38.5)       | 67 (52.3)       | 55 (50.5)       |        |        |        |              |
| GG         | 18 (13.3)       | 21 (16.4)       | 9 (8.2)         |        |        |        |              |
| Allele T   | 182 (67.4)      | 147 (57.4)      | 145 (66.5)      | .018   | .835   | .043   | .075         |
| Allele G   | 88 (32.6)       | 109 (42.6)      | 73 (33.5)       |        |        |        |              |
| rs1004446  |                 |                 |                 |        |        |        |              |
| GG         | 79 (46.9)       | 54 (35.0)       | 62 (56.0)       | .027   | .714   | .198   | .196         |
| GA         | 56 (41.5)       | 60 (46.0)       | 39 (35.0)       |        |        |        |              |
| AA         | 13 (9.6)        | 8 (6.4)         | 6 (7.3)         |        |        |        |              |
| Allele G   | 201 (74.4)      | 184 (72.9)      | 163 (74.8)      | .506   | .934   | .478   | .883         |
| Allele A   | 69 (25.6)       | 72 (28.1)       | 55 (25.2)       |        |        |        |              |
| rs2239681  |                 |                 |                 |        |        |        |              |
| AA         | 57 (42.2)       | 55 (43.6)       | 40 (35.0)       | .335   | .622   | .508   | .544         |
| AG         | 56 (41.5)       | 60 (46.0)       | 52 (47.7)       |        |        |        |              |
| GG         | 19 (14.3)       | 26 (20.3)       | 16 (16.7)       |        |        |        |              |
| Allele A   | 170 (63.0)      | 145 (56.6)      | 134 (61.5)      | .139   | .735   | .287   | .420         |
| Allele G   | 100 (37.0)      | 111 (43.4)      | 84 (38.5)       |        |        |        |              |
| rs680      |                 |                 |                 |        |        |        |              |
| TT         | 52 (38.5)       | 34 (26.6)       | 33 (30.2)       | .118   | .560   | .694   | .389         |
| TC         | 64 (47.4)       | 72 (56.2)       | 61 (56.0)       |        |        |        |              |
| CC         | 19 (14.1)       | 22 (17.2)       | 15 (13.8)       |        |        |        |              |
| Allele T   | 168 (62.2)      | 140 (54.7)      | 127 (68.3)      | .080   | .373   | .435   | .288         |
| Allele C   | 102 (37.8)      | 116 (45.3)      | 91 (41.7)       |        |        |        |              |
| rs3741204  |                 |                 |                 |        |        |        |              |
| TT         | 87 (64.4)       | 73 (57.0)       | 69 (63.3)       | .255   | .765   | .588   | .169         |
| TC         | 38 (28.2)       | 48 (37.5)       | 34 (31.2)       |        |        |        |              |
| CC         | 10 (7.4)        | 7 (5.5)         | 6 (5.5)         |        |        |        |              |
| Allele T   | 212 (78.5)      | 194 (75.8)      | 172 (78.9)      | .455   | .919   | .420   | .827         |
| Allele C   | 58 (21.5)       | 62 (24.2)       | 46 (21.1)       |        |        |        |              |
| rs16835198 |                 |                 |                 |        |        |        |              |
| GG         | 31 (23.0)       | 30 (23.4)       | 28 (25.7)       | .956   | .885   | .893   | .987         |
| GT         | 72 (53.3)       | 66 (51.6)       | 56 (51.4)       |        |        |        |              |
| TT         | 32 (23.7)       | 32 (25.0)       | 25 (22.9)       |        |        |        |              |
| Allele G   | 134 (49.6)      | 126 (49.2)      | 112 (51.4)      | .925   | .701   | .662   | .922         |
| Allele T   | 136 (60.4)      | 130 (50.8)      | 106 (48.6)      |        |        |        |              |
| rs3480     |                 |                 |                 |        |        |        |              |
| GG         | 12 (8.9)        | 11 (8.6)        | 14 (12.8)       | .853   | .590   | .423   | .699         |
| GA         | 42 (31.1)       | 36 (28.1)       | 34 (31.2)       |        |        |        |              |
| AA         | 81 (60.0)       | 81 (68.3)       | 61 (56.0)       |        |        |        |              |
| Allele G   | 66 (42.4)       | 58 (22.6)       | 62 (28.4)       | .629   | .318   | .149   | .538         |
| Allele A   | 204 (75.6)      | 198 (77.4)      | 156 (71.6)      |        |        |        |              |
| Adropin    |                 |                 |                 |        |        |        |              |
| rs2281997  |                 |                 |                 |        |        |        |              |
| CC         | 102 (75.6)      | 95 (74.2)       | 83 (76.1)       | .201   | .287   | .723   | .387         |
| CT         | 30 (22.2)       | 33 (25.8)       | 26 (23.9)       |        |        |        |              |
| TT         | 3 (2.2)         | 0 (0.0)         | 0 (0.0)         |        |        |        |              |
| Allele C   | 234 (75.3)      | 221 (67.3)      | 192 (68.1)      | .725   | .561   | .809   | .822         |
| Allele T   | 36 (75.3)       | 31 (12.7)       | 26 (11.9)       |        |        |        |              |

CAD+H+ = coronary artery disease, CAD-H+ = control, H+CAD+ = coronary artery disease and hypertension.

* Significant difference (P < .05).
Preptin is a 34 (MW 3948 Da) amino acid peptide that is primarily synthesized in pancreatic beta cells pancreas along with insulin, amylin, and pancreastatin. Preptin is the energy balance regulation molecule in the “beta TC6-F7 beta-cells” of rats as reported by Bucham as early as 2001. Unfortunately, this topic has been rarely studied. The physiological amplifier of glucose-mediated insulin secretion is the most important function of preptin,[28] and preptin gene polymorphisms are associated with the risk of diseases. For example, rs1003483 and rs1004446 are notably associated with high myopia, ovarian cancer, and endometrial cancer in different races.[29–31] Preptin is involved in the development of cardiovascular disease. Cai et al reported that plasma preptin levels are decreased in patients with essential hypertension in a Chinese population,[13] whereas Soha found that an increase in preptin level is associated with hypertension among Egyptians.[14] The contradictory results implied us that ethnic differences about the influence of preptin level exist on the incidence of hypertension, but a link between preptin level and hypertension has been found. Our study also uncovered significant differences for the genotype frequencies rs1003483 and rs1004446 and allele frequencies for rs1003483 of preptin between CAD group with and without hypertension.

### Table 4

| rs1003483  | 1     | 2     | 3     | 1 vs 2 | 1 vs 3 | 2 vs 3 | 1 and 2 and 3 |
|------------|-------|-------|-------|--------|--------|--------|---------------|
| FBS (mg/dL) | 6.45±2.19 | 5.87±1.32 | 6.09±1.27 | .015*   | .331   | .363   | .041*         |
| TC (mg/dL)  | 4.60±1.03 | 4.50±1.04 | 4.83±1.07 | .511    | .089   | .229   |               |
| LDL-c (mg/dL) | 2.47±0.74 | 2.50±0.76 | 2.57±0.80 | .728    | .618   | .756   |               |
| HDL-c (mg/dL) | 1.19±0.31 | 1.20±0.37 | 1.29±0.39 | .903    | .185   | .295   |               |
| VLDL-c (mg/dL) | 0.66±0.45 | 0.63±0.35 | 0.62±0.38 | .617    | .917   | .847   |               |
| TG (mg/dL)  | 11.58±1.46 | 1.42±0.77 | 1.31±0.69 | .287    | .438   | .344   |               |

### Table 5

| rs1004446  | 1     | 2     | 3     | 1 vs 2 | 1 vs 3 | 2 vs 3 | 1 and 2 and 3 |
|------------|-------|-------|-------|--------|--------|--------|---------------|
| FBS (mg/dL) | 6.25±1.97 | 5.97±1.33 | 6.22±1.77 | .209    | .955   | .468   | .443         |
| TC (mg/dL)  | 4.65±1.08 | 4.52±0.99 | 4.50±1.03 | .338    | .554   | .919   | .581         |
| LDL-c (mg/dL) | 2.52±0.77 | 2.50±0.73 | 2.40±0.77 | .831    | .532   | .595   | .812         |
| HDL-c (mg/dL) | 1.22±0.35 | 1.19±0.33 | 1.24±0.43 | .454    | .820   | .537   | .701         |
| VLDL-c (mg/dL) | 0.67±0.46 | 0.58±0.25 | 0.70±0.25 | .077    | .798   | .124   | .177         |
| TG (mg/dL)  | 1.60±1.37 | 1.30±0.58 | 1.48±0.79 | .037*   | .730   | .220   | .105         |

FBS = fasting blood sugar, HDL-c = high-density lipoprotein cholesterol, LDL-c = low-density lipoprotein cholesterol, TC = total cholesterol, TG = triglyceride, VLDL-c = very low-density lipoprotein cholesterol.

Continuous and categorical values are presented as mean ± SD and number, respectively.

*Significant difference (P<.05).
indicate the different genotype and allele frequencies of preptin may also be involved in the hypertension progression among patients with CAD by regulating the preptin levels.

We found the association of different allele frequencies of preptin (rs1003483, rs1004446) with susceptibility to CAD compared with the healthy control in this study. This result was consistent with that of Li’s research results from the Chinese. The findings showed that circulating preptin is increased in patients with positive coronary calcification and can independently predict coronary calcification, which is a specific feature of coronary CAD. We assumed that rs1003483 polymorphism was also a CAD marker; however, this finding must be further verified.

Preptin also plays a fundamental role in insulin secretion, which affects the blood sugar levels and other biochemical parameters. The combination of the above findings regarding the association of the polymorphisms of preptin (rs1003483, rs1004446) with susceptibility to CAD and hypertension motivated us to study the association of rs1003483 and rs1004446 genotypes with various biochemical parameter levels. We found that the FBS levels were significantly different in different rs1003483 genotypes of patients with CAD, implying that the rs1003483 may be a critical gene for preptin to increase or decrease blood glucose level by regulating insulin secretion. Another important finding of this study showed that TG level was significantly higher in rs1004446 GG genotype than that in rs1004446 GA genotype, whereas the frequency of the GG genotype in CAD+H+ is significantly higher than that in CAD+H- patients, indicating rs1004446 polymorphism may be a possible genetic susceptibility factor for hypertension in patients with CAD patients altering TG levels. Furthermore, study in Turkey revealed that preptin levels increase with high BMI, and triglyceride glucose-BMI is a simple and clinically useful surrogate marker for insulin resistance. The genetic polymorphism of preptin may be important on regulating TG level, which was a risk factor for hypertension and CAD susceptibility.

This research has some limitations. First is the small sample size. Future studies must be performed with a large sample size to obtain persuasive results. Second, we failed to acquire enough data, including the BMI of the voluteers, the concentrations of preptin, irisin, and adropin, which are crucial indicators closely related to the functions of these peptides, because of various factors. Thus, we cannot assess the relationship of polymorphism and some of these data. Future studies must focus on collecting data to offer support for a profound conclusion.

5. Conclusion

To the best of our knowledge, this study first proposed a potential influence of preptin polymorphism on CAD and hypertension susceptibility in a Chinese population. The findings suggest that further studies must be conducted in different racial and ethnic groups with large sample sizes.

Author contributions

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