INTRODUCTION

Metabolic syndrome (MS) is a pathological condition, characterized by an increase in visceral fat mass, insulin resistance with associated hyperinsulinemia, and impaired metabolism of carbohydrates, lipids, and purines [1]. The prevalence of MS in different populations according to the criteria of the International Diabetes Federation is 27.5–68.7%, and the US National Cholesterol Education Program - 22.6–40.9% [2–8]. Diseases associated with MS such as type 2 diabetes mellitus, arterial hypertension, non-alcoholic fatty liver disease, and the risk of cardiovascular disease [9–12] develop.

The main risk factors for MS are genetic predisposition, sedentary lifestyle, a diet high in carbohydrates and lipids [13–15]. At the same time, the presence of concomitant diseases, combined with metabolic disorders, can have a significant impact on the formation and course of MS. These factors include parasitic infections found in various regions of the world, including Russia.

In the world, up to 56 million people suffer from trematodiasis, including opisthorchiasis [16]. The Ob-Irtysh basin is the global hotbed for Opisthorchis felineus (O. felineus) infection, responsible for up to 80% of known cases [17–19]. In 2017, opisthorchiasis in Russia accounted for 78.5% of the number of biohelminthoses cases (18.7 thousand cases of infection) [20]. Thus, an increase in the risk of metabolic diseases should be considered in the context of continuing high loads of parasitic infections.

The aim of this literature review is to analyze the results of modern epidemiological
and experimental studies regarding the effect of helminth infections on the formation and course of MS, as well as associated disorders of carbohydrate and lipid metabolism.

**EPIDEMIOLOGICAL STUDIES**

The data of epidemiological studies aimed at studying changes in carbohydrate and lipid metabolism associated with helminth infections are extremely scarce (Table 1). Most of these studies were carried out in the regions of Southeast Asia, endemic to various helminth infections.

For example, as part of an epidemiological study (n = 646, Indonesia, 2013), the effect of geohelminths (Ascaris lumbricoides, Necator americanus, Ancylostoma duodenale, Trichuris trichiura, Strongyloides stercoralis) on insulin sensitivity was analyzed in infected individuals. It was found that a lower body mass index (BMI 22.5 vs. 23.2 kg/m2) and a lower insulin resistance index (HOMA-IR 0.81 vs. 0.97) were observed in infected individuals compared to uninfected participants. In the presence of co-infection with other geohelminoses, the HOMA-IR index decreased by 0.10, mainly due to a decrease in the level of insulin with each additional infection. Also, a decrease in BMI of 0.3 kg/m2 was detected with each subsequent type of geohelminth found in an individual [21].

In another study (n = 259, Australia, 2013), the enzyme immunoassay (ELISA) was used to detect Strongyloides stercoralis infection in participants. They also measured hemoglobin levels, glycated hemoglobin levels, serum lipid concentration, blood pressure, and BMI. The results suggest that strongyloidiasis reduces the risk of developing type 2 diabetes in adults by 61% [22].

An epidemiological study (n = 3913, China, 2013) examined the association between prior schistosomiasis (according to anamnesis and register of infectious diseases), type 2 diabetes, and MS in geriatric patients. The participants infected with Schistosoma japonicum (n = 463) had lower fasting plasma glucose levels, postprandial glucose levels, glycated hemoglobin levels, insulin resistance, incidence of type 2 diabetes (14.9 vs. 25.4%), and MS (14 vs. 35%) compared to controls [23].

A similar study (China, 2015) included participants living in a territory with a high prevalence of S. japonicum 40 years ago. Among the participants, there were 465 people with a history of previous infection and 1,132 people representing the control group. An association has been established between prior schistosomiasis and a lower prevalence of MS and its associated conditions (central obesity, hypertriglyceridemia, a low HDL level) [24].

A similar pattern was found in another study (China, 2018) involving patients with schistosomiasis (n = 2,183) and unaffected individuals (n = 1,798). With schistosomiasis, a lower BMI was recorded in comparison with unaffected individuals (23.7 vs. 24.3 kg/m2). Lower fasting glucose (5.3 vs. 5.6 mmol/l), total cholesterol (4.6, 5.3 mmol/l), level of TG (1.85 vs. 2.1 mmol/l), the level of LDL (2.89 vs. 3.1 mmol/l) were also found in the schistosomiasis group compared to the control group [25].

One of the first epidemiological studies on the relationship between obesity and hepatic trematodose infection is a one-step study in the O. viverrini endemic region (n = 730, Thailand, 2015). The study established an association between opisthorchiasis and the presence of 1st and 2nd degree obesity [26].

In contemporary literature, the results of studies carried out by local authors are available in regions endemic to O. felineus infection. Thus, during the study of autopsy materials (n = 319, 2013), the number of adult O. felineus helminths in the bile ducts of the studied liver was estimated. The results indicate that, as a result of O. felineus infection, a lower level of serum cholesterol was observed in comparison with samples without infection. Chronic opisthorchiasis was shown to be a negative predictor of atherosclerosis: the degree of infection was negatively correlated with the area of aortic damage [27].

In one study (n = 77, 2001), liver biopsy specimens from patients with type 1 and type 2 diabetes associated with O. felineus infections revealed manifestations of hepatocyte cell-involutive degeneration, intracellular cholestasis syndrome, and focal lipid infiltration, as well as perportal, pericentral and perigepatocellular fibrosis. Electron microscopy revealed degenerative changes in hepatocytes with nucleic alteration associated with impaired carbohydrate metabolism and high cytoplasmic glycogen content [28].

In a case-control study (n = 99, 2003), a higher level of glycemia was found in the group of patients with both type 1 diabetes and opisthorchiasis as compared to uninfected type one diabetic patients (19.6 vs. 16.7 mmol/l) required to compensate for the insulin dose (0.88 vs. 0.71 U/kg). In the case of infected patients, an increase in liver size
| Автор, год      | Страна     | Дизайн исследования | Средство            | Гельминт                                                | Диагностика  | Изучаемая патология                  | Результат                                                                 |
|----------------|------------|----------------------|---------------------|--------------------------------------------------------|--------------|--------------------------------------|-----------------------------------------------------------------------------|
| Wiria A.E., 2015 [21] | Индонезия | Одномоментное        | Микроскопия         | Trichuris trichiura, Ascaris lumbricoides, Necator americanus, Ancylostoma duodenale, Strongyloides stercoralis | Microscopy   | Инсулинорезистентность               | Individus with infection: - снижение ИМТ, HOMA-IR; - при наличии ко-инвазии к другим видам гельминтов снижение HOMA-IR, ИМТ |
| Hays R., 2015 [22] | Австралия  | Одномоментное        | ELISA               | Strongyloides stercoralis                              | ИФА          | Сахарный диабет 2 типа                | Individuals with previous infection: - на 61% реже СД 2                      |
| Chen Y., 2013 [23] | Китай      | Одномоментное        | Medical history, Local registry data | Schistosoma japonicum                                  | Сахарный диабет 2 типа, метаболический синдром Type 2 diabetes mellitus, metabolic syndrome | Сахарный диабет 2, метаболический синдром Type 2 diabetes mellitus, metabolic syndrome | - более низкая распространенность СД 2, МС                       |
| Shen S.-W., 2015 [24] | Китай      | Одномоментное        | Medical history, liver ultrasound | Schistosoma japonicum                                  | Метаболический синдром | Сахарный диабет 2 типа, метаболический синдром Type 2 diabetes mellitus, metabolic syndrome | Individuals with previous infection: - снижение ИМТ, ОХС, TC, HDL-C; - более низкий уровень ЛПВП; - низкая распространенность МС |
| Duan Q., 2018 [25] | Китай      | Случай – контроль    | Clinical data       | Schistosoma japonicum                                  | Клинические данные | Нарушение углеводного обмена          | Individuals with infection: - снижение ИМТ, уровень глюкозы плазмы, уровни ОХС, TC, ЧЕК, ЛПНП |

"Таблица 1" "Table 1"
| Авторы | Год | Страна | Методы исследования | Основные результаты |
|--------|------|---------|----------------------|---------------------|
| Kaewpitoon S.J. | 2016 | Таиланд | Одномоментное исследование | Ожирение 1-2 степени, ассоциация с Opisthorchis viverrini инвазией. |
| Pavlenko O.A. | 2001 | Россия | Одномоментное исследование | Ожирение 1-2 степени, ассоциация с Opisthorchis felineus инвазией. |
| Beloborodova E.V. | 2003 | Россия | Одномоментное исследование | Дистрофия гепатоцитов, очаговая липидная инфильтрация, тип 1 диабета меллиту. |
| Pavlenko O.A. | 2001 | Россия | Одномоментное исследование | Дистрофия гепатоцитов, очаговая липидная инфильтрация, тип 1 диабета меллиту. |
| Kravetz E.B. | 2006 | Россия | Одномоментное исследование | Дистрофия гепатоцитов, очаговая липидная инфильтрация, тип 1 диабета меллиту. |
| Magen E. | 2013 | Россия | Аутопсийное исследование | Образцы аутопсийного материала с Opisthorchis felineus инвазией: более низкий уровень TC. |

**Примечание:** ПЦР – полимеразная цепная реакция; ИФА – иммуноферментный анализ; УЗИ – ультразвуковое исследование; ИМТ – индекс массы тела; СД – сахарный диабет; МС – метаболический синдром; ДАД – диастолическое артериальное давление; ТГ – триглицериды; ЛПВП – липопротеиды высокой плотности; ЛПНП – липопротеиды низкой плотности; ОХС – общее холестерин.
according to ultrasound data was three times more frequent than in the group with isolated type 1 diabetes, severity of bile ducts was observed, and the walls with periportal echogenicity were thickened [29]. Similar results were obtained in a study performed with the participation of children (n = 90, 2006) with type 1 diabetes in combination with opisthorchiasis. There was a higher level of glycemia, glycated hemoglobin, and insulin dose than in the comparison group. Ultrasound signs of fatty hepatosis were determined in 68% of patients with concomitant pathology [30].

It should be noted that according to the World Health Organization and the International Diabetes Federation, type 1 diabetes is less common in countries in Asia and Africa, which are characterized by high rates of helminth infections in the population [31]. Also, other population studies suggest that helminth infection does not interfere with the development and course of type 1 diabetes [32].

**EXPERIMENTAL STUDIES**

Currently, accumulated experimental data indicate a change in carbohydrate and lipid metabolism linked to helminthiasis (Table 2). Thus, when studying the effect of Nippostrongylus brasiliensis nematodosis (USA, 2013) on the development of metabolic disorders, it was found that in affected animals compared to controls: adipose tissue weight was lowered, fatty degeneration of the liver slowed, and carbohydrate metabolism improved, accompanied by changes to the metabolic hormone profile. Authors note the preventive and therapeutic effect of N. brasiliensis infection on the development of obesity and associated metabolic disorders in mice [33].

In another study (Germany, 2016), infection by Litomosoides sigmodontis was shown to increase the number of eosinophils and activated macrophages in the gonadal epididymal adipose tissue. Improvement in glucose tolerance (in the glucose tolerance test) in mice with experimental obesity was also noted [34].

In an experimental model with the line of apolipoprotein E defective mice (ApoE -/-), the effect of S. mansoni infection on the progression of atherosclerosis was studied (United Kingdom, 2002). The development of aortitis and brachiocephalic artery plaque was reduced by 50% in ApoE -/- mice infected with S. mansoni compared to the control [35]. A decrease in serum cholesterol was observed in the effects of excretory-secretory products and S. mansoni eggs, but not adult worms [36].

In another study (Netherlands, 2013), S. mansoni infection in mice resulted in the reduced size of atherosclerotic plaques by 44% as compared with the control. With the introduction of helminth excretory-secretory products, the number of circulating neutrophils and inflammatory monocytes Ly6C decreased and the content of interleukin 10 increased. Also, inflammation inside the plaques (decreased?) as inflammatory markers decreased: (tumor necrosis factor alpha (TNF-α), monocyctic chemotactic factor 1 (MCP-1), factor cell-cell adhesion 1 (ICAM-1), adhesion factor of vascular endothelium type 1 (VCAM-1), CD68), neutrophil cell count, and macrophage cell count [37].

An experimental study (Netherlands, 2015) showed that chronic infection by S. mansoni (12 weeks) reduces weight gain (~62%), adipose tissue (~89%), and adipocyte size. Also noted was a decrease in insulin resistance (~23%) and an improvement in peripheral absorption of glucose (+25%) and insulin sensitivity of white adipose tissue. The authors note that the injection of soluble S. mansoni antigens prevents metabolic disorders by activating the Th2 immune response, activating eosinophilia, and activating the M2 macrophage of white adipose tissue [38].

The infection by trematode S. japonicum in animals modeling obesity and insulin resistance (China, 2018) was associated with a decrease in body weight 7 weeks after infection, a decrease in fasting blood glucose, and an improvement in glucose tolerance. In addition, when the line of mice spontaneously developing obesity and diabetes was infected, a decrease in body weight and an improvement in glucose tolerance were recorded along with the pronounced expression of proinflammatory cytokines in visceral adipose tissue compared to controls [25].

In the available literature, there are a limited number of studies performed on models of hepatic trematodosis. In a study of O. viverrini infected hamsters (Thailand, 2013), scientists studied the relationship between damage to bile ducts and metabolic changes in the liver using magnetic resonance imaging and IH magnetic resonance spectroscopy. In the group of infected hamsters, intrahepatic and extrahepatic dilations of the ducts in the liver were dependent on the duration of infection. The ratio of choline-lipids in the group of infected animals increased by 2, 3 and 4 times after 7–11, 13–15, 17–21 weeks of the
| Author, year | Helminth          | Experimental model of the disease | Result                                                                                                                                                                                                 |
|-------------|-------------------|----------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Yang Z.,   | Nippostrongyulus brasilensis | Obesity                          | Reduced body weight, adipose tissue mass, hepatic steatosis associated with a decreased expression lipogenic enzymes / mediators; improved carbohydrate metabolism, connected with profile of metabolic hormones |
| Berbudi A., | Litomosoides sigmodontis | Obesity                          | Increased eosinophil cells count and alternatively activated macrophage abundance within epididymal adipose tissue; improve glucose tolerance in obese mice                                                 |
| Doenhoff M., | Schistosoma mansoni  | Atherosclerosis                   | Infection with eggs and excretory secretory products: decrease in serum cholesterol infection with adult worm – a weak effect                                                                               |
| Walker E.,  | Schistosoma mansoni  | Atherosclerosis                   | Increased in body weight gain, adipose tissue, adipocyte size, insulin resistance.                                                                                                                      |
| Hussaarts L., | Schistosoma mansoni  | Obesity                          | Improved peripheral glucose uptake, improve insulin sensitivity of white adipose tissue.                                                                                                                |
| Duan Q.,   | Schistosoma japonicum | Obesity                          | Decreased FBG, improved glucose tolerance. Reduced body weight and adipose tissue mass                                                                                                                  |
| Hanpanich P., | Opisthorchis viverrini | –                               | Increased of the cholin-lipid ratio in the infected group in 2, 3 and 4 times at 7–11, 13–15, 17–21 weeks of the study                                                                                      |
| Chaidee A., | Opisthorchis viverrini | Type 1 diabetes mellitus         | Increased level of ALT, AST, ALP, Heating of liver fibrosis, increased expression of pro-inflammatory interleukins 6, 12, 13                                                                            |
| Pershina A.G., | Opisthorchis felineus | –                               | Increased of the cholin-lipid ratio in the infected group in 2, 3 and 4 times at 7–11, 13–15, 17–21 weeks of the study                                                                                      |

**Note.** ALT – alanine transaminase; AST – aspartate transaminase; GGT – gamma-glutamyltranspeptidase; TG – triglyceride; LDL-C – low-density lipoprotein cholesterol; apoE−/− mice – mice with genetic deficiency in apolipoprotein E.
study, respectively. Choline-lipid coefficients are associated with the degree of cell infiltration in the periductal space in animals infected by O. viverrini [39].

In another study (Thailand, 2018) on the combined course of type 1 diabetes and O. viverrini infection, an experiment revealed jaundice and hepatomegaly, an increase in transaminase levels, alkaline phosphatase, hepatocyte damage, hypertrophy, and proliferation. This study also suggests that the combination of type 1 diabetes and opisthorchiasis increases the expression of pro-inflammatory interleukins 6, 12, 13 by aggravating liver fibrosis and oxidative damage to deoxyribonucleic acid [40].

In an experimental study carried out at Siberian State Medical University, it was shown that O. felineus infection is accompanied by accumulation of cholesterol in the liver. Eight weeks after infection, histological analysis of liver samples revealed impaired hepatic architecture, hepatocyte size variability, periductal and periportal fibrosis, and dilation of intrahepatic bile ducts. There was also an increase in ALT, gamma-glutamyl transpeptidase, TC, TG, and LDL in the serum of infected hamsters compared to the control group of animals. Biochemical analysis of liver tissue showed a statistically significant increase in cholesterol level, the ratio of cholesterol to phospholipids, in O. felineus infected animals [41].

CONCLUSION

Studies in recent years indicate a relationship between helminth infections and MS, diabetes, and obesity, which are accompanied by impaired carbohydrate and lipid metabolism [21, 22, 38, 42]. Helminths are natural inducers of the Th2 immune response. MS, diabetes and obesity are accompanied by a Th1 immune response, while helminth infection shifts the immunological vector towards the Th2 immune response with a change in the production of interleukins, as well as polarization of M2 adipose tissue and activation of eosinophils, basophils, and mast cells [31, 41, 43].

Inflammation associated with obesity, insulin resistance, diabetes, and MS is known to be characterized by the abnormal formation of cytokines, an increase in the concentration of acute phase proteins and other mediators, and an activation of the network of inflammatory signaling pathways [44]. It is possible that a change in the Th1 immunological vector in the direction of Th2 with MS during helminth infection contributes to a decrease in insulin resistance and adipose tissue mass, an improvement in the peripheral absorption of glucose and insulin sensitivity of white adipose tissue, and a decrease in the likelihood of development and severity of diabetes (Tables 1, 2). At the same time, reactive oxygen species play an important role in the pathogenesis of diabetes in initial stages (destruction of pancreatic islets) and in the period of late complications. Numerous studies in this area indicate that the damaging effects of hyperglycemia are mediated by free radicals [45].

Chronic inflammation during helminth infection leads to increased generation of reactive oxygen and nitrogen species, leading to the development of oxidative and carbonyl stress [46, 47]. This may cause a increased hyperglycemia and glycated hemoglobin levels and glycated hemoglobin in patients with concomitant type 1 diabetes and opisthorchiasis infection [30]. It is known that MS and obesity are accompanied by oxidative stress, mainly in adipose tissue due to activation of the production of reactive oxygen species by adipocytes and cells of the immune system [48]. Thus, the inflammatory process and oxidative stress associated with helminthic infection can exacerbate the severity of MS and contribute to the complexity of its clinical manifestations.

CONFLICT OF INTEREST

The authors declare the absence of obvious and potential conflicts of interest related to the publication of this article.

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Метаболический синдром, нарушения углеводного и липидного обмена при гельминтозах: обзор современных данных

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РЕЗЮМЕ
Метаболический синдром (МС) – распространенное патологическое состояние, в основе которого лежат увеличение массы висцерального жира, инсулинорезистентность с гиперинсулинемией, нарушение углеводного, липидного и пуринового обмена. На формирование и течение МС может повлиять наличие сопутствующих заболеваний, сопровождающихся нарушением обмена веществ, среди которых — паразитарные инвазии. В настоящем обзоре представлен анализ результатов современных эпидемиологических и экспериментальных исследований в отношении влияния гельминтных инвазий на формирование и течение МС, а также ассоциированных с ним нарушений углеводного и липидного обмена.

Ключевые слова: метаболический синдром, углеводный обмен, липидный обмен, гельминтозы, трематодозы.

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