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Original Research Article

Association of Metabolic Risk Factors with Serum Orexin Levels in Women of Reproductive Age Group: A Cross-sectional Study

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Abstract:

Introduction: Metabolic syndrome has long been associated with obesity and a sedentary lifestyle due to the resulting metabolic disturbances. Orexin A and B are newly identified neuropeptides produced in the hypothalamus. Orexin A is involved in the regulation of appetite, food intake, and energy expenditure. Metabolic fuel detectors play a critical role in maintaining energy balance both peripherally and centrally. This study aimed to investigate the relationship between serum orexin levels and metabolic risk markers in women of reproductive age (RAG).

Materials and Methods: A random selection of 178 apparently healthy women aged 20–40 years were included. Fasting serum orexin and serum insulin levels were quantified using enzyme-linked immunosorbent assay (ELISA). Additionally, measurements of weight, body mass index (BMI), fasting blood glucose, lipid profile, and blood pressure were obtained.

Results: The findings revealed that serum orexin levels exhibited a significant positive correlation with fasting blood glucose, weight, BMI, and waist circumference. There was also a weak negative correlation with serum insulin levels.

Conclusion: The current study demonstrates that serum orexin levels are significantly correlated with weight, BMI, and fasting blood glucose, while showing a weak negative correlation with serum insulin levels. No correlation was found between serum orexin levels and the lipid profile in women of reproductive age.

Keywords: Orexin, Reproductive Age Group Women, Body Mass Index, Blood Glucose, Insulin.

Introduction

Metabolic syndrome is a cluster of medical disorders that, when present together, elevate the risk of developing cardiac diseases and disrupt glucose homeostasis. The term "metabolic syndrome" has been in use since at least the late 1950s, gaining widespread recognition in the late 1970s to describe the combination of risk factors associated with diabetes observed as early as the 1920s.

Metabolic syndrome is commonly linked to obesity and a sedentary lifestyle, resulting from excessive energy intake and reduced energy expenditure, both of which are modifiable. The health detriments of metabolic syndrome stem from metabolic derangements such as increased body weight, dyslipidemia, hypertension, diabetes mellitus, and insulin resistance [1,2]. Biologically, women across all ages globally tend to have a higher mean Body Mass Index (BMI) and higher rates of obesity compared to men [3], leading to metabolic abnormalities. The metabolic status of an organism is communicated to the brain via metabolic fuel detectors that regulate food intake. These detectors operate at both peripheral (e.g., leptin, insulin, and ghrelin) and central (e.g., neuropeptide Y, orexin, and melanocortin) levels.

Orexin A and B are recently identified hypothalamic neuropeptides involved in the regulation of feeding behavior, sleep-wakefulness, and neuroendocrine homeostasis. Orexin promotes both waking and feeding, suggesting a potential role in metabolic syndrome. Body weight maintenance depends on the balance between energy intake and energy expenditure. Energy

intake is derived from food, while energy expenditure encompasses complex thermogenic processes, including basal metabolism, adaptive thermogenesis, and physical activity. Hormones play a crucial role in regulating energy balance through signals integrated in brain centers, such as the hypothalamus, which modulates feeding and energy expenditure.

The hypothalamus, a key component in the regulation of energy homeostasis, continuously monitors signals reflecting energy status and initiates appropriate behavioral and metabolic responses [4]. The identification of novel factors, such as orexin A, involved in appetite control has introduced new perspectives on energy expenditure. Orexin A is a 33-amino acid peptide with an N-terminal pyroglutamyl residue and a C-terminal amidation residue, produced by a specific subset of neurons in the lateral hypothalamic area. It regulates appetite, food intake, and energy expenditure. Orexin/hypocretin was first described in 1998 by De Lecea et al. [5].

The lateral hypothalamus acts as the feeding center, whereas the ventromedial hypothalamus serves as the satiety center. The satiety center primarily controls food intake by inhibiting the feeding center. The cells of the ventromedial nuclei function as satiety centers due to their role as glucoreceptors, sensing blood glucose levels. Unlike other brain cells, these glucoreceptors require insulin for glucose utilization. Orexin, produced by neurons in the lateral hypothalamus, promotes feeding, which is unchecked in the absence of satiety center control.

A longitudinal study by Marianne et al. [6] on reproductive age group (RAG) women found that younger women are more likely than older women to transition from normal weight to overweight, leading to metabolic complications. Hormonal factors play a significant role in appetite regulation in women [7]. Additionally, orexin neurons are more crucial in regulating energy expenditure than food intake, and an imbalance in energy homeostasis may lead to metabolic complications [8].

A study by Kassie et al. [3] on non-pregnant RAG women indicated that, unlike men, women have higher prevalence rates of raised BMI, overweight, and obesity. The activity of orexin neurons is influenced by energy balance [9]. Research by Kastin and Akerstrom [10] demonstrated that orexin-A rapidly crosses the blood-brain barrier and is found in peripheral tissues, suggesting it may contribute to appetite control and energy expenditure peripherally as well as centrally.

Considering that RAG women are more susceptible to metabolic complications due to hormonal factors, and that orexin is involved in both food intake and energy expenditure, this study aimed to evaluate the association of serum orexin levels with anthropometric variables and metabolic risk factors in women of reproductive age.

Material and Methods

The study included 178 apparently healthy women of reproductive age group (RAG). These participants had no history of systemic disease. Detailed medical histories and obesity-related complications were documented using a standardized questionnaire.

Anthropometric measurements were taken by a single investigator using standard techniques. Waist circumference (WC) was measured at the midpoint between the lowest rib and the iliac crest at the level of the umbilicus, while hip circumference was measured at the level of the greater trochanter. Blood pressure (BP) was measured on the right arm in a sitting position after 5 minutes of rest using a standardized random zero sphygmomanometer. The first and fourth Korotkoff sounds were recorded as systolic and diastolic BP, respectively, and the average of two readings taken 5 minutes apart was used for analysis. Blood samples were collected after overnight fasting at 8 a.m. on day 10 of the menstrual cycle to minimize diurnal and cyclic variations. Serum and plasma were separated as needed for biochemical tests. Serum was separated by centrifugation at 3000 rpm.

Fasting blood sugar samples were collected in fluoride vials, and serum total cholesterol, triglycerides, and HDL cholesterol were analyzed using random access chemistry. Fasting blood sugar was estimated using an enzymatic method with oxidase and peroxidase. Fasting insulin was measured using an enzyme-linked immunosorbent assay (ELISA), and fasting serum orexin levels were measured using the EIA kit.

Statistical analysis was performed using SPSS version 16.0. Data were represented as numbers (%) and mean ± SD. A paired t-test was used to compare parameter changes at two different time intervals. ANOVA was employed to compare within-group and between-group variances, providing an F ratio where a higher value indicated greater inter-group differences. A Student's t-test was used to test the significance of two means, with $P < 0.05$ considered statistically significant. Pearson's correlation was conducted to evaluate the correlation of orexin-A with continuous variables.

Results

Table 1 presents the demographic profile of the study cases, including parameters such as age, BMI (Body Mass Index), WHR (Waist-to-Hip Ratio), SBP (Systolic Blood Pressure), and DBP (Diastolic Blood Pressure). The data are expressed as mean values ± standard deviation (SD).

Table 1: Demographic profile of study cases

Parameters	Mean ± SD
Age	25.14 ± 6.10
BMI (kg/m²)	22.59 ± 4.68
WHR	0.84 ± 0.05
SBP (mm Hg)	117.84 ± 9.13
DBP (mm Hg)	75.50 ± 7.15

Table 2 presents the metabolic profile of the study cases, including various parameters measured with their respective mean values and standard deviations (SD). Serum levels of orexin were quantified at 52.30 ± 13.15 pg/mL. The lipid profile showed a mean total cholesterol level of 163.57 ± 33.78 mg/dL, with high-density lipoprotein (HDL) levels at 40.44 ± 7.59 mg/dL and triglycerides (TGs) at 96.13 ± 34.54 mg/dL. Fasting blood glucose levels averaged at 98.27 ± 16.69 mg/dL, while serum insulin levels were measured at 11.48 ± 5.11 µIU/mL.

Table 2: Metabolic profile of study cases

Parameters	Mean ± SD
S. Orexin (pg/mL)	52.30 ± 13.15
Total cholesterol (mg/dL)	163.57 ± 33.78
HDL (mg/dL)	40.44 ± 7.59
TGs (mg/dL)	96.13 ± 34.54
Fasting Blood glucose (mg/dL)	98.27 ± 16.69
S. Insulin (µIU/mL)	11.48 ± 5.11

Table 3 presents the correlation coefficients (r values) and corresponding p-values for the association between serum orexin levels and various physiological parameters.

The table demonstrates a strong positive correlation between serum orexin levels and serum glucose ($r = 0.763$, $p < 0.001$), indicating a significant relationship between orexin levels and glucose metabolism.

Additionally, a moderate positive correlation was observed with BMI ($r = 0.173$, $p < 0.05$), waist circumference ($r = 0.278$, $p < 0.05$), and weight ($r = 0.185$, $p < 0.05$), suggesting potential links between orexin and adiposity-related parameters.

Table 3: Correlation between S. orexin and various parameters

Parameters	r value	P value
S. Glucose (mg/dL)	0.763	<0.001
BMI (kg/m²)	0.173	<0.05
Waist circumference (cm)	0.278	<0.05
Weight (kg)	0.185	<0.05
WHR	0.148	0.089
Serum insulin (µIU/mL)	-0.122	0.165
SBP (mm Hg)	0.092	0.296
S. Cholesterol (mg/dL)	0.088	0.321
HDL (mg/dL)	-0.066	0.457
Height (cm)	0.067	0.459
DBP (mm Hg)	0.033	0.727
TG (mg/dL)	-0.011	0.943

Discussion

In our study, 178 women of reproductive age group (RAG) were included. The selection of RAG women was based on evidence that the greatest incidence of major weight gain occurs in individuals aged 25–34 years [11, 12], and women in this age group are particularly prone to rapid weight gain, leading to metabolic complications [6]. Our results showed a significant positive correlation between serum orexin levels and various anthropometric parameters (weight, BMI, WC, and hip circumference) as well as biochemical parameters, specifically serum glucose levels. These findings are consistent with previous studies by Tomasik et al. [13], Matsumura et al. [14], and Heinonen et al. [15], which also reported a significant positive association between BMI and serum orexin levels, measured using ELISA.

Orexin-A has been closely associated with increased BMI and obesity [16,17], conditions linked to overeating. As an appetite-inducing neuropeptide, orexin-A also plays a role in energy

homeostasis [8]. Some studies have reported an inverse relationship between WC, BMI, fasting blood glucose levels, and orexin-A levels [18], noting that orexin-A levels are significantly lower in obese women and those with metabolic syndrome compared to non-obese women and those without metabolic syndrome [19]. Obesity, a global health problem, is associated with many leading causes of morbidity and mortality due to metabolic complications.

Our study did not find any correlation between serum orexin levels and lipid profiles of the participants. The activity of orexin neurons is regulated by the energy status and nutrient levels of an individual. Studies in mice have shown that orexin levels increase with elevated lipid levels and obesity induced by a high-fat diet [20]. Typically, elevated glucose concentrations increase the activity of orexin neurons, thereby enhancing energy expenditure [21].

The significant positive correlation between serum orexin levels and fasting blood glucose levels, coupled with a weak negative correlation with serum insulin levels, was observed in this study. The ventromedial hypothalamic nuclei serve as the satiety center, whereas the lateral hypothalamus functions as the feeding center where orexin neurons reside. The satiety center inhibits the feeding center post-ingestion.

The ventromedial nuclei act as glucoreceptors, sensing blood glucose levels and requiring insulin for glucose utilization. When insulin is low, glucose uptake by these glucoreceptors decreases, mimicking fasting conditions and resulting in unrestrained activity of the feeding center, leading to increased orexin release, hyperphagia, obesity, altered lipid profiles, and disrupted glucose homeostasis. This creates a vicious cycle of hyperorexinemia, hyperglycemia, dyslipidemia, hyperphagia, and polyphagia, potentially triggering comorbid conditions such as obesity, hypertension, and atherosclerosis, ultimately leading to metabolic syndrome [11].

The strength of our study lies in exploring the role of orexin neuropeptide in the development of metabolic syndrome and the potential therapeutic benefits of orexin antagonists. Although research on the role of orexin in humans is limited, our study sets the stage for further investigations in the field of metabolic syndrome. However, our study had limitations, including a small sample size. Future studies should involve a larger number of participants to validate these findings.

Conclusion

In the present study, serum orexin levels were found to have a significant positive correlation with several key anthropometric and biochemical parameters. Specifically, higher serum orexin levels were associated with increased weight, body mass index (BMI), and waist circumference (WC). This suggests that as the body fat and overall weight of individuals increased, their serum orexin levels also tended to be higher. This association indicates a potential link between serum orexin and adiposity. Overall, the study underscores the importance of understanding the interactions between orexin and various metabolic parameters, particularly in the context of metabolic syndrome. Further research is needed to elucidate the mechanisms underlying these associations and to explore the potential of targeting the orexin system for therapeutic interventions in metabolic disorders.

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