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HYPERPROLACTINEMIA AND ANTIPSYCHOTIC THERAPY IN SCHIZOPHRENIC PATIENTS WITH HASHIMOTO'S THYROIDITIS

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SUMMARY

Introduction: *Hyperprolactinemia (HPRL) is known as a side effect of some antidepressants and antipsychotics. These medicines are common in treatment of schizophrenia. Thus, HPRL is often observed in schizophrenic patients. It is also known that HPRL can occur in Hashimoto's thyroiditis due to prolactoliberin effect of thyroliberin. The clinical pathophysiology of the patients with the comorbidity of schizophrenia and Hashimoto's thyroiditis, receiving antipsychotics, is of special interest. It's fair to assume that these patients have higher risks of HPRL. To analyze risks of HPRL with antipsychotic treatment, to identify an association between the antipsychotic therapy (AT) and HPRL in Hashimoto's patients receiving AT, to explore the association of HPRL and other laboratory parameters in patients with Hashimoto's thyroiditis and schizophrenia during AT.*

Subjects and methods: *We studied 17 patients with HT in comorbidity with schizophrenia receiving AT (mean age 46.5±12.8 years), all euthyroid or with light hypothyroidism. Different laboratory parameters such as anti-thyroid peroxidase (anti-TPO) and anti-thyroglobulin (anti-TG) antibodies, blood levels of thyroid stimulating hormone (TSH), free thyroxine (FT4), free triiodothyronine (FT3) and prolactin (PRL) were analysed.*

Results: *The study revealed the high levels of PRL, anti-TPO and anti-TG autoantibodies. Thus, patients were classified into 3 groups by the degree of expected HPRL risk from the antipsychotics used: without expected risk, with low and high expected risks. The correlation analysis detected an inverse significant correlation (R=-0.51; p=0.037) between expected level of drug-associated HPRL risk and actual PRL levels in studied group. At the same time, we detected a positive significant correlation between the levels of PRL and FT4 in the groups (R=0.53; p=0.03). The correlations between the levels of PRL and other parameters such as TSH, FT3, anti-TPO, anti-TG, anti-TSH receptor antibodies were not statistically significant.*

Conclusions: *HPRL in the group was not associated with taking of antipsychotic drugs with high expected HPRL risk. Yet, a significant positive correlation existed between the levels of PRL and FT4. Hence, in Hashimoto's thyroiditis accompanied with treated mental illness there are some non-iatrogenic stimulants of prolactogenesis. It cannot be ruled out that antipsychotics may interfere with prolactin metabolism, which creates a false effect of a positive correlation between prolactin and free thyroxine levels, in contrast to common HPRL of hypothyroidism.*

Key words: *hyperprolactinemia – antipsychotics - Hashimoto's thyroiditis – thyroid – autoimmunity – schizophrenia - prolactin*

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INTRODUCTION

Prolactin (PRL) is a polypeptide hormone produced by the pituitary lactotropic cells (Bernard et al. 2019). Yet, hypophysis is not the sole source of PRL in organism. The hormone is also produced in: Neurons, skin, ovaries, placenta, endometrium, mammary epithelium, prostate, adipose tissue and may be derived from the cells of immune system (both lymphocytes and macrophages) (Samperi et al. 2019, Vieira Borba & Shoenfeld 2019). PRL of an extra-pituitary origin has a different molecular weight and biologic activity. It exists in three isoforms with different receptor binding, that's why PRL biological activity depends on a variation in its post-translational modifications. The isoforms of PRL are: The monomeric (free little), dimeric (big), and macro PRL (Shelly et al. 2012). The PRL effects are promoted through its transmembrane receptor (PRL-R), which is a member of the type 1 cytokine/hematopoietic receptor super-family widely expressed through the immune system in monocytes, lymphocytes, macrophages, natural killer cells, granulocytes, and thymic epithelium (Bernard et al. 2015, 2019, Vieira Borba & Shoenfeld 2019). Hence, PRL is both endocrine and paracrine bioregulator, combining properties of a hormone and autacoid depending on its systemic or local action. PRL derived from lymphocytes and hematopoietic cells is known for its role in the immune response modulation under stress and other conditions (Samperi et al. 2019). Well studied are the PRL's roles in pregnancy and lactation, especially as regards to: mammary gland organogenesis and lactation control, maternal behavior, increased neurogenesis, insulin resistance and transfer of glucose to the fetus, expansion of pancreatic B cells, increased appetite, leptin resistance, fat deposition and mobilization, bone and calcium homeostasis, anovulation, anabolic component of stress-related metabolic changes, oxytocin secretion, etc (Lopez Vicchi &

Becu-Villalobos 2017). PRL also renders its effects on endocrinocytes, such as stimulation of androgenesis, cortisol, and aldosterone secretion in the adrenal cortex. PRL is involved in the stress-induced activation of the hypothalamic-pituitary-adrenal (HPA) axis. It increases secretion of ACTH, induces adrenal hypertrophy and lipoprotein consumption by adrenocorticocytes, stimulating steroidogenesis (Samperi et al. 2019). Pituitary PRL secretion stays under inhibitory control from the hypothalamus *via* dopamine. This prolactostatic neurotransmitter acts specifically through the lactotroph dopamine type 2 (D2) receptors. Lactotrophs also respond to the stimulatory signals of hypothalamic thyroliberin hormone (TRH) which has prolactoliberin effect as well (Bernard et al. 2015, Shelly et al. 2012). PRL-Rs and PRL itself are expressed by the cells of immune system and in various hematopoietic organs, where PRL acts *via* paracrine/autocrine modes (Savino 2017).

Hyperprolactinemia (HPRL)- is an increased PRL blood level. The clinical manifestations of HPRL in women are: Galactorrhea, primary or secondary amenorrhea, delayed menarche or a change in the menses either in the amount or in their regularity. Men present HPRL with hypogonadism, infertility and hyposexuality.

HPRL is also associated with numerous multi-organ and organ specific autoimmune diseases, like systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), Sjogren's syndrome (SS), Hashimoto's thyroiditis (HT), multiple sclerosis (MS), psoriasis, hepatitis C, Behçet's disease, peripartum cardiomyopathy (PPCM), ~~Adisson~~'s disease (AD), and lymphocytic hypophysitis (LH) (Shelly et al. 2012).

The causes of HPRL can be classified into three groups: physiologic ones (pregnancy and breast-feeding, variety of stress conditions, sleep), pharmacologic ones (effect of dopaminolytics and other drugs) and pathological ones (due to prolactinomas, non-functioning pituitary adenomas (NFA), parasellar tumours, infiltrating lesions, hypophysitis, aneurisms, and empty sella syndrome). Virtually, hyperprolactinemia may result from any inflammation of the hypophysis, because its edema may block the pituitary stalk and partially disinhibit prolactogenesis from hypothalamic suppressor influence. Also, inadequate hypothalamic production of dopamine or pituitary stalk disruption in cranial traumas may cause it (Glezer & Bronstein 2015, Samperi et al. 2019, Vilar et al. 2014). Pharmacological (medication-induced) HPRL may occur as an effects of such medicines as antipsychotics, antidepressants, anti-emetics, opiates, antihypertensive drugs, estrogens, cimetidine, anticonvulsivants, cocaine, alcohol, sibutramine, etc (Vilar et al. 2014).

Serotonin vs antipsychotics in HPRL

The adverse effect of antidepressants can increase the prolactin level by inhibiting the serotonin re-uptake, which causes serotoninergic hyperactivity. Selective serotonin re-uptake inhibitors (SSRIs) are known as the most common cause of medication-induced HPRL (Park 2017). Nevertheless the majority of clinical trials that evaluated prospectively the rate of short-term (1 day-12 weeks) SSRI-induced HPRL have shown conflicting results: Some studies demonstrated that SSRIs can induce HPRL, whereas others have not revealed such an effect (Laine et al. 1997, Molitch 2008, Mück-Seler et al. 2002, Sagud et al. 2002, Spigset & Mjorndal 1997, Urban & Veldhuis 1991) Early study by Meltzer et al. showed that SSRI's can increase central serotonergic activity in patients due to presynaptic mechanism which potentiates the PRL secretion (Meltzer et al. 1997). To date there are two hypotheses explaining how SSRIs affect PRL secretion. First one postulates that serotonin may regulate prolactin secretion indirectly *via* postsynaptic 5HT1A, 5HT1C/2, 5-HT2, 5-HT2C, and 5HT3 receptors. Another one insists that serotonin inhibits GABA interneurons and this conducts to reduce the inhibition of dopaminergic action over PRL. Thus, it leads to increased PRL secretion (Park 2017). Serotonin (5-HT)-receptor-based effects play a critical role in the mechanisms of antipsychotic drugs (APDs) action in case of atypical APDs (Meltzer et al. 2003). Second-generation APDs are applied in different psychiatric disorders including schizophrenia, bipolar disorder, depressive disorder as an alternative to the first-generation antipsychotics because of their capacity to achieve an antipsychotic effect with lower rates of extrapyramidal side effects (EPS) (Racz et al. 2018, Meltzer 2003). These drugs insure extensive blockade of serotonin 5-HT2A receptors and to a lesser extent dopamine (DA) D2 receptors, but many also serve as partial agonists at the 5-HT1A and/or 5-HT1B receptors. In practice, atypical APDs that are 5-HT1A receptor partial agonists may act either as agonists or antagonists, depending upon the availability of endogenous 5-HT, 5-HT1A receptor density, and brain region (Meltzer & Massey 2011, Racz et al. 2018). Second-generation APDs are 5-HT2A antagonists. The antagonism of 5-HT2A may cause selective activation of 5-HT1A, which at the same time can increase the sensitivity of this receptor to serotonin. Furthermore, here is an evidence that 5-HT2A antagonists boost the 5-HT1A agonist effects and a lot of second generation APDs have demonstrated the 5-HT1A agonistic effect increasing serotonin levels. Altogether, these two mechanisms may lead to HPRL *via* serotoninergic activation (Kusumi et al. 2015, Meltzer & Massey 2011, Racz et al. 2018).

Hyperprolactinemia and hypothyroidism

Hypothyroidism and HPRL are known to be closely interrelated. This association was demonstrated with both overt and subclinical hypothyroidism (Hekimsoy et

al. 2010). The main reason of their relation is prolactoliberin effect of thyroliberin (Bowers et al. 1971, Snyder et al. 1973). Hashimoto's thyroiditis is an autoimmune thyroid disease characterized by an increase in level of antithyroid autoantibodies and by lymphoid infiltration in the thyroid gland. It is the most common cause of hypothyroidism nowadays beyond endemic iodine-deficient areas worldwide. In hypothyroidism because of the decreased production of thyroid hormones the level of thyroliberin is raised, the last factor stimulates both production of thyroid stimulating hormone (TSH) and PRL. As mentioned before, prolactin can facilitate the autoimmune inflammation as a paracrine and endocrine stimulant of autoimmunity, thus creating a vicious circle in pathogenesis of chronic autoimmune thyroiditis (Stroev et al. 2009).

SUBJECTS AND METHODS

We studied HPRL in a group of mentally ill Hashimoto's thyroiditis patients receiving antypsychotics, in order to analyze risks of HPRL in antipsychotic treatment (AT), to identify an association between the antipsychotic therapy and HPRL in Hashimoto's patients, and to explore the association of hyperprolactinemia and other laboratory parameters in patients with Hashimoto's thyroiditis and schizophrenia receiving antipsychotic therapy.

The study was a cross-sectional investigation on a suitable sample of 17 cases (all euthyroid or slightly hypothyroid). We have analyzed a group of patients with Hashimoto's thyroiditis in comorbidity with schizophrenia, all receiving antipsychotic therapy (mean age 46.5±12.8 years). The study has been approved by the Ethical Committee of the Saint Petersburg State University. Each patient signed written informed consent. The criteria for inclusion of the participants were: Age ≥18 years old, voluntary consent to participate, diagnosed schizophrenia under AT and comorbidity with Hashimoto's thyroiditis. The last diagnosis was confirmed in accordance with the criteria of the Japanese Thyroidological Association (JTA) (Akamizu & Amino 2000).

Statistical analysis in order to describe categorical variables, absolute values and fractions of an integer – n (%) were used. Variables with a continuous distribution were described by the median and quartile (Median [Q1;Q3]). Given that the study presented a heterogeneous sample of patients (gender, age, cycle phases, etc.), it seemed impossible to use standard parametric statistical methods for comparing parameters within the group, as well as between groups. Therefore, we applied the method of standardization of parameters, followed by the calculation of the decimal logarithm and used a logistic regression model. The integral risk characteristic of hyperprolactinemia was calculated using the Multiple Correspondence Analysis method. The strength of the association between the variables was calculated using the Spearman or Pearson correlation coefficient (R). The proportion of the explained variance was described by the coefficient of determination (R2). The Benjamini-Hochberg procedure was used as a correction for multiple hypothesis testing. All calculations were performed in the Rv3. 6. 3 programming language.

RESULTS

The level of PRL in the group amounted to 1191 [734.75; 1932.9] mIU/l, the share of patients with HPRL exceeded 76.5%.

Laboratory studies revealed an increased level of antithyroid autoantibodies, both to thyroglobulin (anti-TG) and to thyroperoxidase (anti-TPO) (Table 1, 2, Figure 1).

Table 1. Average standardized levels of laboratory parameters in patients

Parameter	Units	Median	Q1	Q3
FT3.log	log(T-score)	1.672	1.654	1.683
FT4.log	log(T-score)	1.583	1.455	1.671
TSH.log	log(T-score)	1.645	1.596	1.696
antiTPO.log	log(T-score)	1.948	1.539	2.486
antiTG.log	log(T-score)	1.862	1.531	2.070
PRL.log	log(T-score)	1.999	1.856	2.162

Table 2. Average levels of laboratory parameters in patients

Parameter	Units	Median	Q1	Q3
FT3	pmol/l	3.893	3.736	3.998
FT4	pmol/l	12.212	9.474	14.619
TSH	mIU/l	1.601	1.159	2.119
antiTPO	IU/ml	44.459	3.317	209.785
antiTG	IU/ml	108.219	9.160	221.918
PRL	mIU/l	1190.926	734.748	1932.892

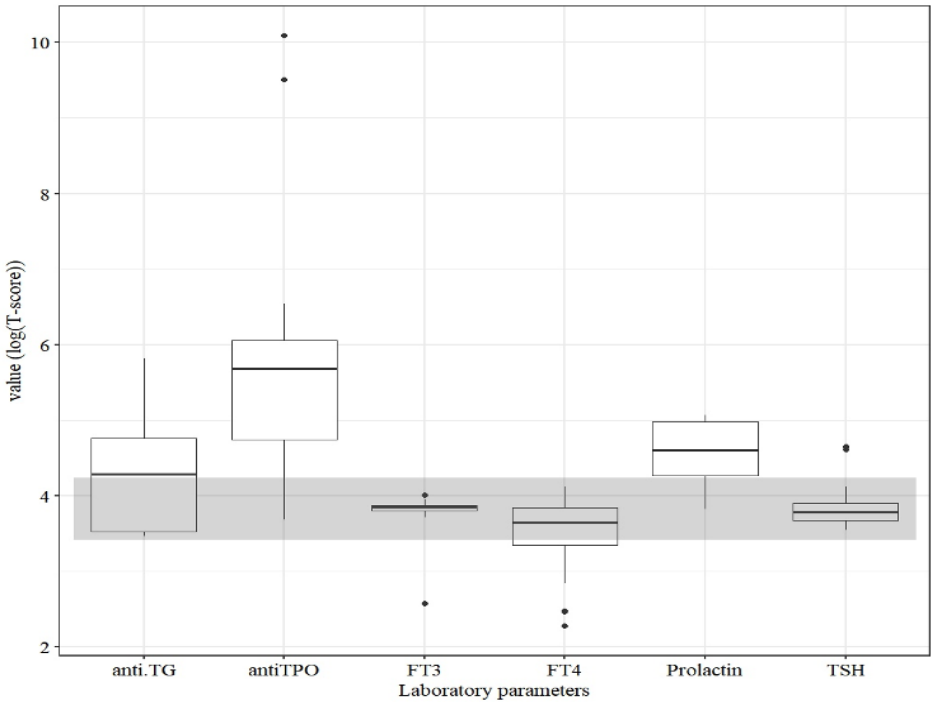

Figure 1. Average standardized levels of laboratory parameters in patients, grey area depicts the normal ranges

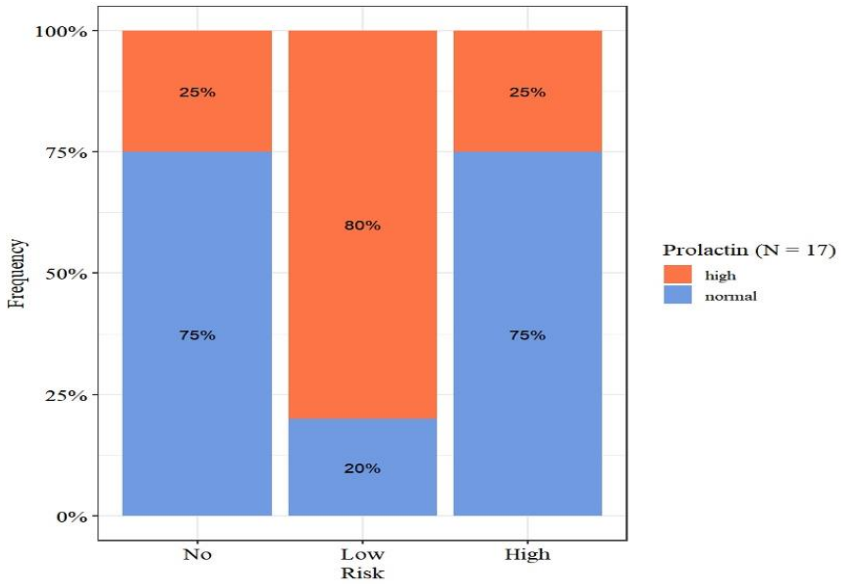

Figure 2. Distribution of patients into groups depending on the expected risk of developing hyperprolactinemia and actual % of HPRL cases in subgroups

Patients were divided into 3 subgroups, depending on the antipsychotics they consumed, which, according existing experience, differed in their expected risk of provoking HPRL as a side effect: antipsychotics of no expected risk (n=8), of low risk (n=5), and of high risk (n=4).

It turned out that the groups taking the drugs with no expected risk of HPRL and with the highest expected risk of it, did not differ in percentage of HPRL cases (25% of cases in each of the groups), The group on the drug with a low expected risk of iatrogenic HPRL, nevertheless actually displayed HPRL in 80%. This suggests that there is a non-medicinal cause of HPRL in patients with Hashimoto's thyroiditis co-morbid with schizophrenia, besides iatrogenic effects (Figure 2).

An inverse significant correlation (R=-0.51, p=0.037, R^2=0.26) was detected between the level of PRL and the expected risk of iatrogenic HPRL attributed to various antipsychotics. Which again indicates a factor independent of drug treatment that causes HPRL in such comorbid psycho-endocrine cases (Figure 3).

There was also a direct significant correlation (R=0.53, p=0.03, R^2=0.28) between the blood levels of PRL and free thyroxine (FT4) (Figure 4).

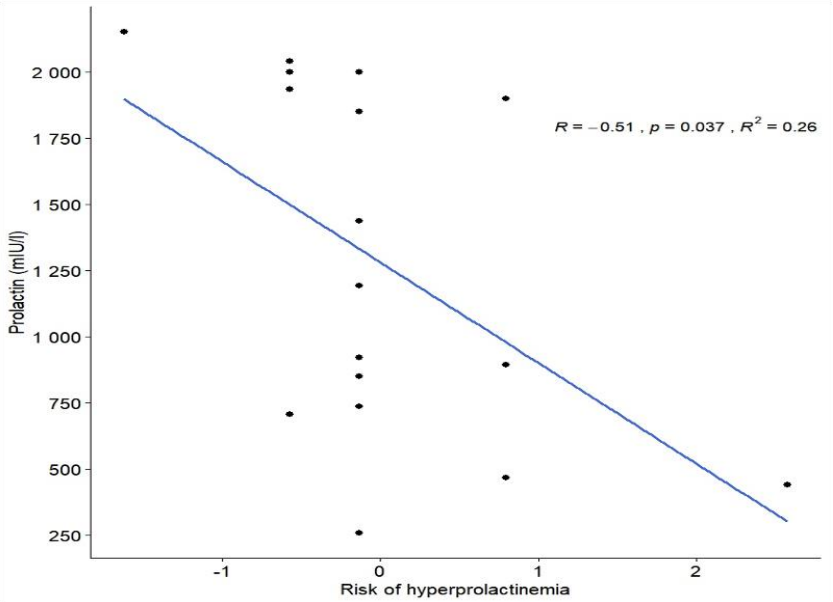

Figure 3. Inverse significant correlation between the level of PRL and the degree of expected risk of iatrogenic HPRL caused by various antipsychotic drugs used

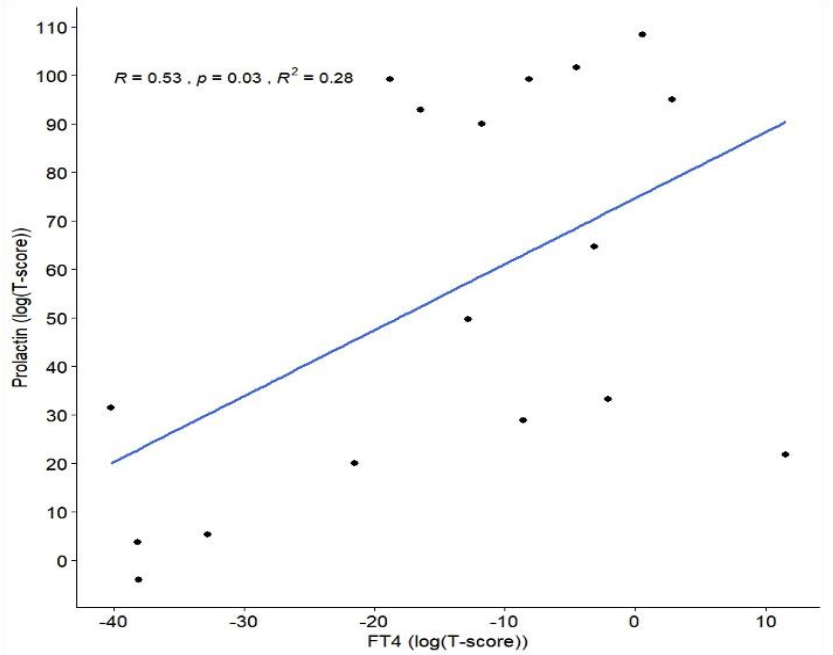

Figure 4. A direct significant correlation between the levels of PRL and FT4

DISCUSSION

In patients with Hashimoto's thyroiditis and schizophrenia, there is a non-iatrogenic cause of HPRL. The revealed direct reliable relationship between the level of PRL and FT4 makes it appropriate to assume that in patients with autoimmune thyroiditis and schizophrenia, antipsychotics, interfering with the metabolism of PRL, create a false effect of correlation between PRL and FT4, since it is known that in experiment and in clinical use thyroid hormones, on the contrary, inhibit the formation of thyroliberin/prolactoliberin and decrease prolactinogenesis (Snyder et al. 1973, Churilov et al. 2019).

A number of medicines: Antipsychotics, neuroleptics, antidepressants, opiates, cocaine, antihypertensive and gastrointestinal drugs, protease inhibitors and estrogens - all may provoke HPRL and even galactorrhea (Molitch 2005). But in our study, HPRL not only did not correlate, but discorrelated with the degree of prolactogenic drug effects. PRL is produced by cells of the immune system, and HPRL is a characteristic of many autoimmune diseases exacerbating them: The list of such ailments includes Hashimoto's thyroiditis, which the patients involved in this research suffered from (Yang et al. 2018, Ali et al. 2018). Although HPRL can aggravate some autoimmunopathies, it is possible to

make also an opposite assumption about the compensatory nature of HPRL in Hashimoto's thyroiditis, since recently it was detected, that PRL, promoting galactosylation of immunoglobulins, can weaken some IgG4-depending immunopathological processes in several organs, including thyroid (Hirschberg et al. 2021).

CONCLUSION

Anyway, our data witness that Hashimoto's thyroiditis patients with psychotic symptoms should be treated differently compared to the classic cases of schizophrenia, due to additional possible driver of HPRL in such cases in plus to well known prolactogenic action of antipsychotics.

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Conflict of interest: None to declare.

Contribution of individual authors:

Polina A. Sobolevskaia: prepared a manuscript, performed the literature review, performed laboratory studies.

Leonid P. Churilov & Yehuda Shoenfeld: reviewed and edited the manuscript.

Tamara V. Fedotkina: performed the literature review.

Anna Stepochkina, Anastasia Dolina & Anton N. Gvozdetckii: collected the data and reviewed the manuscript.

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