Hyperprolactinaemia: metabolic consequences

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Abstract
Prolactin (PRL) is an anterior pituitary hormone first identified in 1933. PRL is secreted in a pulsatile fashion and is under chronic inhibition by dopamine. Hyperprolactinaemia is the most common disorder of the hypothalamic-pituitary axis. Chronic excess of prolactin disrupts the normal pulsatile secretion of gonadotropin releasing hormone (GnRH) and luteinizing hormone (LH) and follicle-stimulating hormone (FSH). It resulted in estrogen deficiency. The primary function of PRL is the initiation and maintenance of lactation and breast development. For some years multifunctional role of PRL has been demonstrated. Hyperprolactinaemia has been reported to be associated with abnormalities of lipid metabolism—hypertriglyceridaemia and hypercholesterolemia. Excess of prolactin links to insulin resistance and reduced glucose tolerance. Hyperprolactinaemia related to hypoestrogenism is involved in decrease of bone mineral density leading to osteopenia and osteoporosis.

Key words: prolactin, hyperprolactinaemia, lipid profile, obesity, reduced glucose tolerance

Introduction
Prolactin (PRL) is an anterior pituitary hormone first identified in 1933 [1]. PRL is secreted in a pulsatile fashion and is under chronic inhibition by dopamine [2]. Hyperprolactinaemia is the most common disorder of the hypothalamic-pituitary axis [3]. Chronic excess of prolactin disrupts the normal pulsatile secretion of gonadotropin releasing hormone (GnRH) and luteinizing hormone (LH) and follicle-stimulating hormone (FSH). It resulted in estrogen deficiency [4]. The primary function of PRL is the initiation and maintenance of lactation and breast development [5]. During the pregnancy prolactin initiate and maintain milk production. PRL acts to increase arginase activity, stimulate the ornithine decarboxylase activity and enhance the rate of transport of polyamines into the mammary glands. It results in increase of spermine and spermidine synthesis which is important for the milk production [5].

For some years multifunctional role of PRL has been demonstrated. Hyperprolactinaemia has been reported to be associated with abnormalities of lipid metabolism—hypertriglyceridaemia and hypercholesterolemia [6]. Excess of prolactin links to insulin resistance and reduced glucose tolerance [7]. Hyperprolactinaemia related to hypoestrogenism is involved in decrease of bone mineral density leading to osteopenia and osteoporosis [8].

Prolactin secretion and forms
PRL is a 23 kDa polypeptide hormone (198 amino acid) syntetised in the anterior lobe of pituitary gland [1]. PRL is secreted in pulsatile way [3]. Day time pulses are modified by meals, stress, exercise and intercourse [3].

Syntesis of PRL is under control of releasing and inhibiting factors. The main mechanism is control by inhibitory effect of dopamine [9]. Thyroid-releasing hormone (TRH), vasoactive intestinal peptide (VIP), oxytocin and galanin stimulate prolactin secretion [10].

PRL circulates in a multiple forms in the serum blood: the predominant form is monomeric PRL (molecular weight 23 kDa), big prolactin (molecular weight 50 kDa) and big-big prolactin (molecular weight more than 150 kDa) [11].

Macroprolactinaemia is a condition in which the large amount of PRL is composed of big-big prolactin. The big-big form of prolactin (macroprolactinaemia) is biologically inactive [12].

Because of variety of PRL molecule patients with high prolactin serum concentration should be screened for the presence of macroprolactin by using polyethylene glycol precipitation test [12].

Pathology of hyperprolactinaemia
Hyperprolactinaemia is one of the most common endocrine disorder of the hypothalamic-pituitary axis [3].

The prevalence of hyperprolactinaemia is 9-17% in women with reproductive disturbances [13]. Its prevalence has been also reported among 20% of women with polycystic ovarian syndrome [14].

Hyperprolactinaemia is regarded as a condition of elevated PRL serum concentration. Excess of PRL inhi-
bits hypothalamic secretion of gonadotropin-releasing hormone (GnRH) which decreases secretion of luteinizing hormone (LH) and follicle-stimulating hormone (FSH). The main consequence is estrogen deficiency (hypoestrogenism) [15].

Hyperprolactinaemia can be related to the physiological processes such as: pregnancy, lactation, breast stimulation, activity and sleep [16].

Pathological hyperprolactinaemia is associated with some endocrine diseases: PCOS, Addison’s disease, acromegaly and hypothyroidism [17].

Excess of PRL can be related to the pharmacological agents: antipsychotics (neuroleptics, opiates, antidepressant), antihypertensive drugs (verapamil, methyldopa, reserpine), gastrointestinal medications (metoclopramide) [18].

Hyperprolactinaemia can also result from disrupted dopamine transport in the portal vessel and it’s reported in prolactinoma, meningoma and severe head trauma [19].

Common signs and symptoms of hyperprolactinaemia can be presented in women and men. It is more easy to diagnose hyperprolactinaemia in women than in men.

Patients with high prolactin serum concentration present menstrual disturbances and galactorrhoea [20]. High prolactin serum concentration is regarded as the important cause of infertility in women and men [21]. Hyperprolactinaemia due to increased dehydroepiandrosterone sulfate secretion can lead to hirsutism and acne problems [22]. In men symptoms of hyperprolactinaemia are mainly connected to gynecomastia, erectile dysfunction and decreased libido [23].

**Metabolic consequences of hyperprolactinaemia**

PRL exerts a wide variety of effects on metabolic processes.

For many years high prolactin serum concentration has been reported as an important factor which induces hyperphagia and promotes the weight gain [24]. Several studies reported higher body weight gain in patients with macroprolactinomas [24]. The mechanisms are not so clear but studies consider a few factors: reduction in dopaminergic tone, decreased adiponectin and hypogonadism [24].

Hyperprolactinaemia impairs lipid metabolism. The possible mechanism is related to the inhibition of the release of adipokines [25]. Hyperprolactinaemia has been linked to hypertriglyceridemia and hypercholesterolemia in patients with prolactinoma [25]. Excess of prolactin in women with secondary amenorrhoea and estrogen deficiency may lead to elevation in total cholesterol (TCH), low density lipoprotein (LDL) and decreased in high density lipoprotein (HDL) [25]. Some studies reported that the presence of prolactinoma has been associated with metabolic abnormalities such as hyperlipidemia, low plasma LDL levels activity and insulin resistance [26].

High prolactin serum concentration is a potent costimulator of platelet aggregation so can be involved in hypercoagulable state observed in pregnancy and the puerperium [26].

Some researches speculated that hyperprolactinaemia reduces glucose tolerance [27]. The prodiabetic effect of PRL was demonstrated in few studies. Excess of PRL seems to play a key role in glucose abnormalities and hyperinsulinemia. Increased insulin resistance using homeostasis model assessment (HOMA) index has been described in hyperprolactinaemic patients [28]. Adiponectin is correlated with obesity and development of the diabetes mellitus type 2. Hyperprolactinaemia inhibits adiponectin secretion in vivo in humans. Probably the same mechanism is leading to hypoadiponectinemia and causes impaired glucose tolerance in hyperprolactinaemic patients [28].

Hyperprolactinaemia is related to the decrease of body mass density and leads to osteopenia or osteoporosis [29]. The possible mechanism of the reduced bone mineral density is probably associated with hypoestrogenism. A lot of studies demonstrated the influence of high prolactin serum concentrations on the bone metabolism. High prevalence of the vertebral fractures in women with prolactin-secreting pituitary adenoma has been reported [29]. The fractures occurred more frequently in patients with untreated hyperprolactinaemia versus patients treated with cabergoline therapy [30]. The main conclusion regarded that hyperprolactinaemia is associated with high prevalence of radiological vertebral fractures in women with prolactin – secreting adenoma [30].

**Conclusions**

Hyperprolactinaemia is mainly related to menstrual disorders and infertility. However it also seems to be associated with some metabolic abnormalities such as: hypercholesterolemia, insulin resistance, reduced glucose tolerance, weight gain and decreased bone mineral density.

**References**


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