Copeptin and Nesfatin-1 are interesting interrelated biomarkers playing a role in the pathogenesis of insulin resistance in Chinese obese children

yanfeng y xiao (✉ xiaoyanfenggroup@sina.com)

Xi'an Jiaotong University Medical College second Affiliated Hospital

Chunyan Yin

Xi'an Jiaotong University Second Affiliated Hospital

Weihua Liu

frist hospital of xi'an

Erdi Xu

Xi'an Jiaotong University Second Affiliated Hospital

LV Weicheng

laojun town central hospital of hantai district

Qi Lu

Xi'an Jiaotong University Second Affiliated Hospital

Research article

Abstract

Background Recently, copeptin and nesfatin-1 have been identified as interesting novel peptides playing a role in the pathogenesis of obesity-related insulin resistance in adults, respectively. However, the relationship between them has not been elucidated; and their circulating levels in obese children have not been adequately studied. Therefore, the current study aimed to investigate whether their levels are altered in Chinese obese children and to study the correlation of these two peptides with each other and with insulin resistance and other biochemical parameters.

Methods A total of 120 children were enrolled in this study, including 80 obese children and 40 lean controls. Anthropometric parameters and clinical data of all subjects were collected and circulating TNF-α, adiponectin, leptin, copeptin and nesfatin-1 levels were detected using enzyme-linked immunosorbent assays.

Results Serum copeptin and nesfatin-1 levels were significantly elevated in obese children and children with insulin resistance compared to control subjects. In addition, nesfatin-1 and copeptin levels were found to be significantly positively correlated with one another in pearson's correlation and partial correlation. More importantly, multiple regression analysis used nesfatin-1or copeptin as the dependent parameters and significant correlation between nesfatin-1 and copeptin with each other and the associations between each of them with HOMA-IR were detected.

Conclusion These findings are novel and shed light on the possible interplay role of these two molecules in obesity-related insulin resistance.

Background

Over the past decade, Insulin resistance (IR) has gained special attention since it has been largely postulated as the fundamental aspect of the etiology of type 2 diabetes, metabolic syndrome, hypertension, atherosclerosis and polycystic ovarian disease [1]. Although insulin resistance in children was found in other diseases, such as polycystic ovary, obesity was still confirmed to be the major risk factor for the development of insulin resistance in children [2−3]. In a recent study conducted in American adolescents, more than 50% obese subjects have insulin resistance [4] and adiposity was considered to be the most important factor affecting insulin sensitivity [5]. However, mechanisms behind obesity development and progression to Insulin resistance have not been fully unraveled, and no specific therapy has been identified yet.

Obesity is a complex disease involving a number of different peptides, and these peptides and their receptors control energy metabolism and participate in progression of obesity-related diseases. Copeptin, a 39-aminoacid glycopeptides, is a cleavage product of the C-terminal part of the preprovasopressin (pre-proAVP). It is released after stress situations and is correlated to AVP levels in plasma[6]. Beside the action of AVP exerts on BP including vasoconstriction, volume control, and direct cardiac effects, VP exerts major effects on glucose and lipid metabolism [7]. Clinical data has showed that elevated copeptin

levels have been associated with increased risk of insulin resistance, type 2 diabetes, hypertension, hyperlipidemia, independently from obesity [7]. Nesfatin-1, a 82 aminoacids anorexigenic peptide, is produced from the nucleobindin2 (NUCB2)precursor, and is expressed in several tissues including neurons, pancreas, liver, adipose tissue and skeletal muscles [8]. Many studies have suggested that nesfatin-1 plays a role in modulating energy metabolism [9−10]. Recently, nesfatin-1 was proposed to contribute to the regulation of insulin secretion from pancreatic beta-cells[11−12].

Up to now, most of research on copeptin and nesfatin-1 have been conducted in animals and adult obese and type 1 and/or 2 diabetic patients [12−14]. To our knowledge, only a few studies investigate the relationship between metabolic parameters and serum copeptin and nesfatin-1 levels in obese children [15−18], and interrelation between copeptin, nesfatin-1and insulin resistance is scarce. The current study aimed to investigate circulating levels of copeptin and nesfatin-1 in Chinese obese children and to identify the correlation of these 2 interesting peptides with one another and between each of them with other biochemical parameters like insulin resistance, adiponectin, leptin, and anthropometric parameters.

Methods

Study population

For this study, we recruited 80 consecutive obese children with a body mass index (BMI) above the 95th percentile, who applied to our outpatient clinics at the Second Affiliated Hospital of Xi'an Jiaotong University with complaint of weight gain, and 40 non-obese controls with a BMI below the 85th percentile[19]. Children with previous diagnosis 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/or a history of drug use were excluded from the study.

Anthropometric measurements

Weight and height were measured in all subjects wearing light clothing without shoes using a scale and a stadiometer with a sensitivity of 0.1kg and 0.1cm respectively. BMI was calculated as the body weight in kilograms divided by the square of height in meters. Waist and hip circumferences were measured using standard techniques to the nearest 0.1 cm. WHtR 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. Tanner stages were used to evaluate pubertal development [20]. A testicular volume of ≥4mL in boys and stage 2−5 of breast development in girls were considered to enter puberty.

Biochemical Measurements

Blood samples were taken after 12 h of overnight fasting. Fasting serum glucose, lipid profile, alanine aminotransferase (ALT), aspartate aminotransferase (AST) concentrations were measured by an

automatic analyser. Serum insulin levels were measured using a double-antibody radioimmunoassay (RIA). Serum copeptin, nesfatin-1, leptin, adiponectin, and tumor necrosis factor-α (TNF-α) concentration were detected using using a commercially available enzyme-linked immunosorbent assay (ELISAs) (USCN Life Science Inc., Wuhan, China). The inter-assay and the intra-assay coeffi-cients of variation were 10 % and 15 %, respectively.

Definition of IR

The homeostasis model assessment of insulin resistance was calculated using the following formula: HOMA- IR = fasting insulin (μU/ml) × fasting glucose (mmol/L)/22.5, Insulin resistance is defined as values of HOMA index for prepubertal > 2.5 and pubertal > 4.0[21].

Statistical analysis

SPSS 19.0 statistical software was used for all analyses, and $p < 0.05$ (two-tailed) was considered statistically significant. Distribution of data was evaluated using the Kolmogorov-Smirnov test, and data was shown as the mean ± SD. Differences between obese and control groups were assessed using Student's t-test. Pearson's correlation and partial correlation were used to analyze the correlation between copeptin and nesfatin-1and metabolic parameters, anthropometric variables. Furthermore, multiple linear regressions analyses were calculated with HOMA- IR, copeptin or nesfatin-1 as the dependent variable adjusted for age, gender and pubertal stage, and with the independent variables including anthropometric variables, metabolic parameters, and some other clinical indicators.

Results

The clinical characteristics of subjects

A total of 80 obese subjects (42 males, mean age: 10.9±2.1 yr) and 40 lean subjects (21 males, mean age: 11.03±1.9 yr) were included in this study. There were no differences of age, gender and pubertal stage distribution between lean and obese groups. Obese children present higher anthropometric indicators including BMI, SDS-BMI, weight, WHtR, WC and WHR. There were statistically significant differences between obese and lean subjects in terms of SBP, DBP, insulin, TG, TC, HOMA-IR, AST and ALT levels (p<0.05), whereas FPG, HDL-C levels were similar (p>0.05). Serum leptin, TNF-a, copeptin and nesfatin-1 concentrations and the leptin-to-adiponectin ratio (LAR) were significantly higher in obese children compared to controls, but serum levels of adiponectin was significantly lower in obese children compared to lean children (p<0.05) (Table 1).

Serum adipokines and peptides concentrations in Subgroups

Adiponectin, leptin, LAR, TNF-a, copeptin and nesfatin-1 values were similar between male and female children (Table 2). Pubertal children had significantly higher leptin, LAR, copeptin and nesfatin-1 levels when compared with prepubertal children (Table 3). However, comparisons of children regarding the presence of pubertal signs showed significant lower adiponectin compared with prepubertal children

(p<0.05), (Table 3). Moreover, all participants were classified into insulin-resistant group (IR group) and non-insulin-resistant group (Non-IR group) according to their HOMA-IR. Children with IR had higher leptin, LAR, copeptin and nesfatin-1 than non-IR group. Serum TNF-a and adiponectin levels were similar in IR and non-IR groups(Fig 1).

Correlations of copeptin or nesfatin-1 with clinical variables

We investigated a potential association of copeptin or nesfatin-1 with other clinical variables by Pearson's correlation and partial correlation in obsese children (Table 4). In subjects, copeptin was significantly positively correlated with weight, BMI, SDS-BMI, WC and WHtR (p < 0.05), while there were no correlations with age and WHR (p > 0.05). In addition, copeptin was positively correlated with insulin, HOMA-IR, blood pressure, HDL-C, leptin, LAR and nesfatin-1. Considering the effects of puberty and weight, we use puberty, age, gender and SDS-BMI as correction factors in the following statistics. After adjustment for the above indicators in partial correlation analysis, we found that HOMA-IR, DBP, HDL-C, leptin, LAR and nesfatin-1 were still significantly correlated with copeptin. After that, we determined a potential correlation between nesfatin-1 with other clinical variables in children. We observed associations between nesfatin-1 with weight, BMI, SDS-BMI, WC and WHR. Interestingly, we also found a positive correlation between nesfatin-1 and FPG, HOMA-IR, blood pressure, HDL-C, TNF-a, leptin, LAR and copeptin levels in the circulation, and this correlation is independent of puberty, age, gender and SDS-BMI (Table 4).

Multiple regression analysis to evaluate the association of HOMA-IR, copeptin or nesfatin-1 with other clinical variables in Chinese obese children

In multiple linear regression analysis, HOMA-IR was used as the dependent variable and the factors associated with it, including SDS-BMI, WC, WHR, TG, FPG, ALT, SBP, DBP, leptin, LAR, copeptin and nesfatin-1 were used as the independent variables. We confirmed that LAR, copeptin and nesfatin-1 were independent predictors of Insulin resistance index in addition to SDS-BMI, WC and ALT, contributing 5%, 8% and 10% to the variability, respectively (Table 5).

In addition, in multiple linear stepwise regression analysis, using copeptin or nesfatin-1 as dependant variable and SDS-BMI, WC, WHR, TG, FPG, ALT, SBP, DBP, leptin, LAR, HOMA-IR and copeptin/ nesfatin-1 as independent variables, we identified that copeptin and nesfatin-1 were remained significantly associated with each other in addition to SDS-BMI, HOMA-IR and DBP (Table 5).

Discussion

Insulin resistance has been largely postulated as the onset of metabolic impairment underlying obesity and metabolic syndrome [22]. As the incidence of childhood obesity rises, Insulin resistance has become the most important risk factor affecting children's health, so it becomes important to discover the early biomarker of IR in children and adolescents with obesity. Recent studies have found that peptides are related to appetite regulation, energy homeostasis, increased blood pressure, inflammation, and immune activity [23]. Therefore, we use the two peptides copeptin and nesfatin-1 as possible markers to predict

insulin resistance and investigate the relationship between these two indicators and the insulin resistance index in obese children. Our data showed that copeptin and nesfatin-1 were significantly elevated in the circulation of obese children. In addition, copeptin and nesfatin-1 levels were found to be significantly positively correlated with each other and were significantly positively correlated with the insulin resistance index independent of puberty, age, gender and SDS-BMI. Moreover, in different multiple linear regression models, when using HOMA-IR as the dependent variable, we confirmed LAR, copeptin and nesfatin-1 as independent predictors of HOMA-IR in addition to SDS-BMI, WC and ALT. When using copeptin or nesfatin-1 as the dependent variable, in addition to BMI, DBP and HOMA-IR, copeptin and nesfatin-1 are significantly associated with each other. The data indicates that these two interrelated molecules are reliable biomarkers of the presence of IR, and these molecules can be used as a diagnostic tool in clinical practice.

Many hormonal peptides which have been found in hypothalamus and pituitary are involved in the regulation of satiety and play important roles in body weight homeostasis. In high-fat-fed mice, Ramanjaneya et al. have found that nesfatin-1 expression was significantly increased and play key roles in controlling food intake [24], but serum nesfatin-1 levels in patients with obesity are still controversial. Ramanjaneya et al. demonstrated increased nesfatin-1 levels in obese subjects and showed significant positive correlation between BMI and nesfatin-1 levels [24], while Abaci et al. [25] found that nesfatin-1 levels decreased and observed a significant negative correlation between nesfatin-1 and BMI-SDS in obese subjects. Our data showed that serum nesfatin-1 levels were significantly higher in the obese children than controls. The reason of conflicting results could be due to the different sample sizes included in these studies or other currently undefined factors that may affect nesfatin-1. In addition, the present study that serum nesfatin-1 concentrations were strongly and positively correlated with WHR, but not correlated with WHtR. In contrast, serum copeptin concentrations were positively associated with WHtR, but not associated with WHR. WHR is a practical index of regional adipose tissue distribution and is correlated with the mass of all adipose tissue including abdominal subcutaneous and visceral fat, but WHR value did not account for the large variations in the level of abdominal visceral adipose tissues [26], whereas WHtR is a good predictor of intra-abdominal adipose tissue and has no correlation with subcutaneous adipose tissue [27]. This result would probably indicates that nesfatin-1 levels are closely related to regional adipose tissue, but copeptin levels are closely related to intra-abdominal adipose tissue.

We did not detect significant differences in nesfatin-1 levels between boys and girls. The finding in children fits well with studies in adults reporting no difference in nesfatin-1 concentrations between males and females [28]. Interestingly, we demonstrated that pubertal children had higher copeptin and nesfatin-1 levels than pre-pubertal children. Regulation during puberty is also well known for other adipokines [29], but the data about copeptin and nesfatin-1 levels in pubertal children are still absence. The underlying mechanism of this difference in prepubertal and pubertal children has not been specifically investigated, and we speculate that this difference may be related to elevated hormone levels in adolescent.

Surprisingly, serum nesfatin-1 was found to be significantly positively correlated with TNF-a, which was not entirely due to obesity. TNF-a which secreted by adipose tissue was proven to affect insulin signaling and to modulate insulin resistance by various mechanisms, and to be a marker of systemic inflammation [30]. Ramanjaneya et al. observed in animal models of subcutaneous adipose tissue explants that nesfatin-1 production was significantly increased by TNF-α [24]. This observation revealed nesfatin-1is involved in the pathological process of inflammation and insulin resistance and the pathogenesis need further research to be elucidated. Although copeptin levels are elevated in inflammatory states in adults [31], we could not show a relationship between TNF-a and copeptin levels in obesity children.

In this study, obese children with insulin resistance had insignificant higher nesfatin-1 and copeptin levels compared with obese children without insulin resistance. In correlation analysis, nesfatin-1 and copeptin were found to relate to plasma insulin and HOMA-IR, and this correlation is independent of puberty, age, gender and SDS-BMI. Multivariate linear regression analysis revealed that copeptin and nesfatin-1 can as independent predictors of Insulin resistance, contributing 8% and 10% to the variability, respectively. Our findings were in agreement with previous reports. In adult studies, Zhang et al and Tan et al reported that plasma nesfatin-1 level was significantly correlated with plasma insulin levels and HOMA-IR [32-33]. Moreover, recently data showed that high copeptin is independently associated with hyper-insulinemia and can predict the development of diabetes mellitus [34]. The activation of the hypothalamic-pituitary-adrenal axis by AVP (copeptin) in chronic stress may be one of the mediators of obesity and insulin resistance, and copeptin can increase insulin release from pancreatic islets by activating V1b receptors located in the islets [35-36]. To the best of our knowledge, datas examining the prospective association between nesfatin-1 and insulin resistance are limited in children. In addition, there are no data regarding the relationship between copeptin and insulin resistance in obese children. Our results indicated that nesfatin-1 and copeptin plays a pathogenetic role in IR in obese children. From a therapeutic point of view, the nesfatin-1 and copeptin are attractive targets for insulin resistance interventions.

Interestingly, we detected significant associations between nesfatin-1 and copeptin with one another in pearson's correlation and partial correlation. More importantly, multiple regression analysis used nesfatin-1or copeptin as the dependent parameters and we did detect significant correlation between nesfatin-1 and copeptin with each other and the association between each of nesfatin-1 and copeptin with HOMA-IR. However, we did not detect any significant correlation with adiponectin or leptin. This finding suggests that nesfatin-1 and copeptin are interrelated peptides and play a role in obesity-related insulin resistance. To the best of our knowledge, these findings are novel and are shed light on the possible interplay between these two bioactive mediators for the first time in children.

In summary, we detect that serum nesfatin-1 and copeptin concentrations are increased in obese children with insulin resistance. Furthermore，we did a novel observation that nesfatin-1 and copeptin were significantly interrelated and associated with HOMA-IR. These findings are shed light on the possible interplay role of these two molecules in obesity-related insulin resistance.

Abbreviations

BMI, body mass index; DBP, diastolic blood pressure; FPG, fasting plasma glucose; HDL-C, high-density lipoproteincholesterol; HOMA-IR, homoeostasis model of insulin resistance; IR, Insulin resistance; LAR, leptin-to-adiponectin ratio; LDL-C, low-density lipoprotein; NUCB2, nucleobindin 2; SDS-BMI, BMI s.d. score; TC, totalcholesterol; 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.

Disclosure Statement

The authors declare that they have no competing interests

Funding

Author contributions

Yanfeng Xiao designed the study. Chunyan Yin completed the entire clinical studies. Wei Hua liu and Erdi Xu collected and analyzed the data. Meizhen zhang prepared the manuscript. Weicheng Lv conducted statistical analysis. Qi Lu edited the manuscript.

Availability of data and materials

The datasets used or analysed during the current study are available from the corresponding author upon reasonable request.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

References

[1] Reaven GM. Insulin resistance and human disease: a short history. Journal of basic and clinical physiology and pharmacology. 1998; 9(2-4): 387-406.

[2]Silfen ME , Denburg MR , Manibo AM , Lobo RA , Jaffe R , Ferin M , et al. Early endocrine, metabolic, and sonographic characteristics of polycystic ovary syndrome (PCOS): comparison between nonobese and obese adolescents. J Clin Endocrinol Metab. 2003; 88:4682-4688

[3] Levy-Marchal C, Arslanian S, Cutfield W, et al. Insulin resistance in children: consensus, perspective, and future directions. The Journal of Clinical Endocrinology & Metabolism. 2010; 95(12): 5189-5198.

[4]LeeJM, OkumuraMJ, DavisMM, HermanWH, GurneyJG. Prevalence and determinants of insulin resistance among US adolescents: a population-based study. Diabetes Care. 2006 ; 29:2427-2432.

[5]Caprio S, Perry R, Kursawe R. Adolescent obesity and insulin resistance: roles of ectopic fat accumulation and adipose inflammation. Gastroenterology. 2017; 152(7): 1638-1646.

[6]Solà E, Kerbert AJC, Verspaget HW, et al. Plasma copeptin as biomarker of disease progression and prognosis in cirrhosis. Journal of hepatology. 2016; 65(5): 914-920.

[7]Barchetta I, Enhörning S, Cimini FA, et al. Elevated plasma copeptin levels identify the presence and severity of non-alcoholic fatty liver disease in obesity. BMC medicine. 2019; 17(1): 85.

[8]Riva M, Nitert M D, Voss U, et al. Nesfatin-1 stimulates glucagon and insulin secretion and beta cell NUCB2 is reduced in human type 2 diabetic subjects. Cell and tissue research. 2011; 346(3): 393-405.

[9]Aydin S. Multi-functional peptide hormone NUCB2/nesfatin-1. Endocrine. 2013; 44(2): 312-325.

[10]Stengel A, Taché Y. Role of brain NUCB2/nesfatin-1 in the regulation of food intake. Current pharmaceutical design. 2013; 19(39): 6955-6959.

[11]Ramesh N, Mohan H, Unniappan S. Nucleobindin-1 encodes a nesfatin-1-like peptide that stimulates insulin secretion. General and comparative endocrinology. 2015; 216: 182-18

[12]Khalili S, Khaniani M S, Afkhami F, et al. NUCB2/Nesfatin-1: a potent meal regulatory hormone and its role in diabetes. Egyptian Journal of Medical Human Genetics. 2017; 18(2): 105-109.

[13]Mohan H, Unniappan S. Ontogenic pattern of nucleobindin-2/nesfatin-1 expression in the gastroenteropancreatic tissues and serum of Sprague Dawley rats. Regulatory peptides. 2012; 175(1-3): 61-69.

[14]Enhörning S, Wang T J, Nilsson P M, et al. Plasma copeptin and the risk of diabetes mellitus. Circulation. 2010; 121(19): 2102.

[15]Rothermel J, Kulle A, Holterhus PM, et al. Copeptin in obese children and adolescents: relationships to body mass index, cortisol and gender. Clinical endocrinology. 2016; 85(6): 868-873.

[16]Tenderenda-Banasiuk E, Wasilewska A, Filonowicz R, et al. Serum copeptin levels in adolescents with primary hypertension. Pediatric Nephrology. 2014; 29(3): 423-429.

[17]Abaci A, Catli G, Anik A, et al. The relation of serum nesfatin-1 level with metabolic and clinical parameters in obese and healthy children. Pediatric diabetes. 2013; 14(3): 189-195.

[18]Anwar GM, Yamamah G, Ibrahim A, et al. Nesfatin-1 in childhood and adolescent obesity and its association with food intake, body composition and insulin resistance. Regulatory peptides. 2014; 188: 21-24.

[19]Li H, Ji C, Zong X, Zhang YQ. Body mass index growth curves for Chinese children and adolescents aged 0 to 18 years. Chin J Pediatr. 2009; 47: 493-498.

[20]Tanner JM. Growth and maturation during adolescence. Nutr Rev. 1981; 39(2): 43-55.

[21]Andrade MI, Oliveira JS, Leal VS, Lima NM, Costa EC, Aquino NB, et al. Identification of cutoff points for Homeostatic Model Assessment for Insulin Resistance index in adolescents: systematic review. Rev Paul Pediatr. 2016; 34(2): 234-42.

[22]Gallagher E J, LeRoith D, Karnieli E. Insulin resistance in obesity as the underlying cause for the metabolic syndrome. Mount Sinai Journal of Medicine: A Journal of Translational and Personalized Medicine. 2010; 77(5): 511-523.

[23]Simpson K, Parker J, Plumer J, Bloom S. CCK, PYY and PP: the control of energy balance. Handb Exp Pharmacol. 2012; 209: 209–230.

[24]Ramanjaneya M, Chen J, Brown JE et al. Identification of nesfatin-1 in human and murine adipose tissue: a novel depot-specific adipokine with increased levels in obesity. Endocrinology. 2010; 151:3169–3180.

[25]Abaci A, Catli G, Anik A, et al. The relation of serum nesfatin-1 level with metabolic and clinical parameters in obese and healthy children. Pediatric diabetes. 2013; 14(3): 189-195.

[26]Pouliot MC, Despres JP, Lemieux S, Moorjani S, Bouchard C, Tremblay A, et al. Waist circumfer circumference and abdominal sagittal diameter: best simple anthropometric indexes of abdominal visceral adipose tissue accumulation and related cardiovascular risk in men and women. Am. J. Cardiol. 1994;73:460-468.

[27]Ashwell M, Cole TJ, Dixon AK. Ratio of waist circumference to height is strong predictor of intra-abdominal fat. Br. Med. J. 1996;313(7056): 559-560.

[28]Ari M, Ozturk OH, Bez Y, Oktar S, Erduran D. High plasma nesfatin-1 level in patients with major depressive disorder. Prog. Neuro-Psychopharmacol. Biol. Psychiatry. 2011; 35: 497-500

[29]Bo ttner A, Kratzsch J, Mu ller G, Kapellen TM, Blu her S, Keller E, at al. Gender differences of adiponectin levels develop during the progression of puberty and are related to serum androgen levels. J Clin Endocrinol Metab. 2004; 89:4053-4061

[30]Bastard J P, Maachi M, Lagathu C, et al. Recent advances in the relationship between obesity, inflammation, and insulin resistance. European cytokine network. 2006; 17(1): 4-12.

[31]Enhörning S, Struck J, Wirfält E, et al. Plasma copeptin, a unifying factor behind the metabolic syndrome. The Journal of Clinical Endocrinology & Metabolism. 2011; 96(7): E1065-E1072.

[32]Zhang Z, Li L, Yang M, Liu H, Boden G, Yang G. Increased plasma levels of nesfatin-1 in patients with newly diagnosed type 2 diabetes mellitus. Exp Clin Endocrinol Diabetes. 2012; 120: 91-95.

[33]Tan BK, Hallschmid M, Kern W et al. Decreased cerebrospinal fluid/plasma ratio of the novel satiety molecule, nesfatin-1/nucb-2, in obese human: evidence of nesfatin-1/nucb-2 resistance and implications for obesity treatment. JCEM. 2011; 96: E669-E673.

[34] Karbek B, Ozbek M, Karakose M, Topaloglu O, Bozkurt NC, Cakir E, et al. Copeptin, a surrogate marker for arginine vasopressin, is associated with cardiovascular risk in patients with polycystic ovary syndrome. J Ovarian Res. 2014;7:31.

[35] Enhorning S, Wang TJ, Nilsson PM, Almgren P, Hedblad B, Berglund G, et al. Plasma copeptin and the risk of diabetes mellitus. Circulation. 2010;121:2102-2108.

[36]Saleem U, Khaleghi M, Morgenthaler N G, et al. Plasma carboxy-terminal provasopressin (copeptin): a novel marker of insulin resistance and metabolic syndrome. The Journal of Clinical Endocrinology & Metabolism. 2009;94(7): 2558-2564.

Tables

Table 1. Characteristics of study population

Variable	lean (40)	obese (80)
Age (y)	11.03±2.25	10.82±2.00
BMI (kg/m^2)	16.20±2.13	27.31 ± 4.05 [b]
SDS- BMI	2.68±0.34	2.96±0.38[b]
Weight(kg)	32.17±9.19	62.48±14.80 [b]
WHtR	0.43±0.11	0.53±0.22 [b]
WC (cm)	61.18±7.51	91.57±9.60[b]
WHR	0.82±0.59	0.98±0.07[b]
SBP (mm Hg)	92.2±19.22	117.96±11.17[b]
DBP (mm Hg)	58.51±5.34	69.92 ±9.53[a]
FPG(mmol/l)	4.36±0.82	5.13±0.63
Insulin(uU/ml)	8.90±2.58	16.58±7.15 [b]
HOMA-IR	1.55±0.68	3.55±1.82 [b]
AST (IU/L)	15.32±6.53	28.65±10.23[a]
ALT(IU/L)	16.92±7.67	37.11±27.67 [b]
TC(mmol/l)	3.75±0.66	4.18±0.77 [b]
TG(mmol/l)	0.94±0.33	1.40±0.64[b]
HDL-C(mmol/l)	1.13±0.29	1.10±0.23
Adiponectin (lg /ml)	3.92±1.04	3.20±0.98 [a]
Leptin (ng/ml)	18.25±9.05	66.30±24.23[b]
LAR (ng/lg)	5.86±1.04	22.38±3.65 [b]
Copeptin (pg/ml)	15.20±4.57	18.61±3.02[b]
TNF-a(ng/ml)	4.53±1.05	16.81±4.52 [b]
Nesfatin-1 (pg /ml)	1090.32±372.64	1616.35±350.37[b]

Abbreviations: BMI, body mass index; SDS-BMI, BMI s.d. score; WHtR, waist-height ratio; WC, Waist circumference; WHR, Waist-to-hip ratio; SBP, systolic blood pressure; DBP, diastolic blood pressure; FPG, fasting plasma glucose; HDL-C, high-density lipoproteincholesterol; HOMA-IR, homoeostasis model of insulin resistance; LDL-C, low-density lipoprotein; TC, totalcholesterol; TG, triglycerides; LAR, leptin-to-adiponectin ratio; TNF-α, tumour necrosis factor-α; Data are expressed as mean ±s.d. [a]p ≤0.05; [b]p≤0.01 compared with obese.

Table 2. Serum adipokines and peptides concentrations of subjects according to gender

Variable	boys (79)	girls(41)
Age (y)	10.99±2.20	10.70±2.08
Adiponectin (lg /ml)	3.40±1.54	3.52±1.12
Leptin (ng/ml)	49.99±10.23	41.11±11.02
LAR (ng/lg)	11.23±4.23	10.36±3.41
Copeptin (pg/ml)	16.01±4.52	16.97±4.16
TNF-a(ng/ml)	5.23±3.25	6.66±3.20
Nesfatin-1 (pg /ml)	1213.57±447.31	1366.42±415.64

[a]p 0.05; [b]p0.01 compared with boys.

Table 3. Serum adipokines and peptides concentrations of subjects according to puberty

Variable	Prepubertal (46)	Pubertal (72)
Age (y)	9.52±1.31	11.74±2.14
Adiponectin (ng /ml)	3.71±0.59	3.3±0.86 [a]
Leptin (ng/ml)	36.90±4.29	63.13±3.64[b]
LAR (ng/lg)	13.68±3.64	23.51±5.32 [b]
Copeptin (pg/ml)	15.13±4.79	17.08±4.00 [b]
TNF-a(ng/ml)	5.86±1.23	6.03±2.15
Nesfatin-1 (pg /ml)	1038.73±328.32	1406.52±404.21 [b]

[a]p⬚0.05; [b]p⬚0.01 compared with prepubertal children.

Table 4. Correlations of copeptin or nesfatin-1 with clinical variables

Parameter	Copeptin				Nesfatin-1			
	r^a	p^a	r^b	p^b	r^a	p^a	r^b	p^b
Anthropometric parameters								
Age (y)	0.037	0.687			0.099	0.280		
Weight(kg)	0.254	0.005			0.350	0.000		
BMI (kg/m^2)	0.309	0.001			0.448	0.000		
SDS-BMI	0.412	0.000			0.523	0.000		
WC (cm)	0.259	0.007			0.465	0.000		
WHR	0.094	0.330			0.453	0.000		
WHtR	0.189	0.039			0.113	0.218		
Metabolic parameters								
FPG (mmol/l)	0.146	0.142	0.135	0.102	0.243	0.008	0.198	0.033
Insulin (uU/ml)	0.222	0.016	0.195	0.033	0.208	0.023	0.187	0.041
HOMA-IR	0.257	0.004	0.189	0.043	0.262	0.004	0.211	0.002
ALT (IU/L)	0.033	0.723	0.051	0.581	0.052	0.571	0.107	0.250
AST (IU/L)	0.062	0.503	0.096	0.302	0.077	0.403	0.154	0.097
LDL-C(mmol/l)	-0.205	0.052	-0.074	0.431	0.182	0.053	0.162	0.076
HDL-C(mmol/l)	0.216	0.018	0.215	0.020	0.199	0.031	0.183	0.048
TG(mmol/l)	0.025	0.079	0.084	0.371	0.147	0.111	0.018	0.884
TC (mmol/l)	0.055	0.551	0.056	0.552	0.031	0.074	0.056	0.547
SBP (mm Hg)	0.228	0.013	0.167	0.074	0.334	0.000	0.227	0.015
DBP (mm Hg)	0.260	0.004	0.227	0.015	0.318	0.000	0.271	0.003
Adipokines and peptides								
TNF-α (pg/ml)	0.102	0.268	0.068	0.471	0.451	0.000	0.431	0.000
Adapoctin(ng /ml)	-0.127	0.166	-0.005	0.961	0.088	0.339	0.044	0.640
Leptin (ng/ml)	0.249	0.006	0.185	0.047	0.402	0.000	0.273	0.003
LAR (ng/lg)	0.325	0.000	0.240	0.010	0.323	0.000	0.216	0.019
Copeptin (pg/ml)	-	-	-	-	0.569	0.000	0.494	0.000
Nesfatin-1 (pg /ml)	0.569	0.000	0.494	0.000	–	–	–	–

a Pearson correlation analysis was performed for copeptin or nesfatin-1 and the indicated parameters.

b Partial correlation analysis after adjustment for puberty, age, gender and SDS-BMI.

Table 5. Multiple regression analysis to determine the association with IR、copeptin or nesfatin-1

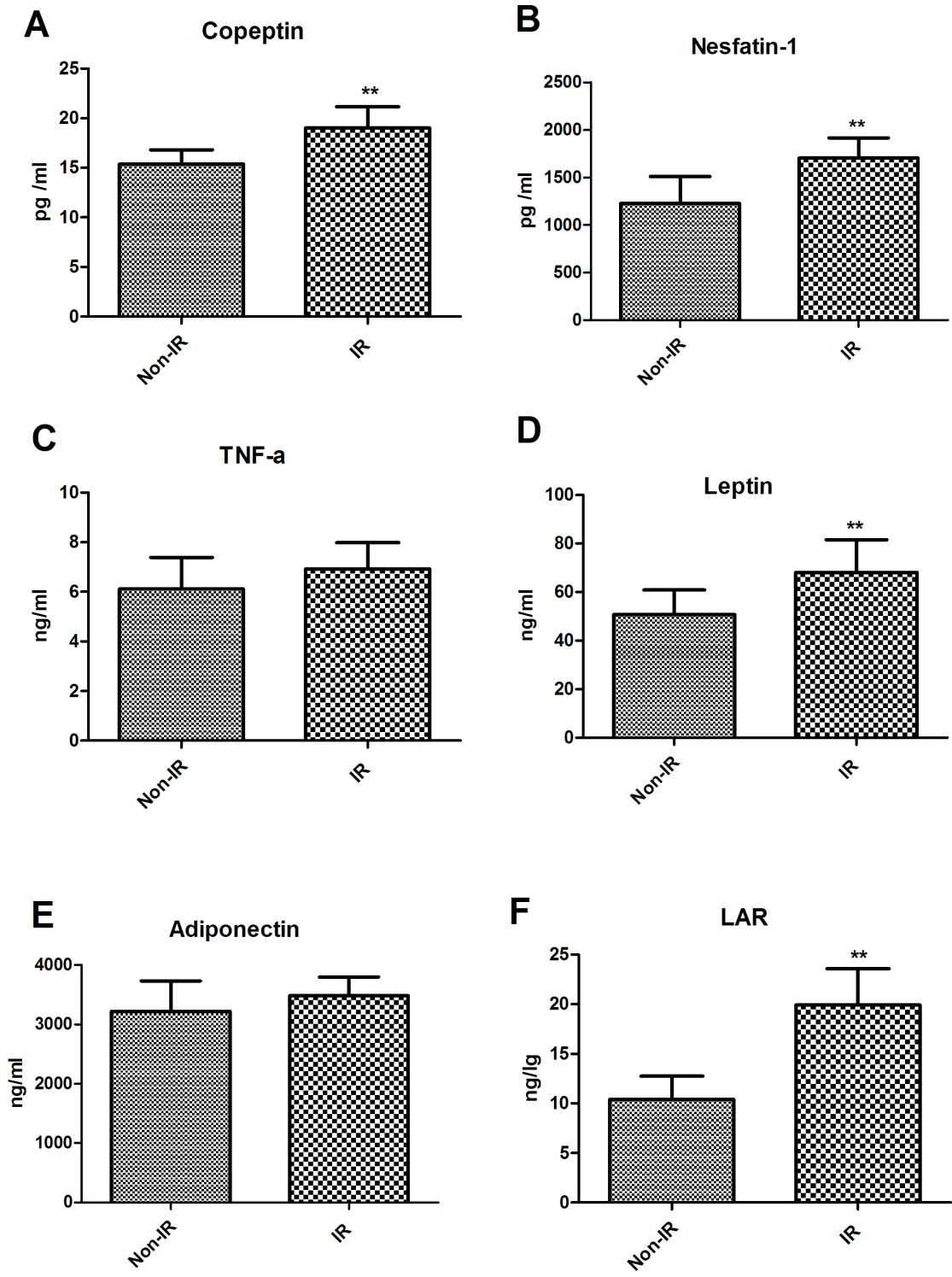| Independent	Dependent					
	HOMA-IR		Copeptin		Nesfatin-1	
	β	p	β	p	β	p
SDS-BMI	0.345	0.021	0.485	0.029	0.375	0.036
WC (cm)	0.370	0.011	0.030	0.963	0.251	0.205
WHR	0.208	0.086	0.166	0.413	0.104	0.527
SBP (mm Hg)	0.118	0.342	0.121	0.624	0.153	0.363
DBP (mm Hg)	0.211	0.076	0.314	0.039	0.313	0.048
AST	0.103	0.412	0.143	0.345	0.165	0.224
ALT	0.250	0.030	0.443	0.035	0.434	0.255
TG(mmol/l)	0.086	0.585	0.056	0.750	0.170	0.208
FPG(mmol/l)	0.018	0.925	0.156	0.482	0.128	0.369
LAR (ng/lg)	0.243	0.038	0.135	0.563	0.178	0.171
Nesfatin-1 (pg /ml)	0.252	0.028	0.528	0.005	—	—
TNF-α (pg/ml)	0.098	0.561	0.177	0.299	0.203	0.224
Copeptin (pg/ml)	0.235	0.044	—	—	0.419	0.001
HOMA-IR	—	—	0.472	0.030	0.342	0.042

Figures

Figure 1

Serum adipokines and peptides concentrations in IR and non-IR groups. (A), Copeptin (B), Nesfatin-1 (C), TNF-a (D), Leptin (E), Adiponectin (F), LAR. * p < 0.05,** p < 0.01; IR, insulin resistance.