Metabolic aspects of hyperprolactinaemia

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Abstract

Hyperprolactinaemia is one of the most common endocrinological disorder in women at the reproductive age. Prolactin is known as a multifunctional hormone involved not only in reproductive function but also in different metabolic processes. Nowadays prolactin is considered also as a hormone responsible for behavior regulation, immunoregulation and body composition. Women suffering from overproduction of prolactin present numerous symptoms such as: menstrual disturbances, infertility, hirsutism, galactorrhoea and even anxiety or depression. Hyperprolactinaemia has been reported to be associated with hypercholesterolemia and links to overweight and obesity. Hyperprolactinaemia is associated with high prevalence of osteopenia or osteoporosis. Another important role of prolactin is connected with glucose metabolism and even with haemostasis system. Therefore relationship between hyperprolactinaemia and metabolism seems to be very essential.

Key words: hyperprolactinaemia, glucose metabolism, bone mineral density, lipids, obesity

Introduction

Prolactin (PRL) was identified in 1928 as a pituitary factor which induces milk production in rabbit mammary glands [1]. It is produced and secreted from lactotroph cells of the pituitary gland and also in some extrapituitary places including adipose tissue [2]. PRL appears in three forms including the biologically active monomeric PRL little PRL 23 kDa, biologically inactive dimeric PRL big PRL 50-60 kDa and very low activity big PRL named macroprolactinemia [3].

Human PRL is a multifunctional pituitary hormone with the main effect on mammary gland development and lactation in humans [4]. PRL induces lactation and stimulates milk production in pregnant and postpartum women.

Nowadays PRL is known as a hormone which plays role in a water balance, nutritional status, other metabolic processes, behavior regulation and immunoregulation [5]. Prolactin affects body composition mainly in 2 target tissues: breast and adipose [6]. Some research scientists add two more issues: pancreas and prostate [7]. Hyperprolactinaemia can result from a number of physiological, pathologic and pharmacologic processes. Hyperprolactinaemia has an important influence on reproductive function in women [8]. Overproduction of PRL disturbs the normal pulsatile secretion of the gonadotropin-releasing hormone (GnRH) and reduces luteinizing hormone (LH) and follicle stimulating hormone (FSH) pulsality. It leads to decrease of ovarian estradiol secretion and causes hypoestrogenic symptoms in patients with hyperprolactinaemia [9].

Women with hyperprolactinaemia present numerous symptoms. The relationship between hyperprolactinaemia and impaired reproductive function has been known for a long time [10]. In the literature they were named as the Chiari-Frommel syndrome, Argonz-Ahumada-Castillo syndrome and Albright-Forbes syndrome. Other complaints are as follow: galactorrhoea, hirsutism, loss of libido, anxiety symptoms and in a case of prolactinoma visual field changes, headaches and cranial nerve palsies [11].

The aim of the study was to evaluate influence of hyperprolactinaemia on different metabolic processes.

Hyperprolactinaemia and obesity

The prevalence of obesity is increasing worldwide [12]. Some endocrinological disorders are related to the weight gain: Cushing syndrome, hypothyroidism, hypogonadism. Studies on rats provide facts on the effects of prolactin on body composition. Long term overproduction of PRL in humans is often sticks by weight gain. Several studies reported higher body weight gain in patients with macroprolactinomas [13]. There are a few possible mechanisms which are considered to be linked to obesity in women with hyperprolactinaemia. Among these factors we can consider: reduction in dopaminergic tone, decreased adiponectin and hypogonadism.

Other researches reported also leptin resistance connected with hyperprolactinaemia. Cintia M. et al. [14] found a higher prevalence of obesity/weight gain in patients with prolactinoma. He compared the study group to the normal general population. Relationship between hyperprolactinaemia and of BMI was checked before and
after treatment with dopaminergic agonist [14]. In this study BMI wasn’t significantly different between the group of patients in which bromocriptine treatment was successful [14]. No differences was also reported when patients were divided in macroprolactinoma or microprolactinoma group.

The mechanism in which hyperprolactinaemia may cause weight changes is poorly understood. The determinant factor is possibly associated with hypogonadism. Greenman et al. [15] demonstrated weight loss after 12 months of treatment.

**Hyperprolactinaemia and plasma lipids**

PRL is known as a multifunctional factor involved also in lipid metabolism [16]. Some studies suggested the influence of overproduction of PRL on lipid profile but mechanism is not well known. Chronic hyperprolactinaemia is associated with amenorrhea and decreased estrogen concentration. Hypoestrogenism may lead to the elevation in total cholesterol, low density lipoprotein LDL and decrease in high density lipoprotein HDL [17].


In 1982 Pelkonen et al. [19] studied total cholesterol and triglyceride levels in 46 women with diagnosed prolactinoma and concluded that pituitary tumor is associated with metabolic abnormalities such as hyperlipidemia, high plasma LDL levels and insulin resistance.

High prolactin serum concentration stimulates food intake and links to gain weight. It was reported that overweight or obesity are seen in hyperprolactinaemic patients in higher number than in normoprolactinaemic patients. However the effect of prolactin on weight gain is still controversial.

**Hyperprolactinaemia and bone mineral density**

Osteoporosis is defined as a reduction in bone mineral density (BMD) 2.5 standard deviations below the mean for a healthy young adult. Osteoporosis is asymptomatic disease which affects 10 milion Americans and annual financial cost of osteoporosis-related fractures in US is estimated at between $10-$15 billion .

Risk factors for osteoporosis can be grouped into genetic and modifiable cases. Genetics factors include female sex, white race and family history. Modifiable factors include low body mass index, diet, smoking, vitamin D deficiency and psychotropic medicaments. Schizophrenia affects 1% of the world’s population and is regarded as a disorder causing disability [20].

Hyperprolactinaemia remains one of the most common side effects of antipsychotic treatment [21]. The first generation antipsychotics (FGA) binds to dopamine D2 receptors on the pituitary cells and inhibits action of dopamine. The prevalence of hyperprolactinaemia with FGAs ranges from 33% to 87% depending mainly on the dose. Second generation or atypical antipsychotics (SGA) lead to hyperprolactinaemia but in much lower rates. Hyperprolactinaemia causes decrease of body mass index what leads to osteopenia or osteoporosis. The possible mechanism of the reduced bone mineral density is associated with hypoestrogenism. A lot of studies demonstrated the influence of high prolactin serum concentrations on bone metabolism. Ataya et al. [22] studied the prevalence of osteoporosis in neuroleptic-induced hyperprolactinaemia in 10 patients. All of them suffered from menstrual disturbances (3 were amenorrhoeic and 7 had oligomenorrhea). They concluded that all of these patients were at increased risk of developing osteoporosis. Bussade et al. [23] studied 24 patients with diagnosed prolactinoma and reported decreased BMD – in 20.83% of young women with prolactinoma.

They suggested the role of hypogonadism in the pathogenesis of osteoporosis. Zadroza-Sliwka et al. [24] studied 32 women with prolactinoma and 43 women with functional hyperprolactinaemia. It was reported, that functional hyperprolactinaemia doesn’t determine such a harmful effect on bone metabolism as hyperprolactinaemia due to prolactinoma.

High prevalence of the vertebral fractures in 78 women with prolactin-secreting pituitary adenoma was reported by Mazzotti et al. [25]. The study demonstrated that fractured patients were significantly older, had lower BMI T score and higher prolactin serum and lower serum IGF-1 concentration compared to patients who didn’t have fracture. Moreover fractures occurred more frequently in patients with untreated hyperprolactinaemia versus patients treated with cabergoline therapy [25]. The main conclusion was as follows: hyperprolactinaemia is associated with high prevalence of radiological vertebral fractures in women with prolactin-secreting adenoma.

**Hyperprolactinaemia and haemostasis system**

A different effect of prolactin on the haemostasis system hasn’t been well established. Some studies demonstrated that patients with hyperprolactinaemia suffer from stroke, acute coronary syndromes and myocardial infarction [26].
Associations between hyperprolactinaemia and platelet aggregations is not clearly understood. Hypercoagulable state and impaired endothelial function was demonstrated in patients with hyperprolactinaemia. Wallaschofski et al. [26] reported that hyperprolactinaemia was a potent co-stimulator of platelet aggregation. According to the authors it can explain the possible reason for hypercoagulable state observed in pregnancy and puerperium.

Erem at al. [27] found some important differences in the haemostatic parameters between the patients with prolactinoma and healthy controls. Increased platelet count, fibrinogen, PAI-1 and decreased TFPI in patients with prolactinoma may represent a potential hypercoagulable and hypofibrinolytic state, which might augment the risk for atherosclerotic and atherothrombotic.

Sauro et al. [28] reported that hyperprolactinaemia mediates the protein kinase C pathway and this mechanism stimulates muscle cell hyperplasia.

A larger number of studies is required to confirm such association.

**Prolactin and glucose metabolism**

Hyperprolactinaemia is also associated with impaired glucose tolerance [29]. Nearly 40 years ago it was speculated, that hyperprolactinaemia reduces glucose tolerance [30]. The prodiabetic effect of prolactin was demonstrated.

Studies in hyperprolactinaemic women with or without prolactinoma have revealed hyperinsulinemia and reduced glucose tolerance [31]. The mechanism in which hyperprolactinaemia influences on pancreatic function is not well understood. One of the possible explanation is connected with adiponectin action which is a peptide hormone produced by adipose tissue [31]. Adiponectin level is correlated with obesity and development of the diabetes mellitus type 2. Considering, that hyperprolactineamia inhibits adiponectin secretion in vivo in humans maybe the same mechanism is leading to hypoadiponectinemia and causes impaired glucose tolerance [32].

Tuzcu et al. [33] demonstrated that hyperprolactinaemic patients were more insulin resistant than control patients. He also reported that insulin resistance in women with hyperprolactinaemia is not associated with obesity.

Yavuz Dilek at al. [34] enrolled 16 women with hyperprolactinaemia with pituitary tumor and reported that hyperprolactinaemia is connected to decreased insulin sensitivity which can be regarded as early marker for atherosclerosis.

Further studies are needed to clarify the relationship between insulin resistance and type 2 diabetes in hyperprolactinaemic women.

**Summary**

Hyperprolactinemia is a common endocrine disorder occurring in 15-20% of women with menstrual disturbances.

Prolactin (PRL) is a polypeptide hormone secreted by the lactotrophs of the anterior pituitary gland. The biological action of prolactin is mammary gland development, inducing milk production and maternal behavior in postpartum women. For some years prolactin is also considered as a multifunctional hormone but the mechanisms are complex and not well known.

Correlations between hyperprolactinemia and hypercholesterolemia were observed. Moreover total cholesterol and LDL concentration decreased significantly after treatment with dopamine agonist. Obesity or weight gain is also noted in hyperprolactinaemic patients.

Studies in human link hyperprolactinaemia to glucose intolerance and hyperinsulinemia. Prolactin seems to inhibit the production of adiponectin in human adipose tissue and it may be a factor for insulin resistance in hyperprolactinaemic patients.

Treatment goals include normalization of prolactin concentrations, resolution of symptoms of hypogonadism and in case of prolactinoma reduction in tumor size.

Metabolic function of prolactin should be always considered in women with hyperprolactinaemia. Treatment with dopamine agonists has beneficial effect on metabolic changes.

**References**


