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## Research Article

# HYPERPROLACTINEMIA: EFFECT ON REPRODUCTION, CANCER, BEHAVIOR, AND OBESITY

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### ABSTRACT

Hyperprolactinemia is usually regarded as the persistent increase of prolactin to the amounts exceeding normal values. Prolactin is a globular protein synthesized and secreted by lactotrophs in anterior pituitary gland. When prolactin levels exceed normal levels, it can cause major problems. Several conditions may cause hyperprolactinemia. Physiological factors such as pregnancy, lactation, sexual intercourse, sleep, exercise, and stress might influence on prolactin level; however, the most prevalent cause of hyperprolactinemia is medicines. The present study was formulated in order to determine the effect of hyperprolactinemia on reproduction, cancer, behavior, and obesity. Also, a short part was dedicated to treatment of hyperprolactinemia.

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## INTRODUCTION

Prolactin is a globular protein synthesized and secreted by lactotrophs in anterior pituitary gland. There are three major types of prolactin in blood: monomeric prolactin (monoPRL), big prolactin (bigPRL), and macro prolactin (macroPRL). The monomeric form's molecular weight is 23 kDa and it is responsible for majority of prolactin immunity reactions in the serums of normal and hyperprolactinemic subjects. bigPRL has a molecular weight of 48-56 kDa and it is considered responsible for 10-15% of immunity reactions of prolactin. Macro PRL has a molecular weight of 150-204 kDa and it is basically an antigen-antibody complex composed of monoPRL and IgG (McCudden *et al.*, 2010).

Hyperprolactinemia is usually regarded as the persistent increase of prolactin to the amounts exceeding normal values. The normal values for females and males is <530 mIU/L (25 ng/mL) and <424 mIU/L (20 ng/mL), respectively. In some patients, sexual problem or menstrual disorder can be symptoms of Hyperprolactinemia; however, the symptoms are not specific symptoms of hyperprolactinemia. Long-term effects of hyperprolactinemia might include gynecomastia, hypogonadism, prolactinoma, and Prl-sensitive tumors.

### Causes of hyperprolactinemia

Several conditions may cause hyperprolactinemia. Physiological factors such as pregnancy, lactation, sexual intercourse, sleep, exercise, and stress might influence on prolactin level. The most prevalent cause of hyperprolactinemia is medicines, especially antipsychotics and sedatives. Furthermore, antihypertensive medicines, calcium channel blockers (verapamil), antidepressants, antiemetic medicines (metoclopramide) and etc. can cause hyperprolactinemia. Besides prolactinoma, diverse conditions of pituitary gland may also cause hyperprolactinemia through damage to dopaminergic neurons, brainstem compression, hormone co-secretion (adenoma which secretes GH and prolactin). During any disorder in kidneys and liver, prolactin amounts may increase due to lower clearance. MacroPLLs, which are accumulated because of decrease clearance, is another cause of hyperprolactinemia. Macroprolactinemia is diagnosed by precipitation of polyethylene glycol (HalperinRabinovich *et al.*, 2013).

### Effect of hyperprolactinemia on reproduction

Hyperprolactinemia is the most common disorder of endocrine hormones leading to oversecretion on hypothalamus-pituitary

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axis. This disorder is prevalently seen in young females (20-30%) and it can cause several abnormal consequences such as infertility. Hyperprolactinemia is diagnosed via high amounts of prolactin in blood. Prolactin is a simple peptide with approximately 200 amino acids. Its biological effects are through interaction with prolactin receptor (PRLR). PRLR belongs to the superfamily of cytokine receptor-I and its isoforms are formed by connection of RNA from only one gene and through post-translational changes. In mice, one long (PRLR-L) and three short isoforms (PRLR-S1, PRLR-S2, and PRLR-S3) are recognized. Expression of these isoforms might change with estrous cycle and it is related to the high amounts of prolactin in blood circulation. In mice, it is possible to mimic hyperprolactinemic symptoms by prescription of metoclopramide. This medicine acts on dopamine D-2 receptor specific antagonist in pituitary gland. This medicine connects to the receptors and increase prolactin production by apoptosis prevention in lactotrophs. Moreover, metoclopramide-induced experimental model, reduced synthesis of ovary steroids during proestrous phase of female and reduction in progesterone during pregnancy have been detected (Amaral *et al.*, 2013).

Evaluation of prolactin level in the patient suffering from recurrent abortion syndrome indicated that prolactin level was profoundly decreased. In addition, variations in prolactin level, whether hyperprolactinemia or hypoprolactinemia, is accompanied by disorder in follicular and luteal phases (Arefi, 2010).

Hitherto, majority of what mentioned was related to women, however, it has been found that it can cause sexual dysfunction in men. It causes disorder in LH release resulting in reduced secretion of serum testosterone (Buvat, 2003).

#### **Hyperprolactinemia and cancer risk**

Prolactin is mainly secreted from lactotrophs cells in anterior pituitary gland. It is also produced out of pituitary gland such as breast glands, placenta, prostate, brain and immune cells. The first choice to cure hyperprolactinemia is dopamine agonists which are effective in normalizing prolactin levels and decreasing tumor size. Nevertheless, there is a risk that hyperprolactinemic patients are subjected to high amount of prolactin for several years. Experimental studies have revealed that prolactin leads to *in vitro* proliferation of breast cancer cells and results in increased growth of breast cancer inflammation. Some other types of tumors might be influenced by prolactin, as well. For instance, experimental data have shown that prolactin stimulates cellular proliferation in prostate and adjusts prostate growth and therefore, it can theoretically influence on carcinogenicity in prostate. However, the role of prolactin in pathogenicity in prostate in humans and epidemiological data on prolactin and carcinogenicity in prostate is very sparse. Furthermore, it has been suggested that prolactin can have a topical role in development of tumor in women cancer, colon cancer, tongue cancer, and blood cancer. According to new medicinal guidelines, non-tumor asymptotic hyperprolactinemia may not be treated in women after menopause or in the women not intending to have pregnancy in future (Berinder *et al.*, 2011).

Prolactin, either directly or indirectly, plays role in growth of tumors. It increases invasiveness of colorectal tumors and it is

effective in proliferation of some cell lines of breast cancer such as MCF-7 and T47-D. Prolactin activates malignant lymphocytes type-B and lymphoma cells and increases the growth of promyelocytes (SiratiSabet and KaramiTehrani, 2006).

#### **Effect of hyperprolactinemia on behavior**

Hyperprolactinemia is directly related to malfunction of sexual glands. However, special attention has been given to its relationship with mental and behavioral symptoms. Anxiety, somatization disorder, aggressiveness, and depression have been found to be related to depression. Prolactin greatly influenced on behavior of some animal species. The relationship between hyperprolactinemia and mental and behavioral symptoms has been clearly proved. Authors have stated that the women with hyperprolactinemia suffer from anxiety and somatization as well as aggressiveness and depression. Compared to control subjects, the men with hyperprolactinemia suffered from higher levels of anxiety (Gomes *et al.*, 2015).

Mental and behavioral effects of hyperprolactinemia have been constantly reported. High prevalence of depression, aggressiveness, and anxiety has been reported in the patients. Also, the effects of hyperprolactinemia such as obesity, amenorrhea, and galactorrhea might cause mental distress in patients (Yavuz *et al.*, 2003).

#### **Hyperprolactinemia and obesity**

Prolactin is a mono-chain polypeptide with several functions such as lactation, luteal function, reproduction, appetite, pregnancy, hemostasis, osmotic balance, immunity, and coagulation. Expression of prolactin-receptor gene has been shown in adipose tissue and increased expression has been detected in mice and humans. Abdominal fat and leptin concentration were lower in the mice with shortage of prolactin receptor than normal ones. In hamsters, inhibition of prolactin secretion by bromocriptine led to reduced accumulation of fat without any effect on food absorption and body weight. In human adipose tissue, prolactin retards lipid storage and adipokine release and it also possesses a paracrine/autocrine function related to adiponectin through connection to its receptors. Prolactin leads to increase in expression of adiponectin receptors. It should be noted that hormonal adiponectin is secreted by adipose tissue and increases insulin sensitivity. In human, other than pregnancy, prolactin secretion changes with higher body weight in adults and children. However, no molecular basis has been found for the relationship between prolactin and higher body fat, weight, and appetite. Nevertheless, there are some data showing the role of prolactin on leptin. In recent years, studies have shown that obesity increased in the patients suffering from prolactinemia and there were also some studies pointing to increase or decrease in body weight after the cure for hyperprolactinemia (Pereira-Lima *et al.*, 2013).

#### **Treatment of hyperprolactinemia**

The purpose of treatment for hyperprolactinemia is to take serum prolactin to the normal level and reduce the symptoms caused by high amount of serum prolactin such as irregular

menstruations, infertility and sexual dysfunctions, and reduced tumor size. Three types of treatments are considered for hyperprolactinemia: medicinal treatment, surgery, and radiotherapy. Medicinal treatment includes macro- and micro-adenoma, which are dopamine agonists. They are very effective in inhibition of prolactin and reduction of tumor size and they also result in tumor control and normal level of prolactin (Sarvi and Safdarian, 2010).

## CONCLUSION

Hyperprolactinemia is one of the disorders related to hormone secretion and is usually defined as persistent increase in prolactin level to a level higher than normal experimental level. The most common cause of hyperprolactinemia is the influence of medicines, especially antipsychotics and sedatives. Hyperprolactinemia might influence on different functions of body. One of the influences of hyperprolactinemia is on reproduction; hyperprolactinemia can cause disorder in reproduction via increased level of prolactin. Also, topical prolactin can play roles in development of tumor in women cancer (such breast and uterus cancers), colon cancer, tongue cancer, and blood cancer. Also, mental and behavioral effects of hyperprolactinemia, such as depression, aggressiveness, and anxiety, have been constantly reported in hyperprolactinemic patients. Studies in recent years have shown that obesity in prolactinemic patients has increased although some studies have shown increase or decrease in body weight after a treatment period for hyperprolactinemia. The purpose of treatment for hyperprolactinemia is to take serum prolactin to normal level and reduce the symptoms caused by higher levels of serum prolactin. There are three types of treatments for hyperprolactinemia, namely medicinal treatment, surgery, and radiotherapy.

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