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Review

Personalized approach to prediction and prevention of haloperidol-induced metabolic syndrome

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Abstract: Haloperidol (HLP) is a general medication in the treatment of psychotic disorders such as schizophrenia and acute mania. One of HLP's advantages compared to other antipsychotics, such as olanzapine or clozapine, is its relatively low risk of significant weight gain, making it more suitable for patients requiring strict weight control. However, despite this comparatively favorable profile, some patients may experience moderate weight gain with long-term use of HLP. This side effect can be attributed to several factors. First, HLP affects metabolic processes, which may lead to changes in appetite and reduced physical activity. Second, the drug can increase prolactin levels, which is associated with the development of hyperprolactinemia—a condition that may contribute to weight gain and the emergence of other components of metabolic syndrome, such as insulin resistance. Third, HLP may promote increased oxidative stress, which plays an important role in the pathogenesis of metabolic disorders. These mechanisms underscore the need for monitoring patients on HLP to promptly detect and manage potential metabolic side effects. **Objective**: To update the knowledge of practicing psychiatrists and clinical pharmacologists about a personalized approach to the prevention of metabolic syndrome in patients with psychiatric disorders when taking HLP. **Methods**: Full-text articles published from 01.09.2013 to 01.09.2024 were searched in PubMed, Science Direct, eLIBRARY.RU, and Google Scholar. **Results**: This review analyses and summarizes the results of foreign and domestic studies on the effect of haloperidol on the development of metabolic syndrome, the role of risk factors and hereditary predisposition in the development of HLP -induced metabolic syndrome in patients with psychiatric disorders. **Conclusion**: Generalized data on the effect of HLP on the development of metabolic syndrome in patients with psychiatric disorders may be required by psychiatrists and clinical pharmacologists when selecting the dose and duration of haloperidol administration. Predictive pharmacogenetic testing may help to reduce the probability of this adverse drug reaction and increase the compliance of haloperidol therapy.

Keywords: *antipsychotic, haloperidol, metabolic syndrome, adverse reaction, metabolism, obesity, hyperglycaemia, type 2 diabetes mellitus, insulin resistance, pharmacogenetic testing, psychiatric disorder, prevention.*

1. INTRODUCTION

Haloperidol (HLP) is a first-generation antipsychotic (AP I) traditionally used in the treatment of schizophrenic spectrum disorders, manic states, delusional disorders, also used in oligophrenic, involutional, epileptic, alcoholic psychoses and other diseases

accompanied by hallucinations, psychomotor agitation and, which continues to be widely used in psychiatric practice both in Russia and abroad. HLP is a butyrophenone with a hydroxyl group that is both a hydrogen bond donor and acceptor, which makes HLP a highly active drug [1,2,3]. In patients receiving HLP, the most common adverse drug reactions (ADRs) are extrapyramidal syndrome (EPS: parkinsonism, akathisia, etc.), hyperprolactinaemia and weight gain. Although, unlike other APs, HLP has less effect on weight gain, which may be due to its low affinity for histamine receptors (H_1), its widespread use requires early diagnosis and correction of this ADR in order to have a predictive effect on one of the key links of metabolic syndrome (MetS).

Objective: To update the knowledge of practicing psychiatrists and clinical pharmacologists about a personalized approach to the prevention of MetS in patients with psychiatric disorders when taking HLP.

Full-text articles published from 01.09.2013 to 01.09.2024 were searched in PubMed, Science Direct, eLIBRARY.RU, and Google Scholar.

2. RESULTS

Taking HLP is associated with antagonistic action against D2, 5-NT2A receptors and α1A, α1B-adrenoreceptors [2]. It is the antagonistic effect of HLP on dopamine D2 receptors that contributes to hyperprolactinaemia [4]. In addition, the risk of HLP-induced weight gain and glucose tolerance is associated with affinity for serotonergic (5HT1, 5HT2a and 5HT2c), histaminergic (H1) and muscarinic M1 and M3 receptors [5].Prolactin (PRL) is a hormone that is synthesized in acidophilic cells of the anterior lobe of the pituitary gland. It is involved in many biological processes of the body, including lactation, osmoregulation, regulation of the immune system, and metabolic homeostasis [6,7]. The regulation of pituitary secretion of PRL is mainly inhibited by dopamine via hypothalamic D2 type dopaminergic neurons on lactotroph cells [6]. Other pathways of stimulation of PRL synthesis such as estrogens, vasoactive intestinal peptide have only limited or no effect [8]. Regardless of the nature of hyperprolactinaemia, excess PRL is known to affect orexigenic-anorexigenic systems that regulate appetite by determining hyperphagia and increasing food intake, leading to weight gain to overt obesity [9,10]. Hyperprolactinaemia is known to be associated with alterations in gluco-insulinaemic metabolism. In particular, impaired glucose tolerance and hyperinsulinaemia have been found in patients with hyperprolactinaemia [11], regardless of body mass index (BMI). Hyperprolactinaemia has little or no effect on changes in lipid levels [4], with increased food intake and weight gain leading to obesity. In patients with hyperprolactinaemia, increased appetite is associated with dopamine receptor blockade. Agonism of dopaminergic regulation plays a key role in decreasing food intake and increasing energy expenditure, supporting the hypothesis of dopamine involvement in body weight regulation [12]. Preclinical studies using a genetically modified hyperprolactinaemic animal model have shown that chronic hyperprolactinaemia is able to modulate the expression of genes involved in the orexigenic-anorexigenic system at the hypothalamic level. In particular, after the development of obesity induced by drug-induced hyperprolactinaemia, experimental animals showed a significant increase in the mRNA levels of the orexigenic hormones agouti-related peptide (AGRP) and neuropeptide Y (NPY) in the hypothalamic arcuate and dorsomedial nuclei, respectively [11]. On the contrary, antagonistic activity of HLP that reduces dopaminergic receptor activity together with increased levels of hypothalamic hormones involved in altering eating behaviour and corticotrophin releasing hormone have been identified as potential mechanisms determining hyperphagia and subsequent weight gain in patients with hyperprolactinaemia [11].

Excess PRL is known to contribute to the development of metabolic syndrome (MetS) in about one third of patients [11]. It has been reported that the risk of developing HLP-induced MetS is higher in middle-aged and elderly male patients with sexual dysfunction and PRL levels < 5 mg/L [13], low PRL levels may correlate with a higher prevalence of metabolic diseases including type 2 diabetes mellitus (T2DM) and non-alcoholic fatty hepatosis [14]. In healthy subjects, a significant trend towards lower PRL levels was found with increasing MetS components in women, although multivariate regression models showed no association between PRL levels and MetS [13].

The gene encoding prolactin (*PRL*) is localized on chromosome 6p21, and the 6p21 region has been identified as a locus of susceptibility to schizophrenia [15, 16]. In humans, *PRL* contains five coding exons that are controlled by a pituitary-specific promoter and a non-coding exon that is controlled by an alternative promoter. The latter promoter drives expression in extrapituitary tissues [17]. Thus, in addition to its role as a pituitary hormone, PRL is also produced as a cytokine by immune cells, and its receptor belongs to the type 1 cytokine receptor family. A functional polymorphism in the *PRL* gene (1149 G/T; rs1341239) was also found, in which the G allele is associated with increased activity of the extrapituitary promoter and increased mRNA levels of PRL lymphocytes. This polymorphism has previously been associated with autoimmune diseases such as multiple sclerosis [18], rheumatoid arthritis [19] and systemic lupus erythematosus [20]. In a study by Ivanova S et al. (2013) demonstrated an association between the polymorphic variant rs1341239 and the development of hyperprolactinaemia in patients with schizophrenia. The concentration of PRL in serum in patients with schizophrenia treated with AP may indicate high activity of the gene that regulates extra-pituitary production of PRL [17].

Several studies have demonstrated the relationship between PRL hyperproduction and changes in the glucose-insulinaemic profile of patients. Thus, increased expression of PRL receptors has been demonstrated on insulin-secreting cell lines in animal model experiments during rat pregnancy. Since pregnancy represents a model of prolonged exposure to hyperprolactinaemia that allows us to study the mechanisms by which PRL may influence glucose-insulinaemic metabolism. Simultaneous increases in PRL levels, β-cell numbers and glucose-induced insulin hypersecretion have been shown to occur during adaptation to pregnancy. Similarly, *in vitro* studies, it has been shown that exposure of isolated rat pancreatic islet cells to PRL results in increased insulin secretion together with β-cell proliferation [21]. In addition, it has been observed that PRL overexpression in β-cells causes inadequately elevated serum insulin concentrations, increased insulin content and sustained β-cell replication [11]. In both rats and humans, PRL was found to promote β-cell proliferation, insulin gene transcription and glucose-dependent insulin secretion. Consequently, chronic HLP-induced hyperprolactinaemia is associated with impaired insulin secretion characterized by postprandial hyperinsulinaemia and excess insulin response to glucose in humans [22]. However, studies have been found supporting the association of low serum levels of PRL and the development of insulin resistance [23]. It has been reported that PRL can increase cellular sensitivity to insulin, and hyperprolactinaemia may contribute to the normal adaptive increase in glucose-stimulated insulin production. Physiological increases in PRL levels also have an indirect effect by increasing hypothalamic dopamine production, which helps to maintain energy and glucose balance [21]. Thus, HLP-induced elevation of PRL levels may represent a compensatory mechanism controlling hyperglycaemia and reducing the likelihood of type 2 DM. Also, PRL may stimulate the expression of peroxisome proliferator-activated receptor gammaa (Pparg) and X-box binding protein 1 (Xbp1s), adiponectin (ADIPOQ) and type 4 glucose transporter in visceral adipose tissue and increase circulating blood levels of adiponectin, which may contribute to healthy

adipose tissue function and systemic insulin sensitivity [24]. PRL acts as an adipokine by downregulating fatty acid synthase and lipoprotein lipase, which regulate the bioactivity of leptin, interleukin-6 and adiponectin, which play an important role in pathogenesis [25].

Lipid profile disorders are common in psychiatric patients with hyperprolactinaemia. Lipid profile disorders are an integral part of MetS and major causes of cardiovascular disease and type 2 diabetes mellitus [26]. Newly diagnosed patients with HLP-induced hyperprolactinaemia may have a higher percentage of body fat. The importance of monitoring total cholesterol (TC), low density lipoproteins (LDL) and triglycerides (TG) levels, as well as lowering high-density lipoproteins (HDL) [27] levels in the blood, has been noted.

However, the available studies on the effect of HLP on serum glucose, TC and TG levels are inconsistent.

Thus, in a study by Bardenstein L.M. et al. involving 50 patients (20 men; 30 women) with a first psychotic episode meeting the criteria of paranoid schizophrenia according to ICD-10, the groups were distributed randomly by 25 people: group 1 - patients taking HLP; group 2 - patients taking AP (olanzapine, clozapine, quetiapine). In the first group was prescribed HLP, in the second group - atypical antipsychotics: olanzapine, clozapine, quetiapine. The study found that therapy with AP had a greater effect on carbohydrate metabolism in patients with paranoid schizophrenia compared to HLP, although the increase in TC levels was significantly more frequent in the HLP group [28].

In a study by Perez-Iglesias R. et al. an average weight gain of 7.1 kg over 1 year and an increase in BMI on HLP therapy were demonstrated [29].

However, previous studies of the effect of HLP on glucose levels demonstrate both the absence of any effect [30] and minimal effect on the glycaemic status of patients [31].

A study by Parabiaghi A. (2015) included 300 patients with schizophrenia. The analysis showed no significant differences in the incidence of MetS between aripiprazole (37%), olanzapine (47%) and HLP (42%) [32].

In the original study by Ventriglio A (2019), involving 151 patients with schizoaffective disorder, and schizophrenia it was shown that a diagnosis of schizoaffective disorder and higher doses of APs were associated with the development of MetS, while oral and injectable APs did not differ in the risk of MetS. Also, the authors determined the gradation of the severity of MetS between different APs: quetiapine ≥ clozapine ≥ paliperidone ≥ olanzapine ≥ risperidone ≥ HLP ≥ aripiprazole, and also identified such risk factors for the development of MetS as female sex, dose, and older age [33].

Other studies have shown that HLP can cause oxidative stress, which is both a risk factor for the development of neuropsychiatric disorders and MetS [34]. Oxidative stress is a condition in which the body accumulates large amounts of free radicals, including reactive oxygen species (ROS), whose intracellular content under normal conditions is maintained at a low level by various enzyme systems involved in redox homeostasis. Oxidative post-translational modification (Ox-PTM), also known as oxidative modification of protein, is a crucial molecular process that regulates proteins that ultimately affect the biological responses of cells. Redox-sensitive proteins include ion transporters, receptors, signalling molecules, transcription factors, cytoskeletal structural proteins and matrix metalloproteases. Proteins are usually the target of reversible Ox-PTM; however, in pathological conditions associated with oxidative stress, such as hypertension, proteins undergo irreversible Ox-PTM, resulting in loss of protein function and consequent cell and tissue damage and target organ failure. ROSs such as H_2O_2 are also required for activation of cellular pathways, including those that interact with vasoactive drugs such as angiotensin II, endothelin-1, aldosterone and prostanoids used

to mediate cellular effects, and those that regulate intracellular calcium homeostasis. ROSs activate transcription factors such as hypoxia-inducible factor (HIF), which regulates angiogenesis, activates the phosphoinositide-3-kinase (PI3K) pathway, which regulates cell growth, nuclear factor kappa light chain enhancer of activated B-cell (NF-kB) pathway, which under normal conditions prevents apoptosis by regulating cell survival, activates the mitogen-activated protein kinase (MAPK) pathway, which regulates cell proliferation. ROS also stimulates pro-inflammatory chemokine transcription and cytokine production, as well as the recruitment and activation of inflammatory and immune cells [35]. Excessive accumulation of ROSs can occur in pathological processes such as obesity, insulin resistance, hyperglycaemia, chronic inflammation and dyslipidaemia, whereby ROSs can cause cellular damage even at the DNA level [35].

In a study on rats it was shown that long-term administration of HLP (5 mg/kg/day) can increase weight [36]. A study by Andreazza A.C. (2015) showed that HLP intake can be considered as one of the triggering factors of MetS pathogenesis — oxidative stress in the brain and liver of rats. The aim of the study was to evaluate markers of oxidative stress associated with APs with emphasis on protein and lipid oxidation and expression of antioxidant proteins peroxiredoxin-2 and peroxiredoxin-6. After 28-day administration of HLP, clozapine or sodium chloride saline to adult rats, samples of brain grey matter, white matter, serum and liver were obtained and lipid oxidation, protein oxidation, peroxiredoxin-2 and peroxiredoxin-6 were quantified. It was shown that in the brain grey matter, the level of peroxiredoxin-6 was significantly increased in animals exposed to HLP. At the same time, there was also a tendency to increase lipid peroxidation in this group. In the liver, lipid peroxidation was increased in clozapine-exposed animals, and a similar trend was observed in the HLP group [37].

The risk factor for the development of HLP-induced MetS may also be influenced by impaired metabolism of HLP in the human body. HLP is actively metabolised in the liver, and only about 1% of the administered dose is excreted unchanged in the urine. In the human body, haloperidol undergoes biotransformation to form various metabolites such as p-fluorobenzoylpropionic acid, 4-(4-chlorophenyl)-4-hydroxypiperidine, reduced HLP, pyridine metabolites and haloperidol glucuronide. In patients receiving HLP on a regular basis, haloperidol glucuronide predominates in plasma, followed by unchanged HLP, reduced HLP, and reduced haloperidol glucuronide. The major pathway of drug metabolism is thought to involve oxidative N-dealkylation of piperidine nitrogen, leading to the formation of fluorophenylcarboxylic acids and piperidine metabolites (presumably inactive), and the reduction of butyrophenone carbonyl to carbinol to form hydroxyhaloperidol. Enzymes such as cytochrome P450 (CYP), including CYP3A4 and CYP2D6, carbonyl reductase, and uridine-glucuronosyltransferase di-phosphoglucose enzymes are also involved in the metabolism of HLP. The bulk of hepatic clearance of HLP is via glucuronidation, followed by HLP reduction and CYP-mediated oxidation (Table 1) [3].

The transport of HLP across cell membranes involves the transporter protein BCRP, an ATP-binding cassette transporter. It is encoded by the *ABCG5* gene. BCRP is one of five members of subfamily G of the human ABC protein superfamily, along with ABCG1, ABCG4, ABCG2, and ABCG8. All members of the subfamily are semitransporters and are thus thought to function as homo- or heterodimers or possibly even larger oligomeric structures [38, 39, 40] (*Table 1*).

The glutamatergic system, in particular the glycine transporter protein SLC6A5, is involved in modulating the effects of HLP treatment, especially with regard to motor ADRs. In patients with schizophrenia receiving AP, carriage of SLC6A5 single nucleotide variant (SNV) (rs2298826) is associated with a rapid increase in motor ADRs at the beginning of treatment with subsequent adaptation, probably in a HLP dose-dependent

manner. Patients with AA genotype receiving HLP monotherapy had an increased risk of rapid motor ADRs amplification at the start of treatment compared with patients with AG or GG genotype. Carriers of the C-A-C haplotype (rs1443548, rs883377, rs1945771) had more pronounced extrapyramidal disorders when receiving HLP [40].

Another feature of the ABC transporter subfamily G is that the nucleotide-binding domain is N-terminal to the transmembrane domain, whereas the opposite is true for other ABC transporter subfamilies [41].

All members of the ABCG family, with the exception of BCRP, are known lipid transporters. In contrast, BCRP exhibits perhaps the broadest substrate specificity and has been shown to transport hydrophobic compounds, cations, anions and drugs conjugates [25]. This protein is known to be involved in the transport of drugs (including AP) and other xenobiotics and may play a role in the development of multidrug resistance to chemotherapeutic agents [20, 25, 29, 32, 33]. The protein consists of 655 amino acid residues, contains one glycosylation site, one intramolecular disulfide bond and one intermolecular bond. The intermolecular S-S bond provides the dimer stability of this transporter protein. It is mainly found on the cell membrane as a dimer, but can form oligomers up to a homododecamer (12 subunits) [42].

BCRP expression in the brain is highest at the level of frontal, medial and mediobasal cortex, in the hippocampus, tail, as well as in other organs: seminal vesicles, testes (in men), small and large intestine, placenta, lungs, thyroid gland, adrenal glands, and myocardium [43].

Table 1. The main pathways of metabolism and haloperidol

Metabolic pathway	Enzyme	Gene (OMIM)	Chromosomal location	Reference
The major P-oxidation enzymes of haloperidol				
P-oxidation	Cytochrome P450 isoenzymes 3A4	CYP3A4 (124010)	7422.1 (GRCh38): 7:99,756,967-99, 784, 184	[44]
	Cytochrome P450 isoenzymes 2D6	CYP2D6 (124030)	22q13.2 (GRCh38): 22:42,126,499-42, 130,810	[45]
The major glucuronidation enzyme of haloperidol				
Glucuronidation	UGT-glucuronosyltransferase 2B7	UGT2B7 (600068)	4q13.2 (GRCh38): 4:69,051,363-69,112,987	[46]
Transporter proteins of haloperidol				
Glycine transporter 2	Sodium- and chloride-dependent glycine transporter 2	SLC6A5 (604159)	11p15.1 (GRCh38): 11:20,599,608-20,659,285	[47]
Breast cancer resistance protein	ATP-binding cassette sub-family B member 5	ABCB5 (611785)	7p21.1 GRCh38): 7:20,615,667-20,757,008	[48]

[1] Tables may have a footer.

Depending on genetically determined changes in the rate of HLP metabolism and efflux in patients with psychiatric disorders, five pharmacogenetic phenotypes can be distinguished: extensive (EM), poor (PM), intermediate (IM), rapid (RM) and ultrarapid (URM) metabolizers (Figure 1). In patients with PM and IM phenotype, a decrease in the metabolic rate of HLP may lead to an increase in its blood levels, which increases the risk of developing ADRs including HLP-induced MetS. Predictive pharmacogenetic testing (PGx) is recommended before starting HLP therapy to reduce the risks of developing this ADR. Predictive PGx helps to identify the presence of non-functional alleles of genes responsible for drug metabolism and to assess the safety of its use for a particular patient and to select the optimal dose of HLP on the basis of its pharmacogenetic profile [49].

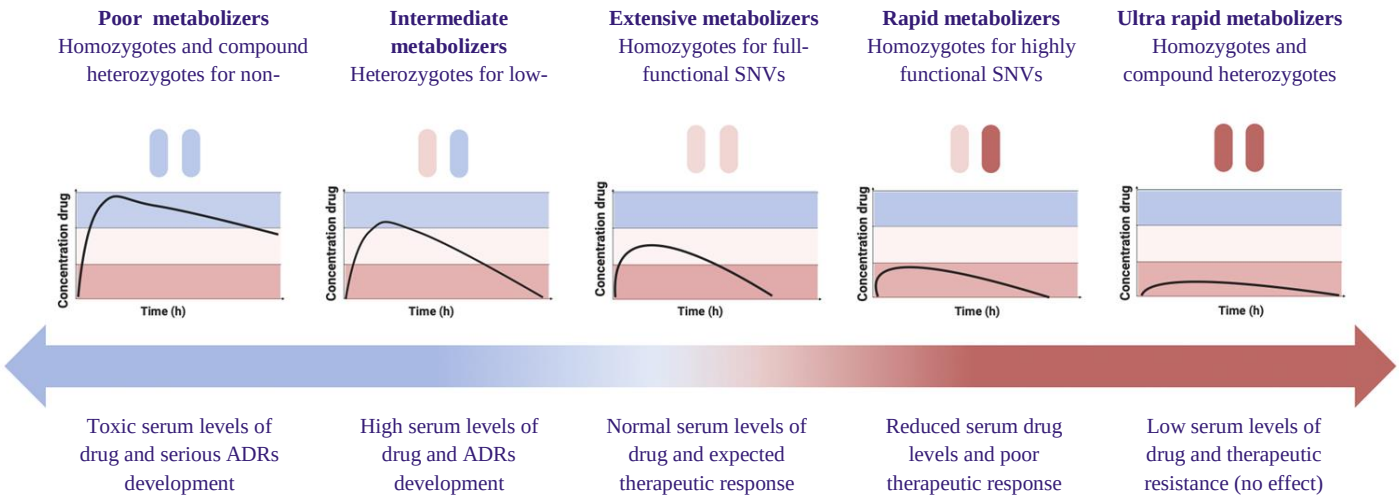

Figure 1. Metabolic phenotypes in patients with psychiatric disorders

3. DISCUSSION

To minimize the risk of MetS development on the background of HLP therapy, it is recommended to apply the following preventive measures aimed at the correction of the identified mechanisms:

1) monitoring of serum PRL levels;
2) regular monitoring of PRL levels in patients receiving HLP, allowing timely detection of hyperprolactinaemia and timely taking measures to correct it, including HLP dose reduction or switching to alternative APs with less prolactinaemic effect;
3) control of body weight and lipid profile;
4) monitoring of BMI, serum levels of TC, LDL, HDL and TG to monitor and prevent lipid profile abnormalities associated with HLP administration;
5) monitoring antioxidant status, including the administration of antioxidants such as vitamins C and E, to reduce oxidative stress associated with HLP intake and reduce the risk of MetS;
6) regulation of metabolism of glucose.

Regular monitoring of blood glucose and insulin levels is recommended for timely detection of impaired glucose tolerance and insulin resistance (if necessary, prescription of metformin or other hypoglycaemic drugs may be considered);

7) physical activity and a diet low in triglycerides and carbohydrates.

These measures can significantly reduce the risk of MetS in patients receiving HLP therapy, improving their quality of life and disease prognosis.

The treatment of HLP-induced MetS is challenging. Withdrawal of HLP prescription and replacement with APs with a lower risk of MetS and hyperprolactinaemia may be considered as therapeutic strategies. Restoration of normal PRL levels is possible with

therapy with dopamine D2 receptor agonists, which can reduce HLP-induced metabolic disturbances. Dopamine agonists represent the treatment of choice for patients with hyperprolactinaemia, allowing significant improvement in glycaemic profile, regardless of concomitant hyperprolactinaemia. The rapidly absorbed form of bromocriptine lowers plasma glucose levels in obese, non-diabetic hyperinsulinemic women on a weight maintenance diet and for improving glucose tolerance and weight loss in both diabetic and non-diabetic subjects. Administration of cabergoline at a dose of 0.5 mg/week to previous therapy reduces glucose levels, with 65% of these patients achieving HbA1c levels < 7% compared with 45% of controls after 3 months of treatment.

In patients with hyperprolactinaemia, activation of D2-type dopamine receptors has been proposed as a potential mechanism by which reductions in BMI and body fat percentage are achieved after normalization of PRL levels on cabergoline therapy. In addition to BMI reduction, waist circumference was found to decrease significantly after long-term treatment (up to 5 years) with cabergoline, indicating a reduction in visceral adiposity, which is known to play a key role in the development of HLP-induced MetS.

4. CONCLUSION

Unfortunately, HLP-induced MetS is an understudied ADR, with HLP-induced hyperprolactinaemia playing a major role in its development, along with known common MetS mechanisms such as systemic inflammation and oxidative stress.

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