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RESEARCH ARTICLE

Gender-based relationship between copeptin level and metabolic syndrome in Albino rats

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ABSTRACT

Background: Arginine vasopressin (AVP) affects liver glycogenolysis, insulin, and adrenocorticotropic hormone release supporting its role in metabolic disorders. Copeptin is established as a stable and sensitive biomarker of AVP level. **Aims and Objectives:** The aim of the study is to investigate the association between serum copeptin level and metabolic syndrome (MetS) parameters in both male and female albino rats. **Materials and Methods:** Sixteen male and 16 female adult rats were subdivided into control and high-carbohydrate high-fat (HCHF)-fed groups. Body mass index (BMI), systolic, diastolic, and mean arterial blood pressure (MABP) were measured. Serum total cholesterol (TC), triglycerides (TG), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), glucose, insulin, highly sensitive C-reactive protein (hs-CRP), and copeptin were estimated. Homeostatic model assessment for insulin resistance (HOMA-IR) and atherogenic index (AI) were calculated. **Results:** There was significant increase in BMI, blood pressures, and levels of TC, TG, LDL-C, AI, glucose, insulin, HOMA-IR, hs-CRP, and copeptin with significant decrease in HDL-C level in male and female HCHF-fed groups compared with their controls. All parameters except HDL-C, blood pressures, and hs-CRP were significantly lower in female HCHF-fed group compared with male HCHF-fed one. There was positive correlation between copeptin level and BMI, insulin, glucose, HOMA-IR, TC, TG, LDL-C, AI, and hs-CRP and negative correlation with HDL-C with insignificant correlation with MABP in both HCHF groups. **Conclusion:** HCHF-fed male rats are more subjected to develop features of MetS with more elevation in copeptin than female rats. Elevated copeptin was correlated with components of MetS as obesity, hyperglycemia, IR, dyslipidemia, and hs-CRP in both sexes indicating the role of the vasopressinergic system in the pathogenesis of MetS. Further studies to evaluate copeptin as a predictive marker for MetS and therapeutic role of controlling AVP based on gender difference are recommended.

KEY WORDS: Metabolic Syndrome; Copeptin; Gender; Rat Model

INTRODUCTION

Metabolic syndrome (MetS) is a complex medical condition characterized by the presence of at least three of the following characteristics: Central obesity, hyperglycemia, hypertension, and dyslipidemia.[1] MetS increases the risk of other diseases such as cardiovascular disease, nonalcoholic fatty liver disease, Type 2 diabetes (T2DM), and cancer.[2] However, the etiology of MetS is still not well known, and different pathophysiological disturbances are described that reflected by diverse biomarkers such as tumor necrosis factor-α, interleukin-1 (IL-1), IL-6, leptin, adiponectin,[3] C-reactive protein, and copeptin.[4]

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Animal and human studies have suggested that the arginine vasopressin (AVP) plays role in adrenocorticotropic

hormone (ACTH) secretion, lipid metabolism, and glucose homeostasis.[5] Since AVP is a short-lived peptide, unstable in serum or isolated plasma and its measurement is difficult,[6] copeptin can serve as a reliable surrogate marker for circulating levels of AVP.[7] Copeptin is the glycopeptide comprising the C-terminal part of the AVP prohormone and it correlates with AVP levels in plasma and may share similar functions.[8]

Several studies in adults have shown that high copeptin levels were associated with T2DM,[9] insulin resistance (IR), and other components of MetS,[10] mainly in the adult or elderly population.[11] Furthermore, there is a remarkable difference in copeptin concentrations between women and men.[12]

It was stated that the association of plasma copeptin with the risk of developing diabetes was stronger in women than in men.[13] On the other hand, it was found that high plasma copeptin was associated with reduced insulin sensitivity and an increased risk for T2DM in men.[9]

Rothermel *et al*.[12] found a significant association between the degree of obesity and copeptin while none of the parameters of the MetS was significantly related to copeptin in obese children. They demonstrated that pubertal boys but not prepubertal boys had higher copeptin levels than girls.

On basis of these conflicted data, investigating the association between serum copeptin level and metabolic syndrome (MetS) parameters in both male and female albino rats is the objective of the current study.

MATERIALS AND METHODS

Animal

A total of 32 albino rats of both genders (16 each), 160–180 g weight and 12–15 weeks old, obtained from the animal house of Veterinary Medicine Faculty, Zagazig University, Egypt, were used.

Animals were acclimatized for 1 week at 25 ± 2°C temperature, 50–60% humidity, and light-dark cycle of 12 h. They were fed standard diet with free access to water.

Both groups: Group (I): Male rats and Group (II): Female rats were divided into two equal subgroups (n = 8):

Subgroups (Ia and IIa) (Control groups) were fed standard rat chow and tap water.

Subgroups (Ib and IIb) (high-carbohydrate high-fat [HCHF]-fed groups) were fed with HCHF diet to induce MetS. The HCHF diet (1 kg) contained 375 g of sweetened condensed milk, 200 g of ghee, 175 g of fructose, 155 g of powdered rat food, 25 g of Hubble, Mendel, and Wakeman salt mixture, and 50 mL of water. The drinking water was supplemented with 25% fructose.[14]

Experimental Protocol

The experiment lasted for 12 weeks. Both food formulae were obtained from Faculty of Agriculture, Zagazig University, Egypt.

At the end of the experimental period, body mass index (BMI) was calculated by the equation: BMI (gm/cm²) = body weight/length² (nose to anus length), this index can be used as an indicator of obesity where BMI = 0.68 gm/cm² is the cutoff value of obesity.

Systolic, diastolic, and mean arterial blood pressures (MABPs) were measured at the end of the experiment by non-invasive tail-cuff device (NARCO, Biosystem, Inc., Huston, Texas).

The rats were sacrificed after 12 h fasting under anesthesia (chloral hydrate) inhalation. Blood samples were obtained by exsanguination at the time of scarification, collected, and allowed to clot for 2 h at room temperature before centrifugation. Sera were examined for levels of insulin and glucose by enzyme-linked immunosorbent assay kits. The homeostatic model assessment for IR (HOMA-IR) was calculated from the formula: [HOMA-IR = insulin (mIU/L) × glucose (mmol/dL)/22.5].

Total cholesterol (TC) was determined by colorimetric method, triglyceride (TG) levels and high-density lipoprotein cholesterol (HDL-C) were assessed by enzymatic assay technique. Low-density lipoprotein cholesterol (LDL-C) was calculated using the formula: LDL-C = [TC−(HDL-C-TG/5)]. The atherogenic index (AI) was calculated from the formula: AI = [Log (TG/HDL-C)].

Highly sensitive C-reactive protein (hs-CRP) and copeptin were estimated by immune-enzymatic assay technique.

Statistical Analysis

Results were presented as mean ± standard deviation. The statistical tests employed were one-way ANOVA and least significant differences for multiple comparisons and Pearson's correlation analysis between MetS parameters and serum copeptin. For all statistical tests done, $P < 0.05$ was considered to be statistically significant.

Statement of Ethics

Animal experiments conform to internationally accepted standards and have been approved by the Institutional Animal Care and Use Committee – Zagazig University (Zu-IACUC/3/F/5/2019).

RESULTS

There was significant increase in BMI, TC, TG, LDL-C, AI, glucose, insulin, HOMA-IR, systolic, diastolic, MABPs,

hs-CRP, and copeptin with decrease in HDL-C in both HCHF-fed groups (Ib and IIb) in comparison to their controls (Ia and IIa) with insignificant change in their levels between male and female control groups, but there was significant decrease in BMI, TC, TG, LDL-C, AI, glucose, insulin, HOMA-IR, and copeptin with insignificant change in HDL-C, all measured pressures, and hs-CRP in female HCHF group when compared with male HCHF one [Table1].

As shown in Figure 1, there were no correlations between copeptin level and all studied parameters in both male and female control groups [Figure 1a and c], while there was positive correlation between copeptin level and BMI, insulin, glucose, HOMA-IR, TC, TG, LDL-C, AI, and hs-CRP and negatively correlated with HDL-C with insignificant correlation with MABP in both male and female HCHF groups [Figure 1b and d].

DISCUSSION

In the present study, adult male and female rats on the HCHF diet showed increased BMI compared with normal chew fed rats and this obesity was associated with dyslipidemia, elevated insulin and glucose, HOMA-IR, and elevation of blood pressure that were lower in HCHF female compared with HCHF male rats.

These metabolic changes come in agreement with Wong *et al*.[14] who demonstrated that MetS is successfully established in rats by the HCHF diet for 12 weeks. In addition, other studies reported the same results in male Wistar rats subjected to high-fat high-fructose diet for 14 weeks[15] or 16 weeks[16] while others concluded the same results except hypertension in male Wistar rats subjected to high-fat high-fructose diet for 8 weeks[17] or the same results except hyperglycemia after 16 weeks of HCHF diet.[18]

Regarding less liability of female rats to develop MetS that supported Cecconello *et al*.[19] who stated that rats exposed to high-fat diet (HFD) for 4 weeks showed increased the adiposity index, the hepatic TG, and blood glucose levels in both sexes, with increased hepatic TC and hyperinsulinemia in males.

Moreover, Hrischev *et al*.[20] found that in Wistar male and female rats fed HCHF diet for 16 weeks, male animals had higher body weight, waist circumference, BMI, and fasting glucose level than female while the gender had no effect on insulin level or HOMA-IR.

This gender difference in HFD-induced obesity and dyslipidemia could be explained by that estrogen attenuates the lipolytic response through upregulation of the number of antilipolytic alpha2A-adrenergic receptors only in subcutaneous (SC) and not in visceral fat depots and thereby shifts the assimilation of fat from intra-abdominal depots to SC depots.[21]

We found that HCHF diet-induced significant increase in hs-CRP level in both sexes when compared with their controls that were by researches which reported that the central mechanism underlying pathophysiology of MetS is

Table 1: Comparison between all studied parameters in all groups

Variables	Male group		Female group	
	Control	HCHF	Control	HCHF
BMI (gm/cm²)	0.49±0.07	0.77±0.14[a]	0.47±0.11	0.65±0.16[b,c]
SBP (mmHg)	121±9	142±15[a]	119±8	139±15[b]
DBP (mmHg)	73±11	94±16[a]	75±14	91±16[b]
MABP (mmHg)	105±7	126±10[a]	104.3±12	123±9[b]
Insulin (mIU/L)	18.2±1.98	36.6±2.73[a]	17.9±1.14	24.8±2.14[b,c]
Glucose (mmol/L)	6.23±0.53	12.1±0.97 [a]	5.9±0.74	8.17±0.33[b,c]
HOMA-IR	5.03±0.6	16.4.26±2.42[a]	4.7±0.23	9.2±0.87[b,c]
TC (mg/dL)	86.7±9.8	155.5±29.44[a]	80.7±4.8	138.1±6.19[b,c]
TG (mg/dL)	56.2±10.81	114±13.24[a]	41±8.81	92.3±13.24[b,c]
HDL-C (mg/dL)	49.9±5.7	30.5±2.1[a]	45.2±4.9	29.1±2.3[b]
LDL-C (mg/dL)	25.6±13.7	102.3±11.2[a]	26.6±3.3	90.3±2.9[b,c]
AI	1.34±0.32	2.28±0.53[a]	1.15±0.18	1.58±0.35[b,c]
hs-CRP (ng/dL)	91.9±16.7	451.1±91.6[a]	89.6±59.4	432.2±64.1[b]
Copeptin (pmol/L)	0.9±0.1	2.6±0.24[a]	0.6±0.07	1.8±0.22[b,c]

n=(8) in each group. Data are represented as mean±standard deviation. BMI: Body mass index, SBP: Systolic blood pressure, DBP: Diastolic blood pressure, MABP: Mean arterial blood pressure, HOMA-IR: Homeostasis model assessment-insulin resistance, TC: Total cholesterol, TG: Triglyceride, HDL-C: High-density lipoprotein cholesterol, LDL-C: Low-density lipoprotein cholesterol, AI: Atherogenic index, hs-CRP: Highly sensitive C-reactive protein. Significance (P<0.05): ([a]) significant when compared with male control group, ([b]) significant when compared with female control group, ([c]) significant when compared with male HCHF group, HCHF: High carbohydrate high fat

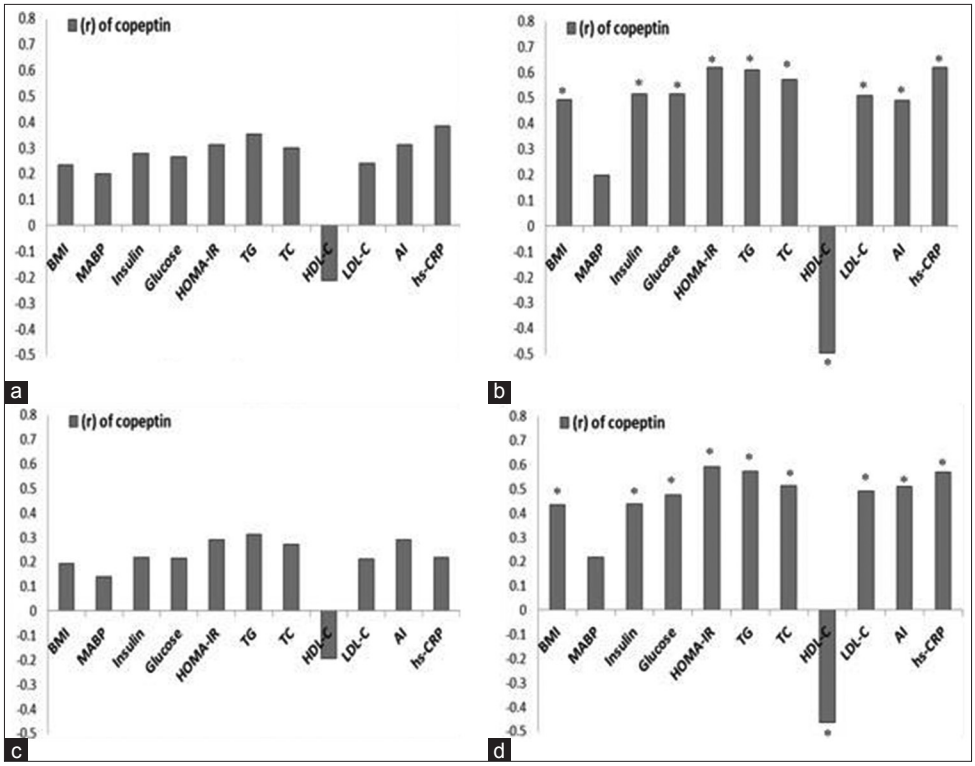

Figure 1: Correlation coefficient between copeptin and all studied parameters. (r): Correlation coefficient of copeptin with other parameters, BMI: Body mass index, MABP: Mean arterial blood pressure, HOMA-IR: Homeostasis model assessment-insulin resistance, TC: Total cholesterol, TG: Triglyceride, HDL-C: High-density lipoprotein cholesterol, LDL-C: Low-density lipoprotein cholesterol, AI: Atherogenic index, hs-CRP: Highly sensitive C-reactive protein. Significance ($P < 0.05$): (*) significant when correlated with copeptin. (a) Male control group, (b) Male high-carbohydrate high-fat (HCHF) group, (c) Female control group, (d) Female HCHF group

seemed to be low-grade systematic chronic inflammation[22] and the positive association between high levels of hs-CRP and MetS had been demonstrated.[23]

Moreover, human-based studies confirmed positive association between high levels of CRP and MetS in adolescents[24] and adults.[25] In contrast, den Engelsen *et al*.[26] in a cross-sectional analysis concluded that hs-CRP has limited capacity to predict the presence of the MetS in a population with central obesity.

We found that HCHF elevated copeptin level in both sexes with more elevation in male rats. In addition, copeptin was positively correlated with BMI, insulin, glucose, HOMA-IR, TC, TG, LDL-C, AI, and hs-CRP and negatively correlated with HDL-C.

These results are in accordance with Roussel *et al*.[9] who suggested that high plasma copeptin was associated with reduced insulin sensitivity and an increased risk for T2DM in community-based cohort. Moreover, the genotypes associated with an increased risk of hyperglycemia were also associated with increased plasma copeptin in men but not in women.

It was documented that elevated copeptin is not only linked to diabetic heart disease[27] but is also a powerful predictor of future development of T2DM,[28] suggesting that elevated AVP has a central role for the development of MetS.

Moreover, Enhörning *et al*.[10] found that copeptin was associated with hypertension, CRP, BMI, T2DM, hyperinsulinemia, and MetS and these associations remained significant in men compared with women.

In human-based study, it was found that among the young adults but not adolescents, plasma copeptin concentrations were associated with IR.[29]

In another human-based study, the increased copeptin levels in MetS and its correlation with the well-established risk factors as dyslipidemia, increased BMI, and T2DM were confirmed.[30]

In contrast, a stronger association of copeptin with the risk of T2DM in women than in men was proved. In women, copeptin was an independent predictor for T2DM with added predictive value together with glucose and inflammatory marker (hs-CRP) and renal function, whereas in men, copeptin showed no added prediction.[13]

The total findings of the current study support a potential role of the AVP system in the pathogenesis of MetS and this hypothesis is supported by finding of other studies that identified high levels of copeptin as a risk factor for the development of diabetes. The most likely pathophysiological mechanism is insufficient fluid intake that leads to increased AVP secretion, which stimulates ACTH and cortisol secretion producing hyperglycemia.[31]

Moreover, Taveau *et al.*[32] postulated the chronic metabolic actions of AVP *in vivo*. The results of their experiment on obese rats revealed a significant influence of the AVP/hydration system on basal glycemia, glucose tolerance, and liver steatosis. They clearly support a causality link between high copeptin level or low water intake and the incidence of hyperglycemia, MetS, and T2DM. In more recent study, Taveau *et al*. demonstrated a link between chronic high AVP and hyperglycemia, thus provide a pathophysiological explanation for the relationship between the AVP-hydration axis and the risk of diabetes in human.[33]

A large number of studies have established high level of AVP as a risk factor for diabetes, MetS, and cardiovascular diseases. This relationship and the favorable effect of AVP reduction with improved hydration status are supported by studies in rodents.[34]

The strengths of the current study are that rat model of MetS is used which is easy and documented by many researches. The measured parameters are enormous and reflect wide range of metabolic changes. Albino rats were used for the present study because the metabolic physiology of the rat is closer to humans. The limitation of this study was that it was done in a limited number of rats.

CONCLUSION

Male rats are more subjected to develop features of MetS than female rats when fed HCHF diet which accompanied by elevation in copeptin level more in male than female rats. Elevated copeptin was correlated with components of MetS as obesity, hyperglycemia, IR, dyslipidemia, and hs-CRP in both sexes indicating the role of the vasopressinergic system in the pathogenesis of MetS. Further studies to evaluate copeptin as a predictive marker for MetS and therapeutic role of controlling AVP based on gender difference are recommended.

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