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THE ROLE OF PROLACTIN LEVELS IN METABOLIC SYNDROME: A SYSTEMATIC REVIEW

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Abstract

Introduction and purpose: Prolactin is primarily associated with lactation and gonadal function, but it also has metabolic effects. Recent research shows prolactin's role in food intake, body weight, glucose, and lipid profile. Both low and excessive prolactin levels can lead to metabolic dysfunctions such as metabolic syndrome, type 2 DM, and dyslipidemia.

Dopamine agonists, like cabergoline, used to treat hyperprolactinemia, may help balance metabolic homeostasis, likely due to their effect on prolactin. This study aims to synthesize current research on prolactin's metabolic effects, focusing on metabolic syndrome.

State of knowledge: Metabolic syndrome is a cluster of dysfunctions like central obesity, atherogenic dyslipidemia, hypertension, and insulin resistance. It increases the risk of diabetes and cardiovascular diseases, affecting a quarter of the European population. Different combinations of metabolic syndrome components require various treatment approaches. New research focuses on prolactin and dopamine agonists in its pathogenesis and treatment.

Materials and methods: This literature review is based on PubMed materials using keywords "prolactin," "hyperprolactinemia," "hypoprolactinemia," "metabolic syndrome," "diabetes mellitus," "obesity."

Conclusions: This study highlights prolactin's importance in metabolic homeostasis, finding a positive correlation between both low and high prolactin levels and metabolic syndrome. However, gender differences and the pathogenesis of metabolic disorders should be further explored.

Keywords: prolactin; hyperprolactinemia; hypoprolactinemia; metabolic syndrome; diabetes mellitus; obesity

Introduction

Metabolic syndrome (MetS) is a cluster of metabolic dysfunctions such as central obesity, atherogenic dyslipidemia, hypertension and insulin resistance. The co-occurrence of those may lead to the premature development of diabetes and cardiovascular diseases. The National Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATP III) recommend diagnosing metabolic syndrome if at least 3 out of 5 criteria, as outlined in Table 1, are met.

Table 1. *Criteria of metabolic syndrome according to NCEP ATP III (2005 revision) [14]*

	Women	Men
Waist circumference (WC)	≥80 cm	≥94 cm
Fasting HDL-C concentration	<1.3 mmol/l (50 mg/dl) or pharmacological treatment	<1.0 mmol/l (40 mg/dl) or pharmacological treatment
Fasting triglyceride concentration	>1.7 mmol/l (150 mg/dl) or pharmacological treatment	
Fasting glucose	≥5.6 mmol/l (100 mg/dl) or pharmacological treatment	
Blood pressure	≥130/85 mm Hg or hypotensive treatment	

According to the National Health and Nutrition Examination Survey (NHANES) nearly a fifth of adult population of US is affected by MetS. The MARE (Metabolic syndrome and Arteries REsearch) Consortium found that MetS had around 25% prevalence in Europe. [1, 2] The prevalence differs by age, gender and race. The problem impacts not only adults, but also children and adolescents.

Based on the systematic review including 85 studies, the median prevalence of MetS in entire non-adult populations was 3.3%. [3] Even though there is a downward trend in lipid disorders, the prevalence of central obesity and insulin resistance continue to increase alarmingly. As a result, many new studies are being created focusing on other previously unknown factors influencing the development of these diseases and potential treatments. Prolactin and its metabolic effect is one of those directions of research. In this review we want to focus on prolactin levels as a risk factor of metabolic syndrome.

Metabolic syndrome - etiopathogenesis

To comprehend the relationship between prolactin and metabolic syndrome, it is essential to understand the causes and pathogenesis of the syndrome. Numerous factors may induce MetS such as adipose tissue dysfunction, insulin resistance, chronic inflammation and oxidative stress. Some of them will be discussed below.

Insulin sensitivity differs from one individual to another due to genetic and environmental factors, particularly obesity. Insulin resistance is a condition where the cells of insulin-dependent tissues (primarily adipose tissue, muscle and liver) respond less effectively to insulin, leading to a compensatory increase in insulin secretion by the β-cells of the pancreatic islets, resulting in hyperinsulinemia. As a result, the number of type 4 glucose transporters (GLUT4) decreases. The diminished effect of insulin leads to the accumulation of glucose in the blood and a decrease lipogenesis, which may cause type 2 diabetes in the future. [4] As the disease progresses, pancreatic β-cells become dysfunctional which itself is a separate risk factor of MetS. [5] HOMA-IR (homeostatic model assessment for insulin resistance) is one of the most widely used methods for assessing insulin sensitivity and it's calculated using the following formula: (Fasting plasma glucose (mmol/L) × Fasting serum insulin (mU/L)) / 22.5. A higher HOMA-IR score indicates lower insulin sensitivity and thus greater insulin resistance. Another indirect measure of insulin sensitivity is the oral glucose tolerance test (OGTT), which provides information about glucose tolerance rather than directly measuring insulin resistance. [6]

Leptin secreted from the adipose tissue is another crucial hormone in MetS pathogenesis. It was discovered that leptin level rise as percentage of body fat increases. [7] Under normal conditions, leptin signals satiety to the brain. However, in obesity, despite high leptin levels, the hunger center is not inhibited, indicating the development of leptin resistance. Furthermore, leptin may regulate insulin secretion through receptors on β-cells and influence insulin sensitivity. As a result, when obesity induce leptin resistance, it becomes another factor contributing to hyperinsulinemia. A recent cross-sectional study suggest that high leptin levels lead to hypertension not only by causing obesity but also directly. [8] Therefore, leptin affects various MetS components.

Aside from leptin, adiponektin is an adipokine with anti-inflammatory, anti-diabetic and anti-atherogenic effects. Decreased adiponektin level was observed in obese patients [9] and corelates with the presence of MetS and type 2 diabetes, mostly affecting HDL cholesterol levels. [10]

Impaired functioning of the adipose tissue and insulin resistance contributes to the development of chronic inflammation. Plasma inflammatory markers such as IL-6, IL-1β, TNFα increase, along with immune cells including macrophages. [11] Chronic inflammation affects adipose tissue, liver, intestine, vascular walls, etc., leading to obesity and metabolic syndrome.

Prolactin physiology

Prolactin (PRL) is a polipeptide hormone synthesized by the anterior pituitary gland and is mainly associated with lactation and gonadal function, however currently we know that it has more complex effect on human's metabolism. Aside from prolactin production in anterior pituitary gland, it's also produced in the brain, the immune system, the adipose tissue and the mammary gland itself. It is expected that prolactin's receptors are present in mammary gland and ovary, however surprisingly they could be found in the brain, pancreas, adipose tissue and many more as well. [12] Considering that, PRL is versatile hormone that influences metabolism on many levels. PRL stimulates food intake inducing leptin resistance [13]. What's more, PRL increases β-cell mass and supports insulin's production, furthermore, promotes adipogenesis and suppresses lipolysis in adipose tissue. [14] These effects typically play a supportive role in pregnant women by providing nutrients for the developing baby. According to research involving rodents and humans, PRL treatment reduced adipocyte hypertrophy, sensitized cells to insulin, decreased proinflammatory mediators and increased adiponektin secretion. [15] Moreover, PRL affects humoral and cellular immune responses and its level increases in infections and autoimmune diseases. [12]

The concentration of prolactin fluctuates throughout the day with the peak during sleep. Prolactin secretion is mainly inhibited by dopamine affecting D2 receptors located on lactotrophs. Other inhibiting factors are gamma amino butyric acid (GABA), somatostatin, acetylcholine, and norepinephrine. Hypothalamic peptides, thyrotropin releasing hormone (TRH), vasoactive intestinal peptide (VIP), epidermal growth factor (EGF), and dopamine receptor antagonists stimulate PRL secretion. Normal serum prolactin levels range from 5 ng/mL to 20 – 25 ng/mL depending on the laboratory. During pregnancy, PRL concentration can reach up to 600 ng/mL. [16, 17]

Recent research proves that not only hyperprolactinemia, but low levels of PRL as well may cause metabolic dysfunctions leading to metabolic syndrome. [15]

Hyperprolactinemia

Hyperprolactinemia is characterized by elevated levels of circulating PRL, which leads to hypogonadism and infertility in both in men and women. Causes vary from physiological such as pregnancy, lactation, sleep and stress, to pathological, the most common of which is prolactinoma. Less common, but also important are other factors, including chronic renal failure, pharmacological treatment or cirrhosis. [16-19]

Irrespective of the causes, hypogonadotropic hypogonadism, galactorrhea, lowered libido, infertility are primary effect of hyperprolactinemia. These symptoms appear with different frequency depending on gender and age. Chronic hyperprolactinemia in humans has been reported to be associated with a relatively high rate of obesity and treating prolactinomas resulted in weight loss. [20, 21] Conversely, a retrospective study involving 47 patients with prolactinoma found no correlation between prolactinoma and body weight. [22]

PRL excess may affect food intake regulation in two different ways. Homeostatic brain circuits, as one of them, involves hypothalamic systems and mediators including leptin and insulin, which reduce hunger sensations and is primarily responsible for food consumption when energy reserves are low. [23]

Although, there are no precisely known molecular mechanisms, it is proven that PRL may cause hyperphagia and lead to obesity by causing leptin resistance. [24, 25] Another way of hunger regulation is based on the reward system associated with the dopaminergic pathway, which is responsible for food intake in situations that do not require additional energy. [23] It is discovered that PRL negatively affects dopaminergic tone resulting in increased food intake. [26]

Another important consequence of hyperprolactinemia is insulin resistance, which may contribute to type 2 diabetes [27-29] A suggested mechanism is that PRL decrease serum adiponectin. [30, 31] On the other hand, higher PRL in physiological range enhance insulin sensitivity. [32, 33] For instance, Sheoran et al. conducted a study involving 50 men and 50 women, finding a statistically significant inverse correlation between HOMA-IR and PRL levels. [33] Furthermore, elevated PRL inhibits production of sex hormone-binding globulin (SHBG) potentially increasing risk of type 2 diabetes. [34, 35]

Increased LDL-cholesterol and lowered HDL-cholesterol concentrations have been recorded in patients with prolactinoma. [36, 37] High PRL level may disrupt the lipid profile, as adipocytes release PRL and express PRL receptors, influencing the differentiation of mature adipocytes. Despite the speculative mechanism, excess prolactin induces lipid disorders through weight gain and its effect on lipogenesis, among other factors.

A prospective study involving 874 postmenopausal women demonstrated that PRL is independently associated with hypertension. [38] A possible mechanism by which prolactin (PRL) could increase blood pressure is through vasoconstriction mediated by β2-adrenergic receptors, which involves the endothelial release of nitric oxide (NO). [39, 40]

Dopamine agonists, including cabergoline and bromocriptine, are generally sufficient for treating hyperprolactinemia in the majority of patients. Their positive effect on metabolic profile implies that PRL might have a notable role in maintaining metabolic homeostasis.

Cabergoline as a pharmacological treatment has beneficial effects on metabolic syndrome, such as lowering plasma glucose levels. Some studies found that dopamine agonists decrease the risk of MetS or its individual components. [41-43] However, dopamine agonists likely do not work solely by reducing prolactin. [42] For example, a prospective study involving 34 patients with prolactinoma who were treated with either cabergoline or pituitary surgery implies that the primary factor improving insulin sensitivity may not be the reduction in prolactin levels alone, but rather the pharmacological action of cabergoline itself. [44] Kok et al. suggest that short-term bromocriptine treatment enhances glucose metabolism and systolic blood pressure through mechanisms that are separate from food intake reduction or body fat loss. [42] In fact, bromocriptine was approved by the Food and Drug Administration (FDA) for the treatment of type 2 diabetes. It likely reduces plasma glucose, free fatty acids, and triglycerides by resetting the circadian neuronal activities that typically regulate seasonal changes in metabolism, body fat stores, and muscle mass. [45, 46]

Hypoprolactinemia

Low levels of PRL, defined as less than 5 ng/mL, generally result in inhibiting lactation in women. Furthermore, a deficiency in PRL has broader implications for health, negatively affecting sexual function in both men and women. [47, 48]

Such deficiencies can arise from various forms of hypopituitarism, which may be secondary to conditions like autoimmune damage, tumors, Sheehan syndrome, or even due to iatrogenic causes, such as certain medical treatments or surgeries.
There is increasing number of new studies suggesting the impact of low PRL levels on metabolic syndrome. [47-51] For example, the higher risk of type 2 diabetes was observed in prospective study in middle – aged women with lower PRL levels. Corona et al. associate decreased PRL levels with metabolic syndrome in man. In contrast, another study involving both men and women, which established a connection between hypoprolactinemia and type 2 diabetes, did not find a link between prolactin levels and an increased risk of metabolic syndrome. [52] These varying results indicate that the role of hypoprolactinemia in metabolic health is complex and may differ by gender. Therefore, further research is needed to unravel these differences and to understand the underlying biological mechanisms.

Conclusions

Globally, the prevalence of metabolic syndrome represents a serious health problem, significantly impacting the development of both diabetes and cardiovascular diseases. Its complex etiopathology requires multiple research approaches, including studies examining the connection between PRL levels and metabolic syndrome. PRL is a hormone presenting a variety of metabolic effects. Both low and high prolactin levels appear to disrupt glucose-insulin and lipid profiles as well as adipose tissue metabolism. Therefore, maintaining PRL levels within the normal range could be beneficial in the prevention of metabolic syndrome. While there are evidences of PRL impact on BMI, glucose-insulin and lipid profile, the results of studies are inconsistent. These findings highlight the need for large prospective studies clarifying the precise metabolic effects of PRL and its potential usefulness in the diagnosis and treatment of metabolic syndrome.

Author's contribution

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