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CARBOXYTHERAPY AS AN ALTERNATIVE OFF LABLE METHOD FOR DIABETES MELLITUS TREATMENT: A REVIEW

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Abstract

Diabetes mellitus (DM) is one of the global medical and social problems of the XXI century. It was found that patients with diabetes mellitus showed an increased severity of coronavirus disease (COVID-19) caused by infection with coronavirus 2 (SARS-CoV-2). At the same time, the development of new modern technologies allows the use of innovative methods for the treatment of diabetes.

The purpose of this literature review was to analyze the possibilities of using carboxytherapy in the treatment of diabetes mellitus.

Materials and research methods. Scientific publications in foreign and domestic journals on relevant topics over the past 5 years, Internet resources.

Research results and their discussion. In the course of the literature review, the mechanisms of realization of the pharmacological effects of carboxytherapy have been summarized with the substantiation of the effect on individual links of pathogenesis in the body of patients with diabetes mellitus or with its complications. The scientific understanding of the role of carboxytherapy as an effective alternative method for treating diabetes mellitus and its complications has been expanded.
Conclusions. Thus, the analyzed data indicate the rationality of the use of carboxytherapy as an alternative method for the treatment of diabetes mellitus and its complications.

Keywords: *diabetes mellitus (DM),*

Introduction

Diabetes mellitus (DM) is one of the global medical and social problems of the XXI century [1, 2]. The WHO has designated it as a non-communicable pandemic. Currently, in terms of the importance of complications, diabetes takes third place after cardiovascular and oncological diseases [3, 4]. Serious complications of diabetes include angiopathy, retinopathy, cardiomyopathy, nephropathy, myocardial infarction, stroke, gangrene of the lower extremities, which lead to early disability and high mortality [3, 5, 6]. It was also found that patients with diabetes mellitus showed an increased severity of coronavirus disease (COVID-19) caused by infection with coronavirus 2 (SARS-CoV-2) [7, 8].

Currently, a fairly large amount of knowledge in the field of the pathogenesis of diabetes and the presence of many modern therapeutic options do not contribute to the improvement of metabolic control of this disease, therefore, the optimization of diabetes therapy through alternative methods of treatment is one of the urgent medical and social problems.

Methods

Scientific publications in foreign and domestic journals on relevant topics over the past 5 years, Internet resources.

Results and Discussion

One of the most important pathogenetic mechanisms of diabetes is associated with the processes of free radical oxidation. It should be noted that in diabetes mellitus, not only the formation of free radicals is activated, but also excessive activation of free radical oxidation processes occurs. Free radicals react with phospholipids of cell membranes, which leads to their structural changes [9, 10]. Damage and destruction of pancreatic β-cells are only observed in cases where there is no restoration of damaged β-cells or there is a deficiency of the protective antioxidant complex [11]. Nowadays, this process is considered as a universal mechanism that combines the main biochemical pathways of the toxic effect of hyperglycemia on the body. Therefore, today priority is given to antidiabetic drugs, the pharmacodynamics of which are not limited to hypoglycemic action, but allows a positive effect on several main pathogenetic links of diabetes, which ultimately affects the prognosis of the disease, the quality, and duration of the patient's life [2].

At the same time, with the development of new modern technologies in medicine, carboxytherapy has become widely used for the treatment of diabetes, as well as its complications [12, 13]. Carbon dioxide is a universal inhibitor of the generation of reactive oxygen species - free radicals, exhibiting a superoxide-inhibiting effect. According to research, carbon dioxide inhibits the generation of reactive oxygen species not only in blood phagocytes and alveolar macrophages but also in the cells of tissues of internal organs. This effect of CO_2 was confirmed on seven types of phagocytic cells (blood phagocytes, alveolar macrophages, tissue phagocytes - macrophages of the liver, kidneys, brain, lungs, stomach pylorus), on seven types of tissues (total parenchymal and interstitial) cells of internal organs (liver, brain, heart, lungs, kidneys, skeletal muscles). Besides, at direct contact, carbon dioxide is capable of inhibiting the generation of ROS in mitochondria [14, 15, 16].

Also, carboxytherapy can significantly alleviate the condition of such patients due to vasodilation, increased oxygenation, antihypoxic, antioxidant, anti-inflammatory properties, being a worthy auxiliary and alternative method of diabetes therapy [13, 17].

In patients with diabetes, under conditions of persistent hypoxia, the biochemical process of oxidative phosphorylation is uncoupled, which is accompanied by serious manifestations of tissue hypoxia [18, 19]. It was found that carbon dioxide increases the degree of conjugation of tissue respiration and phosphorylation, disturbed during the pathological process in the cell [15, 20].

The main complication of diabetes mellitus is diabetic angiopathy [21, 22]. It is conventionally divided into micro- and macroangiopathy. The latter, by localization and clinical manifestations, is subdivided into vascular lesions of the heart (coronary artery disease, atherosclerosis), of the brain (acute and chronic disorders of cerebral circulation), and peripheral arteries. The prolonged course of diabetes, an increase in blood sugar levels, lead to damage of all blood vessels of the body, their walls become fragile and begin to thin, then deform and eventually collapse, which interferes with the normal blood flow, the supply of nutrients and oxygen to all cells and tissues of the body. As a result, oxygen starvation of tissues begins and internal organs get damaged [23, 24].

Lesions of small vessels in diabetes (microangiopathy) are characterized by damage to the basement membrane and proliferation of the endothelium. Identical microcirculation disorders are found in the retinal vessels (retinopathy) and the capillaries of the glomerulus of the kidneys (nephropathy). Microcirculatory disorders play an important role in the pathogenesis of diabetes. The resulting trophic disorders of organs and tissues contribute to the long-term course or progression of this disease [25].

Another mechanism of carbon dioxide action on pathological processes in the body in patients with diabetes is the Verigo-Bohr effect [15]. This effect characterizes the dependence of the degree of dissociation of oxyhemoglobin on the partial pressure of carbon dioxide in the alveolar air and blood. Due to the Verigo-Bohr effect, carbon dioxide therapy can reduce the severity of microcirculation disorders. As a result of an increase in pCO_2, oxygen release is enhanced, which leads to an improvement in tissue oxygenation. At the vascular level, this provides active microcirculatory vasodilation and an improvement in blood flow in the capillary arterioles. The vasodilatation caused by CO_2 is due to its direct action on the receptors of the smooth muscle fiber of the arterioles, as well as the release of vasoactive compounds: histamine, acetylcholine, serotonin, and kinins, due to which vasodilation, including coronary vessels, and a decrease in blood pressure occur [26,27,28].

Several researchers have analyzed the parameters reflecting the nature of microcirculation in patients with diabetes after dry carbon dioxide baths using laser Doppler peakfluometry. Under the influence of CO_2, there was a statistically significant increase in the following indicators: the level of microcirculation by 28.3% and the coefficient of variation by 29.2%, the index of fluxmotions (characterizing the efficiency of regulation of blood flow modulations in the microcirculation system during edema) by 36.8%, an increase in the amplitude of low-frequency oscillations by 13.9%, and a decrease in the amplitude of pulse rhythms by 23.2%. There was also a decrease in the reserve of capillary blood flow by 13.3% with a significant increase by 68.9% in the half-recovery time of capillary blood flow and an increase in its speed, density of the capillary network, a decrease in the number of lipid inclusions, the duration of stasis, the number of sludges and the size of the perivascular zone to normal values (fig. 1). Thus, with video capillary examination, an increase in the number of vertical capillaries (black dots) and transverse capillaries is observed [29].

When carrying out a non-invasive CO_2 therapy (baths) in such patients, there is an improvement in the volumetric parameters of intracardiac hemodynamics and a decrease in the total peripheral vascular resistance with an increase in physical performance [30].

Diabetes mellitus is characterized by a persistent level of increased blood pressure, as well as impaired diastolic function of the left ventricle [31, 32]. In such patients, after complex treatment with the use of dry carbon dioxide baths, the average ratio of the peaks of early and late filling of the left ventricle increased significantly (about 10%). The obtained positive results of the dry carbon dioxide baths' influence on indicators of left ventricular diastolic function deserve attention in the complex of preventive measures for arterial hypertension [33]. Therefore, the pronounced vagotonic, vasodilatory effects and a positive effect of dry carbon dioxide baths on lipid metabolism can be used in a complex of antihypertensive and antiatherosclerotic therapy.

When analyzing the results of lipidograms in patients with the syndrome of metabolic disorders with various dyslipidemias, taking dry carbon dioxide baths, a tendency to an increase in high-density lipoproteins and to a decrease in the amount of low and very-low-density lipoproteins was found. After administration of dry carbon dioxide baths, these patients showed a tendency towards a decrease in total cholesterol and atherogenic coefficient. Besides, when studying the intensity of LPO processes and antioxidant activity by the method of induced biochemiluminescence, it was found that after dry carbon dioxide baths, the antioxidant system is activated, as evidenced by a 21.2% decrease in the content of free radicals in the blood plasma, a significant decrease in the malondialdehyde index by 11.9 %, an increase in erythrocyte catalase activity by 6.5% and a tendency towards a decrease in diene conjugates was revealed [34].

Analysis of hemodynamic parameters before and after carboxytherapy demonstrates the superiority of dry carbon dioxide baths over ozone therapy in terms of influence on the parameters of blood pressure and heart rate. The hypotensive effect of the course of dry carbon dioxide baths is manifested by a decrease not only in systolic blood pressure but also, which is especially important, in diastolic pressure. This is due to the improvement in neurohumoral regulation of vascular tone and reactivity, which is due to the vagotonic and vasodilating effects of carbon dioxide (Table 1).

Analysis of the kinetics of oxygen metabolism in patients with diabetes (initially inhibited processes of tissue respiration) showed that after the use of dry carbon dioxide baths, an increase in the functional reserves of respiratory enzymes was noted by 14.4%, which was manifested in a decrease in the critical oxygen concentration by 11.7% [35].

Also, there was a decrease in the oxygen reserve ratio by 18.5%, which indicated an improvement in the ratio of the processes of delivery and consumption of oxygen by tissues resulting from treatment [35].

In severe forms of diabetes, irreversible glycosylation of antioxidant enzymes such as catalase and superoxide dismutase is observed, with the loss of antigenic properties and their subsequent inactivation, which also contributes to the growth of FRO lesions [6, 9]. In diabetic patients, there is an increase of malondialdehyde (MDA), one of the markers of LPO in erythrocyte membranes. Oxidative stress disrupts the rheological properties of blood with the development of hemostasis and thrombosis, activates the expression of molecular adhesion cells that regulate the interaction between endothelial cells and leukocytes [36, 37].

With hyperglycemia, a non-enzymatic glycosylation of proteins occurs with the formation of an intermediate compound, which is called the Amadori product [38, 39]. In the future, this leads to an increase in permeability and a decrease in the elasticity of blood vessels, a change in the function of enzymes, the metabolism of lipoproteins and free fatty acids. The consequences of insulin deficiency in diabetes are manifested by disorders of all types of metabolism, of which disorders of carbohydrate metabolism are the most pronounced. The degree of impaired carbohydrate metabolism reflects the level of glycosylated hemoglobin (HbA1c) since impaired glucose metabolism leads to glycosylation of proteins. It also contributes to the formation of glycosylation end products, which are considered the most important mediators of micro-and macroangiopathies in the late stages of diabetic complications [2].

Clinical observations have shown that the use of carboxytherapy in the form of dry CO_2 baths not only contributed to a decrease in fasting glycemia but also had a normalizing effect on the parameters of glycosylated hemoglobin and glucose during the postprandial test. The symptomatic positive effect of carboxytherapy was expressed in a decrease in hyperglycemia, thirst, symptoms of polyuria, itching of the skin, and weakness [40]. Dry carbonic baths stimulate antistress systems, eliminate the imbalance of autonomic regulation and increase the nonspecific resistance and adaptive capabilities of the body, which is especially important for patients with discirculatory encephalopathy due to the small vessels impairment in diabetes mellitus [41].

Consequently, carbon dioxide baths have a large arsenal of metabolic effects that have a universal normalizing effect on the course of pathological processes in diabetes.

Clinical trials have been carried out to confirm the effectiveness of carboxytherapy in the treatment of diabetic foot [42]. Thus, a study was conducted at Al-Ahliyya Amman University, Jordan to assess the condition of patients with diabetes mellitus and diabetic foot syndrome. Daily sessions of injectable carboxytherapy were conducted. The effect of CO_2 therapy on diabetic foot syndrome was assessed using a Doppler study of the state of blood vessels. The effectiveness of CO_2 therapy was taken into account in terms of blood flow to the peripheral vessels of the legs, the size of the ulcerative region, the degree of blood supply to the ulcerated area, tissue color, as well as the patient's subjective sensations in the foot (Table. 2).

After carrying out daily sessions of carboxytherapy for two weeks, there was an improvement in blood flow in the area of the affected foot and skin color, a decrease in pain due to improved oxygenation of tissues, the occurrence of hypercapnia, which led to an increase in oxygen exchange between hemoglobin of blood and myoglobin of muscles of peripheral tissues, expansion of arteries in skin and muscles by lowering the pH and other effects of carboxytherapy [14, 43]. Carbon dioxide therapy promotes an increase in oxygen exchange between blood hemoglobin and myoglobin of peripheral tissues, causes a change in the tone of arteries in the skin and muscles, which expand due to a decrease in blood pH and the release of growth factors for angiogenesis. The change in pH makes hemoglobin a more efficient transporter of O_2 [15]

When analyzing the data obtained during the observation, it was noted that the introduction ofCO_2 caused the release of endothelial growth factor to improve angiogenesis and allowed increased tissue oxygenation [43]. Due to the antibacterial properties of CO_2, the development of aerobic flora in the affected area has been reduced. The improvement of blood circulation in the tissues of the lower extremities was evidenced by positive changes in skin color in the ulcer area and the healing of foot ulcers. The subjective sensations of patients with diabetic foot syndrome during CO_2 therapy also improved due to the anti-inflammatory, antioxidant, and analgesic effects of CO_2 [20]. The latter was associated with the effect of CO_2 on the enhancement of endorphin synthesis, stimulation of afferent innervation (Zakharyin-Ged zones, trigger points), which accordingly, caused a reflex efferent reaction to the segmented organs in the central nervous system. As a result of these effects of carboxytherapy, there was a decrease in pain sensitivity in the area of hyperalgia (diabetic ulcer) [45].

Thus, the analyzed data indicate the rationality of the use of carboxytherapy as an alternative off lable method for the treatment of diabetes mellitus and its complications.

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Table 1. Hemodynamic parameters of patients with diabetes mellitus
before and after a course of carboxytherapy

Indicators		Control (DM)	DM + Ozone therapy	DM + CO_2 -baths
Heart rate, beats/min	before treatment	87.9 ± 1.6	88.6 ± 1.9	88.6 ± 2.0
	after the treatment	86.1 ± 1.8	84.4 ± 2.2*	82.3 ± 2.5*
SAP, mmHg	before treatment	153.1 ± 2.9	153.4 ± 3.2	152.9 ± 3.0
	after the treatment	149.2 ± 3.1	144.5 ± 2.7*	141.2 ± 3.4 **
DAP, mmHg	before treatment	93.5 ± 2.1	94.2 ± 2.6	94.2 ± 3.0
	after the treatment	90.7 ± 2.3	88.6 ± 2.9 *	86.6 ± 2.8 *

Notes:
** - significance of indicators ($p \leq 0.05$) relative to the control group;*
*** - significance of indicators ($p \leq 0.05$) of comparison groups relative to each other*

Table 2. *Results of parameters measurement before and after sessions of carboxytherapy in the treatment of diabetic foot*

Parameters		Value
Doppler study, mm (vascular lumen width)	before	*9.81 ± 1.11*
	after	*13.77 ± 1.01*
The size of the ulcerative area, cm	before	*3.18 ± 0.40*
	after	*3.00 ± 0.38*
Skin color, points (0 - cyanosis, 10 - hyperemia)	before	*4.18 ± 0.17*
	after	*3.36 ± 0.27*
Subjective sensations of the patient, points	before	*4.36 ± 0.15*
	after	*3.45 ± 0.23*

Figure 1. *Video capillaroscopy before and after using carbon dioxide therapy*

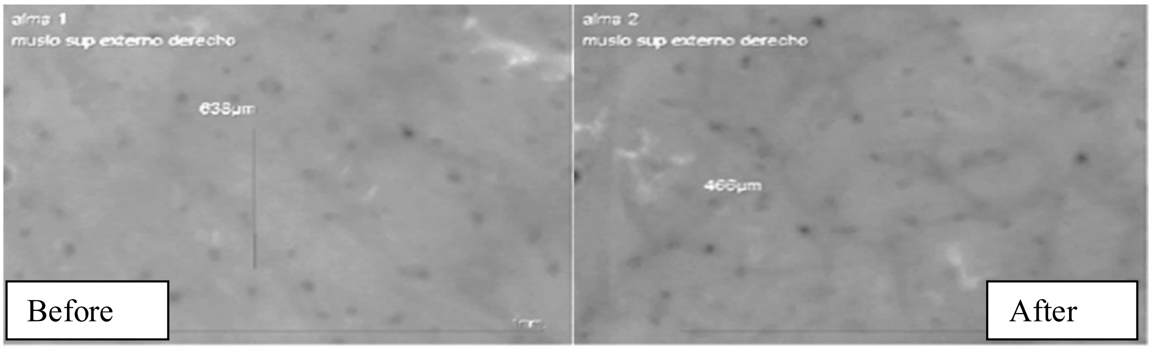

Fig. 1.