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Hyperprolactinaemia and insulin resistance

Marcin Gierach*, *Malwina Bruska-Sikorska*, *Magdalena Rojek*, *Roman Junik

Department of Endocrinology and Diabetology, Collegium Medicum, Nicolaus Copernicus University, Jurasz University Hospital 1, Bydgoszcz, Poland

Abstract

Hyperprolactinaemia is the most common dysfunction of the hypothalamic-pituitary axis and occurs more commonly in women. The prevalence of hyperprolactinaemia ranges from 0.4% in the general adult population to as high as 9–17% in women with reproductive diseases. It is accompanied by the phenomenon of insulin resistance (IR), which is also a significant clinical problem nowadays. The prevalence of IR is increasing, particularly in developing countries and in younger populations, with estimates of prevalence ranging from 20 to 40% in different populations.

The aim of our review is to summarize recent data on the possible association between IR and hyperprolactinaemia.

This review is based on an electronic search of the literature in the PubMed database published from 2000 to 2022 using combinations of the following keywords: IR, hyperprolactinemia or IR and hyperprolactinemia. The references included in previously published review articles were also checked, and any relevant papers were also included.

Numerous scientific studies have shown a relationship between IR and hyperprolactinaemia. Increased plasma prolactin (PRL) levels are often associated with an increase in tissue resistance to insulin. There are many scientific theories explaining the probable mechanisms of this phenomenon. One is the finding that glucose and PRL act synergistically in inducing the transcription of insulin genes. It is also suggested that PRL may act as a regulator of insulin sensitivity and metabolic homeostasis in adipose tissue. The topic of the mutual correlation of hyperprolactinaemia and IR is important, and it certainly requires further research and observation. **(Endokrynol Pol 2022; 73 (6): 959–967)**

Key words: *hyperprolactinaemia; insulin resistance; metabolic syndrome*

Introduction

Hyperprolactinaemia is one of the most common problems in clinical endocrinology. It is the most common dysfunction of the hypothalamic-pituitary axis and occurs more commonly in women. The prevalence of hyperprolactinaemia ranges from 0.4% in the general adult population to as high as 9–17% in women with reproductive diseases [1, 2].

It has been implicated in the pathogenesis of obesity and glucose metabolism abnormalities. It is accompanied by the phenomenon of insulin resistance (IR), which is also a significant clinical problem nowadays. The prevalence of IR is increasing, particularly in developing countries and in younger populations, with estimates of prevalence ranging from 20% to 40% in different populations [3, 4].

The aim of our review is to summarize recent data on the possible association between IR and hyperprolactinaemia.

This review is based on an electronic search of biomedical literature in the PubMed database published from 2000 to 2022 using combinations of the following keywords: IR, hyperprolactinemia or IR and hyperprolactinemia, and then combinations with other phrases: pathology, prevalence, and other diseases: metabolic syndrome, polycystic ovary syndrome (PCOS). The references included in previously published review articles were also checked, and any relevant papers were included.

Insulin resistance

Insulin metabolically affects excretion and regulates the metabolism of carbohydrates, lipids, and proteins through a specific low-membrane receptor, which is present on the surface of hepatocytes, adipocytes, and striated muscle cells [5–7]. Insulin stimulates the reduction of glucose, free fatty acids, and ketone levels [8]. The activity of insulin is also influenced by many hormones; (e.g. the growth hormone, glucocorticoids, thyroid hormones, catecholamines, androgens, parathyroid hormone, aldosterone, glucagon, or somatostatin, which acting antagonistically and reduce the activity of insulin) [9, 10]. This leads to disturbances in the carbohydrate metabolism and an increase in IR in the pre-receptor, receptor, and post-receptor mechanisms [11]. In addition to the genetically determined

Marcin Gierach, Department of Endocrinology and Diabetology, Collegium Medicum, Nicolaus Copernicus University, Jurasz University Hospital 1, Bydgoszcz, Poland; e-mail: marcin_gierach@wp.pl

defect of the insulin receptor, IR may be caused by genes encoding post-receptor proteins, such as glucose transporters or insulin receptor substrates [12].

The hyperinsulinaemic-euglycaemic clamp is considered the gold standard method for assessing insulin sensitivity [9, 13–15]. The test consists of an intravenous infusion with insulin, which allows its concentration in the serum to be maintained at about 100 mIU/L, and an intravenous infusion with glucose to provide specific blood glucose levels [5, 9, 14, 16]. Exogenous hyperinsulinaemia allows for complete blockage of insulin production by pancreatic β cells and glucose production by the liver. This test allows the diagnosis of IR, which plays an important role in the development of the metabolic syndrome. It is a significant risk factor for the development of diabetes and cardiovascular complications but may also be secondary to the presence of many other metabolic disorders, such as in the case of a patient with ROHHAD syndrome [17–20]. It is limited because it is relatively invasive, as well as cost- and labour-intensive, requiring 6 or more hours of continuous bedside monitoring and infusion adjustments. Simpler measures of insulin sensitivity such as fasting insulin concentrations and leptin/adiponectin ratios [21] are often used as a surrogate marker for insulin sensitivity. Fasting insulin and glucose levels can also be used for homeostasis model assessment (HOMA). HOMA-IR is used as a measure of insulin sensitivity and has the advantage of being simple to obtain, but it is not directly comparable to the clamp measure [22]. It is calculated by the formula (insulinemia [μU/mL] × glycaemia [mmol/L])/22.5 [23]. The most commonly used oral glucose tolerance test (OGTT)-based measure of whole-body insulin sensitivity is the Matsuda index [24].

There are also many examples of the relationship between thyroid function and IR described in the literature. Studies have shown that the reduction of tissue sensitivity to insulin among obese men is significantly associated with impaired thyroid function [25]. On the other hand, another study showed that thyroid function in euthyroid people is associated with components of metabolic syndrome, mainly serum lipids and IR. Additionally, it has been shown that low normal free thyroxine (FT4) levels are significantly associated with increased IR in tissues [26]. The initiation of levothyroxine treatment in a patient with previously untreated hypothyroidism and secondary obesity as well as with unregulated diabetes and diagnosed IR resulted in an improvement in the parameters of peripheral insulin sensitivity [27].

IR is also significantly associated with polycystic ovary syndrome [28–30], acromegaly [31], hypercortisolism [32], hypopituitarism [33], primary hyperparathyroidism [34], and disorders of the adrenal gland [35, 36].

Hyperprolactinemia

Prolactin (PRL) is produced by the anterior pituitary gland, more specifically by lactotrophic cells. Its main function in women is the regulation of milk production after childbirth and the growth of the mammary glands during pregnancy. It also affects the reproductive organs [37]. Prolactin levels are highest during sleep [38]. It has been proven that the pituitary gland is not the only structure in the human body that is responsible for the production of prolactin. The second such structure is human adipose tissue. PRL inhibits the storage of lipids as well as adipokines (adiponectin, interleukin 6, and leptin) and has been implicated in the regulation of adipogenesis. It also affects energy homeostasis through its action as an adipokine and is involved in the manifestation of IR [39].

Hyperprolactinaemia is a common disease that interferes with fertility and causes hypogonadism in both genders and galactorrhoea in women, rarely in men. Hyperprolactinaemia impairs the pulsatile secretion of hypothalamic gonadoliberin (GnRH) and thus the secretion of follicle stimulating hormone (FSH) and luteinizing hormone (LH). In this way, the maturation of the Graaf follicle is inhibited and there is no ovulation. A correlation between elevated PRL levels and PCOS has not been noted [40]. There are also cases of asymptomatic hyperprolactinaemia. The most common cause of this condition is adenomas called prolactinomas. They constitute as much as 40% of all pituitary tumours [37, 41]. The pathogenesis of the prolactin tumour is not fully understood. The likely mechanism is suppression of dopaminergic activity in the hypothalamus neurons. The prolactinoma tumour, as well as other pituitary tumours, are monoclonal tumours. The participation of the pituary tumor-transforming gene (*PTTG*), expression of which is modulated by oestrogens and the heparin-binding secretory transforming gene (*HST*), is likely. Both genes promote angiogenesis through fibroblast growth factors.

It also happens that hyperprolactinaemia may be induced secondarily to pharmacological treatment and pathological disruption of the dopaminergic, hypothalamic-pituitary, or idiopathic pathways. Other factors that can trigger this state are stress in patients, renal failure, or hypothyroidism [37]. When assessing the cause of hyperprolactinaemia, pregnancy, primary hypothyroidism, and medications should be taken into account.

The laboratory test used to differentiate the types of hyperprolactinaemia is the metoclopramide test. This consists of determining the baseline PRL, then administering 10 mg of metoclopramide orally and re-measuring PRL 1 h and 2 h after the start of

the study. Excessive stimulation of prolactin secretion after the use of metoclopramide means functional hyperprolactinaemia (a 6-fold increase in PRL after administration of metoclopramide). However, when such an increase is not observed but the concentration of prolactin before the test is high, prolactinoma should be suspected. As part of the diagnosis of hyperprolactinaemia, it is necessary to perform a head magnetic resonance imaging (MRI) at a later stage, after excluding other causes. Depending on the result of the head MRI, further steps are taken. In other cases, treatment will mainly be conservative therapy.

Pharmacological treatment should be considered when a patient has a tumour larger than 1 cm, has hypogonadism, infertility, troublesome galactorrhoea, acne, hirsutism, or headaches. The treatment of choice is dopamine agonists — mainly bromocriptine or cabergoline. In patients in whom pharmacological treatment is ineffective, resection should be considered, especially when this change is large [41].

A prolactinoma tumour is also found in multiple endocrine neoplasia 1 (MEN1). In this case it due to a menin inactivating mutation. As a result, adenomas are generally larger and more invasive than other prolactin-producing adenomas. In the case of MEN 1 and prolactinoma, cabergoline is the treatment of choice [42].

Experimental evidence of the relationship between hyperprolactinaemia and IR

Many studies have shown a relationship between elevated serum prolactin (PRL) levels and the resistance of peripheral tissues to insulin [43–46]. Pancreatic ß cells, adipocytes, type 2 dopaminergic receptors, and dopamine play key roles as modulators of insulin action. Excess prolactin may contribute to the development of disorders in the metabolism of glucose and insulin, thus reducing the sensitivity of peripheral tissues to glucose in both obese and non-obese people. In vitro studies on rats showed that by acting on isolated pancreatic islets prolactin stimulates insulin secretion and influences the proliferation of pancreatic ß cells. The physiological increase in PRL concentration in rodents during pregnancy increases insulin secretion in ß cells. Both in rodents and humans, PRL increases β-cell proliferation, insulin gene transcription, and glucose-induced insulin secretion [47]. The results of studies from the United States suggest that glucose and prolactin act synergistically to induce transcription of the insulin gene. The conducted observations indicate that PRL exerts both a glucose-independent and glucose-dependent influence on the expression of insulin genes [44]. It has been suggested that PRL may act as a regulator of insulin sensitivity and metabolic homeostasis in adipose tissue. Visceral and subcutaneous adipose tissue biopsies in patients with normal body weight, overweight, and obesity showed a correlation between serum PRL concentration and adipose tissue fitness markers such as peroxisome proliferator activated receptor gamma (PPARG), adiponectin (ADIPOQ), and glucose transporter type 4 (GLUT4) [47]. Among women with hyperprolactinaemia the tissue sensitivity to insulin is lower than in women with normoprolactinaemia [48]. Correction of elevated PRL concentration is associated with an improvement in endothelial function and insulin sensitivity [49].

According to other studies, IR in patients with hyperprolactinaemia is not associated with obesity nor with anthropometric parameters such as fat content, waist circumference, and bod mass index (BMI) [50]. Among humans the mechanism responsible for tissue IR in severe hyperprolactinaemia seems to be, at least in part, downregulation of insulin receptors [51]. The results of various studies suggest that in humans the effects of PRL may be complex or may vary depending on different conditions. In addition to the effect of PRL on the growth of pancreatic ß cells there are reports of a decrease in the threshold of glucose-stimulated insulin, which may indicate that PRL has a protective effect against type 2 diabetes [52]. Scientists from China, examining a population of men and women without diagnosed hyperprolactinaemia, showed that prolactin freely circulating in the blood at physiological concentrations is associated with a lower incidence of diabetes and IR [53]. Subsequent studies also found a positive association between serum prolactin levels and metabolic parameters such as hypertension, waist circumference, aortic stiffness, and mortality. Studies in humans with high serum PRL levels induced by antipsychotics suggest that increased PRL levels may adversely affect the metabolism, leading to type 2 diabetes. Since the serum PRL concentration is regulated differently depending on sex, the correlations between the serum PRL concentration and any other factors should be assessed separately for each gender. The release of prolactin from the pituitary gland is regulated by the dopaminergic pathway through the type 2 dopaminergic receptor (D2R), activation of which inhibits the release of PRL. An experimental study in which a genetic disorder of D2R function was assessed showed that the studied patients developed glucose intolerance with impaired insulin secretion. Prolactin is a hormone produced by adipose tissue, among others. As the amount of this tissue increases in obese women, the amount of the hormone increases proportionally, and weight loss reduces the release of PRL. Kok et al. [54] showed that PRL secretion was significantly enhanced in obese women (total daily release, 137 ± 8; lean controls, 92 ± 8

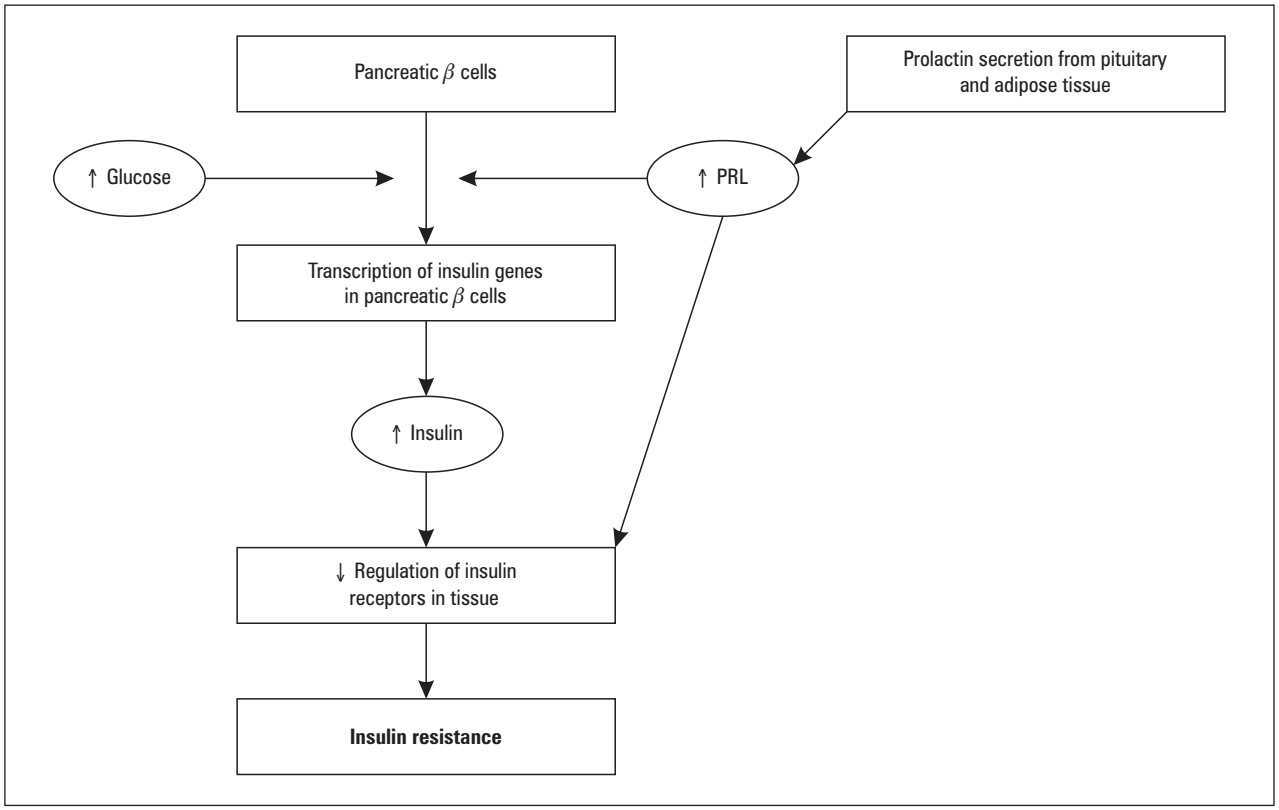

Figure 1. *The mechanism of the relationship between hyperprolactinaemia and insulin resistance (IR) [56]. *Arrows indicate the increase or decrease of the variable. PRL — prolactin*

μg/L·24 h; p = 0.001) in proportion to their BMI (r2 = 0.55; p < 0.001). Interestingly, PRL release was particularly associated with the size of the visceral fat mass (total PRL secretion *vs*. visceral fat area, r2 = 0.64; p = 0.006). In addition, adipose tissue macrophages have been shown to synthesize PRL in response to inflammation and high glucose levels. Therefore, obesity and/or higher glucose (glycemia) levels seem to affect the observed relationship between serum PRL and HOMA-IR [52]. Another study looked closely at the relationship between body weight, prolactin levels, and IR. It was shown that prolactin in the population of healthy young men is secreted cyclically and shows a certain circadian rhythm (the so-called bimodal secretion profile of PRL both during the day and at night). In obese men a change in the rhythm of prolactin secretion was noted in relation to the healthy group, which returned to normal after 12 days of an adequate, low-calorie diet. Also, in obese women a correlation was noticed between the BMI value, the amount of insulin released, and the related increase in the concentration of prolactin secretion. Data found in the literature seems to confirm that it is the reduction in caloric content and the reduction in the number of meals rich in fat, and not the loss of body weight itself, that normalize the concentration and secretion of prolactin [55]. Scientists from the University of Chicago also tried to explain the aetiology of obesity associated with hyperprolactinaemia in humans, as well as the role of PRL as a regulator of metabolism in adipose tissue. One of the forms of the receptor for prolactin (PRL-RL) has been studied, and it has been shown that this receptor is located on the surface of adipocytes. Its activation by prolactin stimulates the deposition of lipids in adipose tissue. Moreover, it has been proven that the expression of GLUT4 (the main glucose transporter in adipose tissue) does not change in the adipose tissue of mice (in which PRL-RL receptors are also present), which indicates that insulin resistance is not caused by a defect in GLUT4 expression in this tissue [56] (Fig. 1).

Clinical evidence of the relationship between hyperprolactinaemia and IR

Metformin is one of the key drugs used in the treatment of diabetes. The use of metformin affects the levels of some hormones in the pituitary gland. It reduces the concentration of PRL, but mainly in patients who had an increased level of PRL before treatment [57].

Patients who develop prolactinoma are sometimes refractory to treatment with a dopamine agonist. In this case metformin can be used, because in the studied patients it lowered the level of prolactin to 12 ng/mL

Table 1. *The effect of metformin therapy in patients with hyperprolactinaemia and impaired glucose tolerance [57, 58]*

No.	Feature	Conclusions
1	PRL level	Lowering the level of PRL[1]
2	Lipid metabolism	Lowering the level of triglycerides
3	Insulin resistance	Decrease (lowering HOMA-IR)
4	Plasma glucose concentration	Reduction in plasma glucose concentration

[1]patients with previously elevated prolactin levels, unsuccessfully treated with bromocriptine/cabergoline agonists; PRL — prolactin; HOMA-IR — homeostasis model assessment — insulin resistance

and significantly reduced the size of the tumour after one year of treatment. For example, in a patient who was refractory to treatment with bromocriptine alone the level of PRL increased, but in combination with metformin the concentration of PRL decreased significantly [57, 58] (Tab. 1).

For patients who cannot use metformin in combination with statins to lower lipids, glucose, and cardiometabolic risk factors, bromocriptine or cabergoline can be used instead of metformin. The effect of the therapy is very similar [59]. Bromocriptine/cabergoline are agonists of dopamine D2 receptors and are used primarily in the treatment of hyperprolactinaemia. It is known that it significantly reduces hyperglycaemia and improves glucose tolerance in patients with type 2 diabetes [60]. Bromocriptine-QR and cabergoline have been officially approved by the Food and Drug Administration (FDA) for patients with type 2 diabetes [47]. Studies in rodents have shown that dopaminergic transmission is reduced in insulin resistance. Administration of bromocriptine/cabergoline within 2 hours of waking is believed to increase low levels of dopamine in the hypothalamus and inhibit central nervous system (CNS) sympathetic tone, which results in a reduction in postprandial plasma glucose due to increased hepatic suppression of glucose production [61]. (Fig. 2).

Patients suffering from hyperprolactinaemia also suffer from insulin resistance; therefore, effective treatment of hyperprolactinaemia has a positive effect on glucose tolerance [48]. In patients with type 2 diabetes who showed poor glycaemic control with one or two oral medications, the use of fast-release bromocriptine (bromocriptine QR) significantly improved glycaemic control [62, 63]. Treatment with bromocriptine must be longer than 6 months to observe an improvement in metabolic parameters in patients [46]. Bromocriptine tested in mice with disturbed and undisturbed circadian rhythms has the same effect on glucose metabolism [60]. Another drug that can be used to treat hyperprolactinaemia and thus also IR is cabergoline [64]. Cabergoline therapy may improve glucose tolerance not related with weight loss in obese individuals. However, this impact must be confirmed in long-term studies [65].

The table below summarizes the positive and negative aspects of the use of dopamine agonists (cabergo-

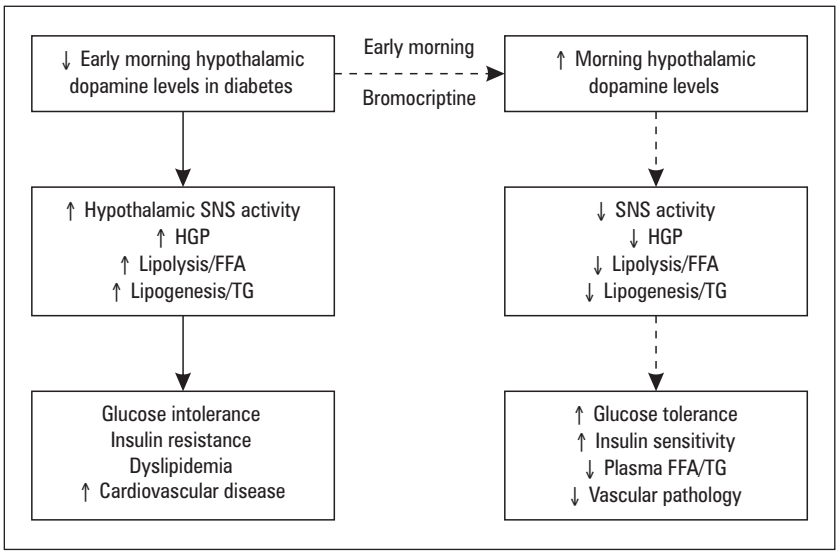

Figure 2. *Proposed mechanism of action of bromocriptine to improve glucose homeostasis and insulin sensitivity [61]. SNS — sympathetic nervous system; HGP — hepatic glucose production; FFA — free fatty acids; TG — triglycerides*

Table 2. *The result of bromocriptine/cabergoline in the treatment of hyperprolactinaemia [47, 60]*

No.	Variable	HyperPRL	Treatment with bromocriptine/cabergoline
1.	Fasting glucose	↑	No impact
2.	Glucose tolerance	↓	↑
3.	Postprandial glucose	↑	↓
4.	HbA_{1c}	↑	↓
5.	Body weight	↑	↓
6.	BMI	↑	↓
7.	Lipid profile	↑	↓
8.	Metabolic syndrome	↑	↓
9.	Adverse events from the cardiovascular system	↑	↓

PRL — prolactin; HbA_{1c} — glycosylated haemoglobin; BMI — body mass index

line, bromocriptine QR) in the treatment of hyperprolactinaemia, for the improvement of insulin resistance or metabolic profile among the respondents [47] (Tab. 2).

Increased concentration of PRL and resistance of peripheral tissues to insulin often coexist not only with endocrine disorders. We can also observe both irregularities, e.g., while taking antipsychotics [66–69] (Tab. 3).

Conclusions

Numerous scientific studies have shown a relationship between insulin resistance and hyperprolactinaemia. There are many scientific theories explaining the probable mechanisms of this phenomenon. One is the finding that glucose and prolactin act synergistically in inducing the transcription of insulin genes. It has also been suggested that PRL may act as a regulator of insulin sensitivity and metabolic homeostasis in adipose tissue. Increased plasma prolactin levels are often associated with an increase in tissue resistance to insulin. The topic of the mutual correlation of hyperprolactinaemia and IR is extremely interesting, and it certainly requires further research and observation.

Table 3. *The mechanisms of insulin resistance (IR) and hyperprolactinaemia in other diseases*

Main disorders	Elevated prolactin secretion	IR
PCOS	Correlation has not been noted. Hyperprolactinaemia occurs at the same rate as in non-PCOS women [40]	The excess of androgens and the increased amount of adipose tissue may interfere with the mechanisms of insulin [7, 10, 70]
Prolactinomas	Suppression of dopaminergic activity in hypothalamus neurons [37, 41]	The excess PRL causes a decrease in the regulation of insulin receptors [45]
Psychiatric disease	The main mechanism of antipsychotics is antagonism of D2 receptors. Their blockade in the hypothalamus increases the release of prolactin [71]	As a result of the antagonistic effect of antipsychotics in relation to the 5-HT2A receptors, there may be a decrease in glucose uptake by muscle and adipose tissue, and a decrease in insulin sensitivity [72]
Hypothyroidism	In patients with hypothyroidism, the increase in prolactin is caused by a compensatory increase in the central hypothalamic TRH output as a result of a low thyroxine level [25]	Slowing of the intestinal absorption of glucose. Reduction of adrenergic activity leading to a reduction in muscle and liver glycogenolysis. Reduction of gluconeogenesis and resting insulin secretion. Reduced blood flow in peripheral tissues [25]
Hyperthyroidism	Correlation has not been noted	We observed: • an increased peripheral and hepatic insulin resistance • an increase in endogenous production of insulin with elevated peripheral degradation of this hormone [11] • thyroid hormone excess leads to enhancement of endogenous glucose production by increased gluconeogenesis and glycogenolysis in the liver due to increased expression of the glucose transporter GLUT-2 protein in hepatocytes [73, 74] • hyperthyroidism increases the concentration of cytokines and markers of inflammation such as IL-6 and TNF-α, which also correlate with peripheral IR [75]

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Table 3. *The mechanisms of insulin resistance (IR) and hyperprolactinaemia in other diseases*

Main disorders	Elevated prolactin secretion	IR
Goitre and thyroid cancer	Correlation has not been noted	People without diabetes with nodular goitre, despite similar age, sex, BMI, waist circumference, TSH levels, and metabolic parameters, were characterised by higher HOMA-IR [75]
Acromegaly	Mixed tumours producing GH and PRL	The pathomechanism of IR is complex. Long-term supraphysiological GH concentration interferes with both insulin action in the liver and the other peripheral tissues. This leads to enhanced production of glucose by the liver and decreased utilisation of glucose in peripheral tissues. It is probably due to disturbances in the production and action of a second messenger in the insulin receptor. In addition, GH increases lipolysis of adipose tissue, and increased concentration and oxidation of fatty acids enhances IR [76].
Hypercortisolism	Correlation has not been noted	Glucocorticoids affect the activation of the liver enzyme phosphoenolpyruvate carboxykinase, increasing proteolysis in skeletal muscle and lipolysis in adipose tissue, which ultimately provides more substrate for gluconeogenesis. Enhanced lipolysis in adipose tissue results in an increase in circulating FFAs and affects the development of the phenomenon of reduced insulin sensitivity. IR induced by hypercortisolaemia probably has a post-receptor nature [77]
Hypopituitarism	Impairment of the production or transmission of dopamine to lactotropic cells	Abnormal glucose metabolism in GH deficiency results from increasing IR. Damage to the central nuclei of the hypothalamus is responsible for IR and leptin resistance and may also result in disinhibition of the vagus nerve impulse and thus in increased stimulation of pancreatic β-cells, hyperinsulinaemia, and obesity [78]
Primary hyperparathyroidism	Correlation has not been noted	Probably the long-term status of hypercalcaemia and hypophosphataemia triggers IR and hyperinsulinaemia, and reduces the number of insulin receptors [79]
Disorders of the adrenal gland	Correlation has not been noted	Pheochromocytoma produce adrenalin, which by its affinity to the β2 receptors, inhibits insulin secretion, stimulates the secretion of glucagon from the pancreatic islet cells, and decreases glucose uptake by skeletal muscles as well as increases gluconeogenesis and glycogenolysis in hepatocytes [80] Lower concentrations of adiponectin, and higher HOMA-IR in this group of patients with pheochromocytoma were shown [81] Aldosterone alone decreases glucose-dependent insulin secretion. Activation of the mineralocorticoid receptor results in a decrease of insulin sensitivity in fat and muscle tissue [82]

PCOS — polycystic ovary syndrome; PRL — prolactin; 5-HT2A — serotonin 2A receptor; TRH — thyrotropin-releasing hormone; GLUT-2 — glucose transporter 2; IL-6 — interleukin 6; TNF-α — tumour necrosis factor alpha; BMI — body mass index; TSH — thyroid-stimulating hormone; HOMA-IR — homeostasis model assessment — insulin resistance; GH — growth hormone; FFAs — free fatty acids

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