Adropin and Apelin -12, two better predictors of metabolic syndrome in obese children

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Abstract

Objective

Metabolic syndrome (MetS) is the most extensively described condition associated with childhood and adolescent obesity and is a challenging public health issue. Studies regarding the specificity and sensitivity of serum levels of adropin and apelin -12 as predictors of MetS are limited. The aim was to evaluate the prospective association between adropin and apelin -12 concentrations and MetS and sensitivity as predictors of MetS in the obese children.

Methods

This study involved 138 children. The study group included obese subjects with MetS and the two control groups included obese without MetS and normal weight subjects. Anthropometric parameters and clinical data were collected. Plasma levels of apelin -12, adropin, leptin, adiponectin and TNF-α were measured.

Results

Obese children with MetS had significantly higher levels of apelin -12 and significantly lower levels of adropin compared to those without MetS. In logistic regressions, we identified that apelin -12 was risk factor for metabolic syndrome and adropin was the protecting factors of having MetS after adjustment for age, sex and puberty. Furthermore, adropin and apelin -12 are two more sensitive predictors of metabolic syndrome than leptin and adiponect using ROC method.

Conclusion

Serum adropin and apelin -12 levels can be useful biomarkers for evaluation of the risk of MetS in obese children. This may provide a novel approach for treatment or prevention of MetS development.

Background

The growing worldwide prevalence of childhood obesity has become most of the health-threatening consequences of juvenile and early-onset obesity increases the risk related to morbidity and mortality, particularly the metabolic syndrome [1, 2]. Metabolic syndrome (MetS) is by far the most extensively described condition associated with childhood and adolescent obesity and has traditionally been supposed to be a risk factor for adult cardiovascular and metabolic
complications[3]. In adolescents as in adults, MetS is defined as a clustering factors, including central/abdominal obesity, hypertension, impaired glucose tolerance and dyslipidaemia, particularly decreased high density lipoprotein cholesterol (HDL-C) and hypertriglyceridemia (high blood triglycerides (TG)) [4]. Although obesity is fundamental to MetS, however, the pathogenesis behind obesity development and progression to MetS has not been clearly determined. Therefore, it becomes important to discover new biomarkers of metabolic syndrome in childhood obesity and this may be helpful in preventing development of its complications including diabetes and cardiovascular disease (CVD).

Several peptide hormones which secreted by the gut, adipocytes and liver can regulate energy metabolism and maintain glucose homeostasis[5–6]. Therefore, these hormones are considered to provide new clues for the treatment of metabolic syndrome and type 2 diabetes. Adropin, a product of the Energy Homeostasis Associated (Enho) gene, was recently identified as a novel factor involved in nutrient intake and metabolic homeostasis in obese insulin resistant mice[7]. It reported that a decline in adropin may associate with a higher risk of obesity, insulin resistance, and probably MetS, whereas overexpression of adropin may contribute to promot glucose utilization, improve hyperinsulinemia, fatty liver, and dyslipidemia in obesity[8].

Apelin, a bioactive peptide were first isolated from bovine stomach, is an endogenous ligand of the orphan G protein-coupled receptor, APJ [9]. Apelin has several active molecular forms in different tissues including apelin-36 or apelin-13 and apelin-12. Apelin are widely expressed in mammal tissues and play an important role in energy metabolism[10–11]. Previous research found that serum levels of apelin were significantly correlated with nutritional status and parallel insulin plasma levels in mice [12]. Furthermore, some studies have found apelin to be increased in obese and diabetic persons as well as in hyperinsulinemic subjects[13]. Recently, other studies have found that apelin expression was regulated by insulin and it may be involved in regulation of glucose homeostasis in obesity [14].

Up to now, only a few studies investigate the relationship between MetS and serum adropin or apelin − 12 levels in obese patients, respectively. To our knowledge, adropin and apelin − 12 have not been studied together in obese patients with MetS compared with obese patients without MetS and normal
subjects, especially among children, and consequently, their possible combined roles in relation to MetS are unknown. The aim of current study was to examine the prospective association between adropin and apelin – 12 concentrations and MetS or its components in children and to investigate the applicability of adropin and apelin – 12 levels for the diagnosis of childhood MetS.

Methods

Subjects

138 children and adolescents (75 boys, 63 girls) aged 7 to 14 years were consecutively included in this study. Of these, 100 were referred to the pediatric endocrinology outpatient clinic with complaint of excessive weight gain and constituted the study group. Thirty eight healthy children were recruited as controls. The exclusion criteria were presence of endocrine disease (e.g., hypothyroidism and Cushing’s disease), any syndrome associated with obesity (e.g., Prader–Willi and Laurence–Moon–Biedle syndromes), acute or chronic infectious disease, and a history of drug use. Written informed consent was obtained from all subjects and their parents. The study protocol was approved by the ethics committee of Xi’an Jiaotong University.

Anthropometric Measurements

Height was measured in a standing position without shoes using stadiometer with a sensitivity of 0.1 cm). Weight was measured wearing light clothing using a scale sensitive to the nearest 0.1 kg. BMI was calculated by dividing weight (kg) by height squared (m²). Waist and hip circumferences were measured using a plastic tape to the nearest 0.1 cm. WHR was calculated as the ratio of waist and hip circumferences. Systolic and diastolic blood pressures (SBP and DBP, respectively) were obtained using the oscillometric device OMRON705IT after a rest for a minimum of 10 min. Hypertension was defined as a systolic or a diastolic blood pressure above the 95th percentile for age and sex according to BP reference standards for Chinese children[15].

Biochemical Measurements

Peripheral venous blood samples were collected from all subjects after a 12-hour overnight fast. Fasting serum glucose, triglyceride (TG), total cholesterol (TC), and high-density lipoprotein cholesterol (HDL-C) concentrations were assayed by an autoanalyzer (Hitachi 747; Hitachi, Tokyo,
Japan). Serum insulin was measured using an automated immunoassay analyzer. The homeostasis model assessment of insulin resistance (HOMA-IR) was calculated by fasting glucose (mmol/L) \times fasting insulin (IU/L)/22.5.

Serum apelin – 12 and adropin analyses were performed by enzyme-linked immunosorbent assay (ELISA) (USCN Life Science Inc., Wuhan, China) according to the manufacturer’s instructions. The intra- and interassay coefficients of variation were < 7% for apelin – 12 and < 12% for adropin. Serum leptin, adiponectin and tumor necrosis factor-α (TNF-α) concentrations were also measured by Elisa kits (Excell, Shanghai, China) with all inter-and intraassay CV < 10%.

Definition Of MetS

According to the Chinese definition of pediatric metabolic syndrome [16], we classified subjects as having the MetS if they had central obesity (waist circumference greater than 90th percentile for age and sex) in addition to two or more of the following characteristics: (i) hyperglycaemia: FBG ≥ 5.6 mM or 2 h OGTT ≥ 7.8 mM, but < 11.1 mM or type 2 diabetes. (ii) hypertension: systolic BP ≥ 95th percentile for age and sex or diastolic BP ≥ 95th percentile for age and sex. (iii) HDL-C < 1.03 mM; (iv) TG ≥ 1.47 mM.

Statistics

All the statistic procedures have been performed using SPSS 22.0. Normal distributions were evaluated using the Kolmogorov-Smirnov test, and variables were shown as mean ± SD. The Bonferroni-adjusted ANOVA test was performed to compare means between more than two subgroups for normally distributed data. Frequency differences were evaluated using \( x^2 \) test between quartiles of apelin – 12 and adropin. Multiple logistic regressions were performed to determine risk factors of MetS. Receiver operating characteristic (ROC) curve was constructed to determine the best threshold value for apelin – 12 and adropin in predicting MetS diagnosis. P value < 0.05 was considered statistically significant.

Results

Clinical and biochemical characteristic of subjects

A total of 138 subjects were enrolled in this study, including 100 obese children and 38 control
children. Of these, 100 obese children were further classified into obese without MetS and obese with MetS two subgroups according to the presence of MetS. Table 1 shows anthropometric and clinical indices for the subjects. In terms of age, gender and pubertal state, there were no significant differences among the 3 groups. MetS components, including blood pressure, BMI, SDS-BMI, WC, TG, FBG and 2hPG levels were significantly higher among MetS children compared with both without MetS children and control subjects, while HDL-C was lowest in the case patients (Table 1).

**Table 1**
Clinical and biochemical characteristic of control and obese study population according to the presence of MetS

| Variable | Control (38) | Obese without MetS(50) | Obese with MetS(50) | p value ANOVA | p value Bonferroni post hoc test |
|----------|-------------|------------------------|---------------------|---------------|---------------------------------|
| Age (y)  | 10.68 ± 2.61| 10.78 ± 2.10           | 10.03 ± 1.82        | 0.005         | 0.297<sup>a</sup> 0.065<sup>b</sup> 0.078<sup>c</sup> |
| BMI (kg/m²) | 16.20 ± 2.13| 25.82 ± 4.09           | 28.81 ± 3.15        | 0.000         | 0.000<sup>a</sup> 0.000<sup>b</sup> 0.000<sup>c</sup> |
| SDS- BMI | 2.68 ± 0.34 | 2.73 ± 0.42<sup>b</sup> | 3.01 ± 0.51         | 0.000         | 0.000<sup>a</sup> 0.000<sup>b</sup> 0.000<sup>c</sup> |
| WHtR     | 0.43 ± 0.05 | 0.51 ± 0.22            | 0.53 ± 0.21         | 0.020         | 0.073<sup>a</sup> 0.008<sup>b</sup> 0.938<sup>c</sup> |
| WC (cm)  | 61.01 ± 6.84| 87.87 ± 7.72           | 95.29 ± 9.88        | 0.000         | 0.000<sup>a</sup> 0.000<sup>b</sup> 0.000<sup>c</sup> |
| WHR      | 0.85 ± 0.05 | 1.00 ± 0.05            | 0.97 ± 0.07         | 0.000         | 0.000<sup>a</sup> 0.000<sup>b</sup> 0.059<sup>c</sup> |
| SBP (mm Hg) | 92.2 ± 19.2 | 112.5 ± 10.4           | 123.1 ± 11.1        | 0.000         | 0.000<sup>a</sup> 0.000<sup>b</sup> 0.001<sup>c</sup> |
| DBP (mm Hg) | 60.2 ± 5.8  | 68.7 ± 9.40            | 71.0 ± 9.6          | 0.000         | 0.000<sup>a</sup> 0.000<sup>b</sup> 0.239<sup>c</sup> |
| FPG(mmol/l) | 4.80 ± 0.33 | 5.05 ± 0.38            | 5.15 ± 0.55         | 0.001         | 0.010<sup>a</sup> 0.000<sup>b</sup> 0.307<sup>c</sup> |
| 2hPG(mmol/l) | 5.43 ± 0.52 | 5.99 ± 0.74            | 6.10 ± 0.84         | 0.036         | 0.006<sup>a</sup> 0.000<sup>b</sup> 0.546<sup>c</sup> |
| Insulin(uU/ml) | 8.90 ± 2.58 | 14.56 ± 6.62           | 18.63 ± 7.32        | 0.000         | 0.000<sup>a</sup> 0.000<sup>b</sup> 0.002<sup>c</sup> |
| HOMA-IR  | 1.55 ± 0.68 | 3.26 ± 1.47            | 4.20 ± 1.75         | 0.000         | 0.000<sup>a</sup> 0.000<sup>b</sup> 0.003<sup>c</sup> |
|                  | Control | Obese without MetS | Obese with MetS | p-value
|------------------|---------|-------------------|-----------------|---------|
| AST (IU/L)       | 28.17 ± 7.19 | 30.4 ± 10.04     | 31.45 ± 14.45   | 0.424  |
| ALT (IU/L)       | 16.92 ± 7.67 | 34.08 ± 17.06    | 39.4 ± 19.5     | 0.000  |
| TC (mmol/l)      | 3.75 ± 0.66  | 4.15 ± 0.85       | 4.21 ± 0.67     | 0.011  |
| TG (mmol/l)      | 0.94 ± 0.33  | 1.16 ± 0.44       | 1.64 ± 0.71     | 0.000  |
| HDL-C (mmol/l)   | 1.13 ± 0.29  | 1.19 ± 0.21       | 1.02 ± 0.22     | 0.007  |
| Adiponectin (lg/ml) | 3.92 ± 1.04 | 3.53 ± 1.70       | 2.88 ± 1.44     | 0.019  |
| Leptin (ng/ml)   | 18.25 ± 2.07 | 66.21 ± 25.21     | 71.46 ± 23.12   | 0.000  |
| LAR (ng/lg)      | 4.62 ± 1.01  | 22.51 ± 17.82     | 33.51 ± 18.43   | 0.000  |
| TNF-a (ng/ml)    | 4.53 ± 1.05  | 14.23 ± 3.65      | 19.62 ± 5.62    | 0.000  |
| Apelin − 12 (pg/ml) | 2.01 ± 0.93 | 1.60 ± 0.59       | 1.56 ± 0.42     | 0.128  |
| Adropin (ng/ml)  | 9.68 ± 3.04  | 7.91 ± 2.40       | 7.05 ± 2.06     | 0.001  |

ANOVA test. Comparison between the following: a Control vs Obese without MetS; b Obese without MetS vs Obese with MetS; c Control vs Obese with MetS; Data are expressed as mean ± SD.

Abbreviations: BMI, body mass index; SDS-BMI, BMI s.d. score; WHR, waist-height ratio; WC, Waist circumference; WHtR, Waist-to-hip ratio; SBP, systolic blood pressure; DBP, diastolic blood pressure; HDL-C, high-density lipoprotein cholesterol; LDL-C low-density lipoprotein, AST, aspartate aminotransferase; ALT, alanine aminotransferase; FPG, fasting plasma glucose; HOMA-IR Homeostasis Model Assessment of insulin resistance, MetS metabolic syndrome, TC, total cholesterol; TG, triglycerides; LAR, leptin-to-adiponectin ratio; TNF-α, tumour necrosis factor-α; 2hPG, 2 h plasma glucose.

Adropin, Apelin − 12, Leptin, Adiponectin and Leptin / Adiponectin Ratio

In one-way ANOVA, a significant difference existed between 3 groups with regard to TNF-a and adropin levels (Table 1). Obese children with MetS had significantly higher apelin − 12 levels than obese individuals without MetS. Serum adiponectin and leptin concentrations was not statistically different between obese with MetS and without MetS groups, but the LAR levels were significantly higher in obese with MetS than without MetS groups (Table 1).

Prevalence of MetS and its components by quartile of adropin and apelin − 12

When comparing prevalence of MetS and its components of obese children in relation to the
circulating adropin and apelin – 12 levels, we observed that patients belonging to the highest apelin – 12 quartile had a higher prevalence of hypertriglyceridemia, hypo-high-density lipoproteinemia and MetS than those belonging to the lowest quartile (Table 2). However, prevalence of hypertriglyceridemia, hypo-high-density lipoproteinemia and MetS significantly reduced with increasing quartile of adropin (Table 3). Prevalence of hypertension and hyperglycaemia was not statistically different between quartiles of adropin and apelin – 12.

| Apelin – 12 Quintiles | Q1 (346–1071) | Q2 (1110–1514) | Q3 (1527–2057) | Q4 (2063–7363) | p value |
|-----------------------|---------------|----------------|----------------|----------------|---------|
| Hypertension          | 11.25%        | 11.25%         | 12.50%         | 11.25%         | 0.926   |
| Hypertriglyceridemia  | 6.25%         | 7.50%          | 11.25%         | 12.50%         | 0.041   |
| Hyper-high-density lipoproteinemia | 8.75%       | 10.00%         | 10.00%         | 13.75%         | 0.039   |
| Hyperglycaemia        | 6.25%         | 6.25%          | 3.75%          | 5.00%          | 0.613   |
| MetS                  | 7.50%         | 12.50%         | 13.75%         | 16.25%         | 0.021   |

| Adropin Quintiles | Q1 (5.21–6.64) | Q2 (6.74–8.41) | Q3 (8.48–9.95) | Q4 (9.96–20.82) | p value |
|-------------------|----------------|----------------|----------------|----------------|---------|
| Hypertension      | 13.75%         | 11.25%         | 13.75%         | 7.50%          | 0.721   |
| Hypertriglyceridemia | 12.50%       | 10.00%         | 8.75%          | 7.50%          | 0.032   |
| Hyper-high-density lipoproteinemia | 15.00%       | 10.00%         | 10.00%         | 8.75%          | 0.042   |
| Hyperglycaemia    | 5.00%          | 6.25%          | 6.25%          | 3.75%          | 0.685   |
| MetS              | 18.75%         | 13.70%         | 8.70%          | 8.70%          | 0.013   |

*Multivariate Logistic Regression Analysis For MetS*

In the logistic regressions, using MetS as the dependent variable, we identified that apelin – 12 was risk factor for metabolic syndrome in addition to WC and WHR, after age, sex and puberty adjustment. However, adropin was the protecting factors of having MetS after adjustment for age, sex and puberty (Table 4).
### Table 4

Logistic regression analysis using MetS as the dependent variable in obese children

| Variable          | β    | S.E.  | Wald  | β-standardized | p     |
|-------------------|------|-------|-------|----------------|-------|
| WC (cm)           | 0.186| 0.065 | 8.231 | 1.205          | 0.004 |
| BMI               | -0.037| 0.146 | 0.063 | 0.964          | 0.801 |
| WHR               | -1.925| 1.192 | 3.072 | 0.000          | 0.079 |
| WHtR              | -13.162| 6.080 | 4.660 | 0.000          | 0.031 |
| LAR (ng/l)        | 0.018| 0.020 | 0.786 | 1.018          | 0.375 |
| Adiponectin (lg/ml) | 0.000| 0.000 | 0.008 | 1.000          | 0.929 |
| Leptin (ng/ml)    | 0.000| 0.000 | 0.000 | 0.000          | 1.000 |
| Apelin −12(pg/ml) | 0.206| 0.092 | 5.010 | 1.288          | 0.025 |
| TNF-α (ng/ml)     | 0.276| 0.282 | 0.952 | 1.371          | 0.323 |
| Adropin (ng/ml)   | 0.000| 0.000 | 3.993 | 1.000          | 0.046 |

**ROC Curves For Identification Of Subjects With MetS**

In order to predict a threshold value for the diagnosis of MetS by using adropin and apelin − 12, the ROC method was used. The area under the ROC curve was 0.71 for adropin levels (P = 0.002). The sensitivity and specificity values of adropin levels were 83% and 74%, respectively (cutoff value 6.71). Area under the curve was 0.63(P = 0.042) and cut-off point was 1.44 for apelin − 12 with a sensitivity of 65% and specificity of 72%. Area under the curve was low for adiponectin and leptin and the P-value was not significant in obese children(Fig. 1).

**Discussion**

To the best of our knowledge, there were no reports of using ROC analysis for prediction of MetS using serum adropin and apelin − 12 levels. The current study is the first to report sensitivity, specificity, and cut-off points as predictors and risk factors of MetS in obese children.

In one-way ANOVA, we found that lower levels of serum adropin in obese children with MetS compared without MetS patients and controls, and significantly higher serum apelin − 12 levels were observed in obese children with MetS than without MetS, but there was no difference between obese without MetS and the controls. Limited studies have investigated adropin and apelin − 12 levels in patients with metabolic disorders [17–20]. Our findings are consistent with those of previous studies.

We speculated that decreased adropin in circulation may promote fat accumulation in the body and accelerated the progress of "healthy obese" to metabolic disorders. However, high levels of apelin − 12 in the circulation mainly play a role in the process from obesity health to metabolic disorders.

These data suggest that adropin may be associated with the prevention of MetS in healthy obese children.
subjects, but apelin − 12 plays a role in promoting progression of metabolic syndrome in healthy obese subjects. Furthermore, Serum adiponectin and leptin concentrations have significant differences between obese with MetS and the controls, while there was no difference between obese with MetS and without MetS. These two adipokines which secreted by adipose tissue, may be mainly related to fat accumulation in body[21–22].

In obese children, with increasing quartile of adropin, prevalence of hypertriglyceridemia, hypo-high-density lipoproteinemia and MetS significantly reduced, in contrast, prevalence of hypertriglyceridemia, hypo-high-density lipoproteinemia and MetS significantly increased with increasing quartile of apelin − 12, while prevalence of hypertension and hyperglycemia has not changed. The above results show that high levels of serum adropin and low levels of apelin − 12 have an important function in maintaining normal metabolic state even if the person was obese, the so-called “healthy obese phenomenon”, and changes in serum adropin and apelin − 12 have significant effects on lipid metabolism. Our results are in agreement with previously published studies. Kumar et al. confirmed that AdrKO mice rapidly exhibited dyslipidemia[23], therapy with synthetic adropin improves fatty liver and dyslipidemia in mouse models of obesity[24]. There is very limited research on the relationship between apelin − 12 and lipid metabolism. Future studies are needed to clarify the potential role of apelin − 12 in lipid metabolism.

Previous research demonstrated that leptin and adiponectin predicts the development of the MetS independently of obesity, and measuring the plasma concentration of leptin and adiponectin may be useful for management of the metabolic syndrome[25–26]. For determining the efficacy in identification of subjects with MetS, we analyzed the optimal cut-off points, AUC, sensitivity, specificity, and P-value of the ROC curves for leptin, adiponectin, adropin and apelin − 12. AUC from leptin and adiponectin ROC curves were 0.59 and 0.39 in obese children, respectively, and the P-value was not significant. AUC from adropin and apelin − 12 were higher than leptin and adiponectin, was 0.62 and 0.70 respectively in obese children, and the P-value was 0.046 and 0.002. The above results suggest that adropin and apelin − 12 are two more sensitive predictors of metabolic syndrome than leptin and adiponectin. The optimal cut-off point for adropin and apelin − 12 levels were
8.79 ng/mL and 1.44 ng/mL respectively in obese children, calculated by ROC curve. These data suggest that if plasma adropin does not remain higher than 8.79 ng/mL or apelin – 12 levels does not remain lower than 1.44 ng/mL along with developing obesity, then MetS may develop. Cut-off points for serum adropin and apelin – 12 levels in predicting MetS have not been studied in children.

**Conclusion**

Data from the present study suggest that obese children with MetS had significantly higher levels of apelin – 12 and significantly lower levels of adropin compared to those without MetS. In logistic regressions, we identified that apelin – 12 was risk factor for metabolic syndrome and adropin was the protecting factors of having MetS after adjustment for age, sex and puberty. Furthermore, adropin and apelin – 12 are two more sensitive predictors of metabolic syndrome than leptin and adiponect using ROC method. This may provide a novel approach for treatment or prevention of MetS development.

**Abbreviations**

MetS, Metabolic syndrome ; BMI, body mass index; DBP, diastolic blood pressure; FPG, fasting plasma glucose; HDL-C, high-density lipoprotein cholesterol; HOMA-IR, homoeostasis model of insulin resistance; IR, Insulin resistance; LAR, leptin-to-adiponectin ratio; LDL-C, low-density lipoprotein; SDS-BMI, BMI s.d. score; TC, total cholesterol; TG, triglycerides; SBP, systolic blood pressure; TNF-α, tumour necrosis factor-α; WHtR, waist-height ratio; WC, Waist circumference; WHR, Waist-to-hip ratio.

**Declarations**

**Acknowledgement**

Not applicable.

**Ethics and consent to participate**

This study was approved by the Ethics Committee of the Second Affiliated Hospital of Xi’an JiaoTong University. The study was in compliance with the Declaration of Helsinki for clinical research. All children and their parents both provided written informed consent before participating in the study.

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Competing interests

The authors declare that they have no competing interests.

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Figures

Figure 1

The area under the receiver operating characteristic (ROC) curve for MetS in obese children.

A. Apelin -12, B. Adropin.