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Hyperbaric Oxygen Therapy and Vascular Complications in Diabetes Mellitus

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Abstract

Vascular complications in patients with diabetes mellitus (DM) are common. Since impaired oxygen balance in plasma plays an important role in the pathogenesis of chronic DM-associated complications, the administration of hyperbaric oxygen therapy (HBOT) has been recommended to influence development of vascular complications. Hyperbaric oxygen therapy involves inhalation of 100% oxygen under elevated pressure from 1.6 to 2.8 absolute atmospheres in hyperbaric chambers. Hyperbaric oxygen therapy increases plasma oxygen solubility, contributing to better oxygen diffusion to distant tissues and preservation of the viability of tissues reversibly damaged by atherosclerosis-induced ischemia, along with microcirculation restoration. Hyperbaric oxygen therapy exerts antiatherogenic, antioxidant, and cardioprotective effects by altering the level and composition of plasma fatty acids and also by promoting signal transduction through membranes, which are impaired by hyperglycemia and hypoxia. In addition, HBOT affects molecules involved in the regulation of nitric oxide synthesis and in that way exerts anti-inflammatory and angiogenic effects in patients with DM. In this review, we explore the recent literature related to the effects of HBOT on DM-related vascular complications.

Keywords

diabetes mellitus, vascular complications, hyperbaric oxygen therapy, fatty acids, nitric oxide

Introduction

The trend of an increase in the number of patients with diabetes mellitus (DM) is continuing.[1] The medical and economic burden of DM is not only associated with hyperglycemia management but also with the management of DM-related complications.[2] Most of the chronic DM-associated complications are vascular.[3] The primary prevention of such complications has consisted of high-quality hyperglycemia management and administration of treatment, such as antiplatelet and lipid-lowering drugs.[4] If vascular complications are already present, secondary preventive measures (such as intensification of DM and vasculoprotective management) are recommended aiming to stop or delay the deterioration in already existing chronic vascular complications and to delay the development of new ones.[5]

Hyperbaric oxygen therapy (HBOT) could be used as both primary and secondary preventive vascular complication tool but also as an active treatment in some, such as diabetic foot.[6] By further unraveling the mechanisms involved in DM vascular complications, new targets for their prevention and treatment will be defined. This objective is important since vascular complications associated with DM dramatically impact on patients' quality of life and contribute to morbidity and mortality.[5] In this context, the use of HBOT should be further investigated.

Diabetes Mellitus: Etiology and Diagnosis

Etiology

Diabetes mellitus is one of the most common chronic endocrine diseases of the 21st century.[7] It is defined by chronically elevated blood glucose level (hyperglycemia) caused by impaired secretion and/or reduced biological action of insulin, leading to severe disorders in carbohydrate, fat, and protein metabolism.[8] Causes, as well as the mechanism of DM development, are still not fully elucidated. Nowadays, it is considered that interaction between environmental factors (malnutrition, insufficient

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physical activity, infections, toxins, etc) and genetics leads to increased susceptibility for the development of DM type 1 (DMT1; or insulin-dependent DM).[9] According to the latest data, 15% of newly diagnosed patients with DM have close relatives affected by DM.[10] Data from genome-wide association study suggest that >50 gene loci have been associated with the risk of the development of DMT1.[10] A significant number of genes on these loci are expressed in human pancreatic β-cells and have an important role in the response of β-cells to inflammation, immune system activation, and the regulation of β-cells apoptosis in both types of DM.[11-13]

The exact time of DM onset cannot be determined precisely due to natural history of the disease and the fact that DM may begin many years before its clinical manifestation. The clinical signs of the DMT1 occur when pancreatic β-cells are damaged rendering it insufficient to maintain euglycemic levels.[9] Data from numerous studies indicate that immune system activation is one of the key events in the pathogenesis of DMT1 due to the infiltration of mononuclear cells, such as macrophages and T-lymphocytes in the Langerhans islets (insulitis).[14,15] Inflammatory cytokines secreted from immune cells, together with growth factors and reactive oxygen species (ROS), contribute to the accumulation and activation of immune cells (self-stimulation of the immune system) and initiate apoptosis of β-cells.[16,17] Damaged β-cells further release antigens against which the immune system produces specific antibodies.[18] Biomarkers of autoimmune β-cells destruction are circulating antibodies, such as islet cells antibodies, insulin autoantibodies, glutamic acid decarboxylase, zinc transporter eight antibodies as well as tyrosine phosphatase antibodies in islets of Langerhans.[19] In patients with DMT1, lifelong insulin therapy is necessary. Treatment of DMT1 consists of human insulin or insulin analog therapy and can be administered via 2 routes: inhalation and subcutaneous, such as pen injection as conventional regimen (1 to 2 single doses/d) or as intensive insulin regimen (≥3 single doses/d) and by using a continuous subcutaneous insulin infusion via an external transfer pump.[20] In individual cases, DMT1 treatment also involves endocrine pancreas transplantation usually performed simultaneously with kidney transplantation. Transplantation of the pancreas could improve renal function, slow down the process of atherosclerosis, and consequently inhibit the progression of microangiopathies and polyneuropathies.[21]

Type 2 DM (DMT2) accounts for about 90% of patients with DM, previously referred to as non-insulin-dependent DM or adult-onset DM.[22] Hereditary factors, insufficient physical activity, and overweight alter insulin sensitivity and secretion lead to insulin resistance (IR) and the development of DMT2.[23,24] At the initial stage of the DMT2 pathogenesis, pancreatic β-cells are capable to maintain glucose homeostasis by compensatory hyperinsulinemia, although there is an underlying defect in insulin secretion. Patients with DMT2 develop hyperglycemia gradually, and at earlier stages, it is often not severe enough for the patient to notice some of the classic symptoms of DMT2.[23] In the latter stage, compensatory hyperinsulinemia becomes insufficient to maintain normal glucose levels, and IR becomes more severe, which increases the production of fatty acids (FA) in visceral fat, increases glycogenolysis, and gluconeogenesis in the liver, contributing to hyperglycemia.[25,26] Moreover, the chronic inflammatory state in DMT2 is characterized by increased production of cytokines, which induce apoptosis of β-cells.[27] In addition, autoimmune aspects are also recognized in DMT2, based on the presence of circulating autoantibodies against β-cells, self-reactive T cells, and the glucose-lowering efficacy of some immunomodulatory therapies in DMT2.[19] Treatment of DMT2 includes oral anti-hyperglycemic therapy as well as the administration of anti-platelet, lipid-lowering, and antihypertensive drugs.[24,28] Although patients with DMT2 do not need insulin treatment initially, in cases where dietary control and lifestyle modifications followed by oral anti-hyperglycemic agents fail to maintain glucose homeostasis, insulin treatment becomes necessary.[29,30]

Diagnosis

According to the World Health Organization and the International Diabetes Federation recommendations, standard methods for the diagnosis of DM are a measurement of the fasting glycemia level and the oral glucose tolerance test (OGTT).[31] Also, the international expert committee included the level of glycosylated hemoglobin A_{1c} (HbA_{1c}) ≥6.5% as the criterion for the diagnosis of suboptimal glycemic profile.[31,32] Glycosylated hemoglobin A_{1c} presents a reliable measure of glycaemia because it reflects an average level of glycemia during 2 to 3 months.[33] Also, HbA_{1c} shows a great affinity for oxygen and decreases the ability of Hb for oxygen release, causing hypoxia in peripheral tissues and contribute to the development of DM complications.[34] Data from the Diabetes Complications and Control Trial (DCCT) and United Kingdom Prospective Diabetes Study (UKPDS) suggest that HbA_{1c} level ≥7% increases the risk of developing microvascular and macrovascular complications in patients with DM.[35,36]

According to the American Diabetes Association, diagnostic criteria for DM include the following[37]: (1) level of HbA_{1c} compared with total Hb ≥6.5%, (2) fasting glycemia ≥7.0 mmol/L (270.7 mg/dL); (3) level of glycemia during OGTT (75 g glucose in 120 minutes) ≥11.1 mmol/L (429.24 mg/dL), or (4) a random level of glycemia ≥11.1 mmol/L (429.24 mg/dL) in patients with typical DM symptoms such as polyuria, polydipsia, and weight loss.

Vascular Complications in DM

The development of vascular complications in patients with DM is a complex process. Numerous biochemical changes arise from abnormalities in glucose metabolism that could lead to injury of small blood vessels (arterioles, capillaries, and venules) and subsequent tissue hypoxia.[38,39] Small blood vessels have an essential role in the maintenance of normal blood pressure and membrane permeability.[40] Diabetes mellitus causes pathophysiological changes in small blood vessels,

thereby affecting membranes of arterioles and capillaries in the glomeruli, retina, myocardium, and muscles, which lead to altered regulation of regional blood flow, insufficient tissue perfusion, increased membrane permeability as well as the altered thickness of the blood vessel wall.[41] The altered endothelial function of small blood vessels and an impaired vasomotor function of resistance vessels induced by DM could subsequently result in the development of microangiopathy, tissue hypoxia, and ischemic lesions.[38,42] Diabetes mellitus has been linked with carotid artery pathology and may have a negative influence on the outcome of surgical procedures required for these patients.[43] Whether modifying risk factors (eg, glycemia and dyslipidemia) in patients with DM can improve the outcomes of these procedures needs to be established. Furthermore, DM is a risk factor for contrast-induced acute kidney injury.[44] The latter should be recorded in patients with DM undergoing carotid stenting since it can influence both short- and long-term outcomes.[43] From a pathophysiological perspective, functional changes in the carotid artery may precede morphological ones.[43,45,46]

In prolonged untreated DM, hyperglycemia leads to major glucose pathways overloading and nonenzymatic glycosylation of various substrates, which contribute to increased oxygen consumption in mitochondria, production of ROS, and subsequently to hypoxia.[47] The state of hypoxia further impair intracellular oxidative processes and decrease cell function by activating alternative pathways of glucose metabolism, such as polyol, protein kinase C, and hexosamine pathway as well as a pathway of excessive accumulation of advanced glycation end product.[48] The activation of alternative pathways of glucose metabolism leads to an increase of oxidative stress and subsequently to the endothelial dysfunction and acceleration of atherosclerosis.[47,48] Accelerated atherosclerosis in patients with DM is clinically manifested as a decreased function of the tissues and organs caused by insufficient vascularization (ischemia). Vascular complications resulted from deleterious effects of hyperglycemia and hypoxia in DM are divided into microvascular complications: diabetic retinopathy, nephropathy and polyneuropathy, and macrovascular complications: coronary artery disease, cerebrovascular disease, and peripheral arterial disease.[48]

The occurrence of vascular complications is related to the level of glycemia in patients with DM.[3,49] Chawla et al observed a positive correlation between inadequate glycemic control and the development of diabetic retinopathy and nephropathy in patients with DM.[3] Data from clinical studies also show that developed microvascular complications, especially diabetic retinopathy and nephropathy, are significantly associated with an increased risk of accelerated atherosclerosis that subsequently culminates in cardiovascular and cerebrovascular disorder as well as premature death.[50,51] Myocardial infarction is one of the leading causes of morbidity and mortality among patients with DM.[28,52] Additionally, the risk of the development of cerebral infarction and peripheral arterial disease is 2- to 4-fold higher in patients with DM compared to a population without DM.[53]

Risk Factors for the Development of Vascular Complications in Patients With DM

Genetic predisposition and familial history of DM are important risk factors for the development of vascular complications in patients with DM.[54,55] Researchers from the DCCT and the study of epidemiology of diabetes interventions and complications have identified numerous genetic variations located at loci 3q, 7q, and 18q, which are considered to be responsible for the increase in the risk of the development of retinopathy and nephropathy in patients with DM. This evidence supports a genetic basis for the onset of DM and vascular complications.[54] Also, age and duration of DM $\geq$10 years affect the development of vascular complications.[55] Older persons with DM developed at an early age have a greater risk of macrovascular complications, especially women.[56] On the other hand, the development of microvascular complications depends on the length of DM duration regardless of the age of life at which DM occurred, and every 5-year prolongation of DM duration increases the risk of developing microvascular complications by 28%.[55]

Among well-known risk factors for the onset of vascular complications are hypertension (HT), obesity, IR, dyslipidemia, hyperhomocysteinemia, and inflammation.[51,57-59] As a consequence of HT, blood vessels become less elastic with time, leading to the thickening of the artery wall and the formation of atherosclerotic plaques.[57] Hypertension also causes remodeling of small blood vessels and decreases the number and length of blood vessels, thus reducing blood flow and tissue nutrition that impair the integrity and function of cells and tissues.[60]

Results from a recent study indicate a significant increase in the prevalence of patients with DM,[61] suggesting that obesity plays an important role in the pathogenesis of DMT1 and DMT2.[62,63] Insulin resistance associated with dyslipidemia, inflammation, and HT lead to earlier onset of DM and accelerated atherosclerosis.[24,64,65] The development of atherosclerosis further causes peripheral arterial disease in patients with DM by narrowing or obstructing the lumen of arteries and consequently reducing blood flow and tissue nutrition, which over time, diminishes the functional capacity of the extremities.[66] The process of accelerated atherosclerosis, before the clinical manifestation of DM, is also caused by changes in lipid concentration and composition,[24,67] which is reflected in the increased incidence of morbidity and mortality caused by various cardiovascular complications.[68] An independent risk factor for the development of numerous vascular complications in DM is the elevated serum homocysteine (Hcy) levels, formed during the metabolism of the essential amino acid methionine in the methylation cycle.[69] Several studies show that the Hcy level positively correlates with IR development and increases the generation of ROS, as well as oxidation of low-density lipoprotein, which leads to endothelial dysfunction and contribute to the development of HT, atherosclerosis, and vascular complications in DM.[70-72]

Table 1. Positive Effects of HBOT in Human Studies and Animal Models.

Effects	Model	References
↑Systemic hemodynamics and microcirculation	Rat ischemic skeletal muscle	96
↑Angiogenesis	Irradiated rabbit	95
↑Antioxidant protection	Multiple sclerosis patients	96
↑Fibroblast proliferation and collagen synthesis	Rat diabetic wounds	97
↓Inflammation	Rat ischemic wounds, diabetic patients with vascular complications	100,101
↓Atherosclerotic plaque area	Diabetic foot patients	89
↓Apoptosis of the pancreatic β-cells	Rat ischemic wounds	100,104
↓Leukocyte adhesion	Nonobese diabetic mice	103
↓Bactericidal activity of leukocytes	Healthy human blood-derived monocyte–macrophages	104
↓Endothelial dysfunction	Patients undergoing coronary stent implantation	105

Abbreviations: HBOT, hyperbaric oxygen therapy; ↑, increase, ↓ decrease.

Inflammation plays an important role in the development of IR, atherosclerosis, and vascular complications in patients with DMT2.[73-75] Current knowledge indicates that disorders of glucose and fat metabolism in DM can be responsible for the stimulation of the inflammatory processes.[76,77] Hyperglycemia and dyslipidemia stimulate the synthesis of inflammatory cytokines that can inhibit pancreatic β-cell function and reduce the activation of signaling molecules involved in the molecular mechanism of insulin action.[78,79] Increased cytokine expression induces the synthesis of acute-phase inflammation proteins in the liver, including C-reactive protein (CRP), which is an important marker of inflammation, but also an indicator of microvascular and macrovascular complications in DM.[80,81] Results from numerous studies demonstrate a positive relationship between elevated CRP serum concentration and HbA_{1c} level[82] as well as risk of diabetes development,[83,84] atherosclerosis, and IR.[85,86]

Hyperbaric Oxygen Therapy and Treatment of Vascular Complications in DM

Today, HBOT has been proven as an effective noninvasive therapy in the treatment of ischemic lesions and vascular complications caused by DM.[87] The main principle of this treatment is 100% O_2 inhalation under elevated atmospheric pressure from 1.6 to 2.8 ATA in hyperbaric chambers.[88] Given that impaired plasma oxygen balance plays an important role in the pathogenesis of DM and that insulin therapy does not always lead to adequate daily glycemic control,[89] additional therapies, such as HBOT, are needed to slow the onset and development of vascular complications in patients with DM. Hyperbaric oxygen therapy exerts a beneficial effect in the treatment of numerous ischemic conditions accompanying DM, such as cerebral ischemia, peripheral artery disease, gangrenous wounds (diabetic foot), ischemia and reperfusion injury, central retinal artery occlusion, and other vascular complications.[90,91]

Indications for the application of HBOT, besides in patients with DM, include decompression sickness, delayed radiation damage, refractory osteomyelitis, thermal burns, carbon monoxide poisoning, and arterial gas embolism.[92,93] Hyperbaric oxygen therapy is not recommended for people with lung disease, respiratory and sinus infections, ear infections, fever, and so on. Depending on the dose and duration of HBOT, as well as the patient's condition, exposure to HBOT may lead to oxidative toxicity in the lungs and nervous system, acidosis, and hemolysis.[94]

Hyperbaric oxygen therapy triggers a number of molecular mechanisms in the body that lead to positive therapeutic effects in patients with DM and vascular complications (Table 1). Numerous studies have shown that HBOT improves systemic hemodynamics and microcirculation,[95,96] accelerates angiogenesis,[97] stimulates the antioxidant protection,[98] increases fibroblast proliferation and collagen synthesis,[99] inhibits inflammation,[100,101] exerts antiatherogenic effects,[102] and reduces the atherosclerotic plaque area.[91] Increase in the pO_2 that remains for 4 to 6 hours after HBOT, provides mitochondrial respiration and cell survival in the state of hypoxia,[103] inhibits apoptosis of the pancreatic β-cells,[100,104] reduces leukocyte adhesion,[105] enhances bactericidal activity of leukocytes,[106] and reduces endothelial dysfunction,[107] thereby contributing to the reduction in inflammation and following vascular complications in patients with DM.[91]

Chronic hyperglycemia is linked with the abnormal synthesis of nitric oxide (NO), which is associated with DM-related vascular complications.[108,109] Hyperbaric oxygen therapy can differently regulate the synthesis of NO in patients with DM and vascular complications by affecting the activity of NO synthase (NOS). Hyperbaric oxygen therapy increases NO production by endothelial NOS and NO levels in plasma and ischemic tissue and improves vascular dysfunction, leading to wound healing and angiogenesis.[110-112] Conversely, results from animal and human studies show that HBOT may decrease NO synthesis by downregulating inducible NOS (iNOS) and neuronal NOS and thereby reduce inflammation and extent of atherosclerotic lesions.[101,113-115] Saluja et al emphasized that there was a direct relationship between NO synthesized by iNOS and the early onset of diabetic retinopathy.[116] We have previously shown that HBOT causes downregulation of iNOS expression and activity via signaling pathways of protein kinase B (Akt), extracellular signal-regulated kinases, and nuclear factor kappa B in patients with DMT2 and thereby

exerting anti-inflammatory effects.[101] Also, HBOT decreases the level of inflammatory markers such as cytokines (interleukin 1 and tumor necrosis factor α),[113,105] C-reactive protein,[101,117] free fatty acid (FFA), and NO[101,102] in the blood of patients with DM. In addition, HBOT improves glucose metabolism in patients with DM and vascular complications, most probably by increasing insulin sensitivity[118-120] via upregulation of peroxisome proliferator-activated receptor gamma (PPAR-γ) expression[121,122] as well as increase in adiponectin level, which further regulates the expression of glucose transporter 4 by Akt and mediate glucose uptake.[123] Hyperbaric oxygen therapy exerts a beneficial effect on glucose metabolism by reducing hypoxia and inflammation, known for the ability to synergistically inhibit the activity of molecules involved in the insulin signaling cascade.[124]

It is well known that high levels of lipids and FFA in plasma are associated with inadequate glycemic control, and the interaction between FFA and hyperglycemia can lead to oxidative stress, inflammation, atherosclerosis, and increase the risk of vascular complications in DM.[125,126] High level of FFA in plasma and membrane phospholipids impairs the structure, activity and permeability of cell membranes, and cell signaling, thus promoting transcription of various genes such as iNOS gene.[127] Alteration of FFA composition leads to the cell dysfunction and consequently impaired microcirculation leading to tissue hypoxia and vascular complications.[128] Our results show that HBOT exerts anti-inflammatory and antiatherogenic effects by a mechanism involving changes in plasma FA level and composition by lowering plasma levels of pro-inflammatory FA and elevating levels of anti-inflammatory and antiatherogenic n-3 polyunsaturated fatty acids (n-3 PUFA) in plasma of patients with DM, especially docosahexaenoic acid.[102] High level of n-3 PUFA in plasma improves insulin sensitivity and decreases hyperglycemia by the mechanism which involves the binding of n-3 PUFA to membrane receptors such as G-protein-coupled receptor 40 (GPR40) in β-cells and GPR120 in adipocytes as well as activation of peroxisome proliferator-activated receptor alpha (PPAR-α) and PPAR-γ by n-3 PUFA in the liver.[129-132] High levels of n-3 PUFA in plasma and erythrocyte membranes have beneficial effects on glucose and lipid metabolism and are associated with a reduced risk of developing IDDM.[102,133-135] The literature data show that HBOT affects the composition and level of FFA in plasma and cell membranes by inhibiting the hypoxia-induced signaling cascade, which disrupts membrane structure, prevents FA release from cell membranes, reduces ROS synthesis and lipid peroxidation, and affects the activity of enzymes involved in elongation and desaturation FFA.[72,136,137] Hyperbaric oxygen therapy also improves dyslipidemia associated with an increased risk of accelerating the process of atherosclerosis and cardiovascular disease in patients with DM and vascular complications,[63,138,139] which was also shown in our prospective pilot study.[102] Teshigawara et al reported that HBOT regulates lipid metabolism in mice with DM, by increasing expression of enzyme involved in β-oxidation of FA in mitochondria-carnitine palmitoyltransferase 1 (CPT-1), as well as expression of PPARα and peroxisome proliferator gamma coactivator-1 α, involved in transcription of CPT-1 and regulation of lipid metabolism.[140] All these data together indicate that HBOT is an effective component of the complex treatment of patients with DM and associated microvascular and macrovascular complications.

The Economic Aspect of HBOT

For the past 2 decades, critics have discussed the additional costs of HBOT. Increasing evidence shows that diabetic foot ulcers and vascular complications are a financial burden to patients and health service providers. The annual costs of treating diabetic foot ulcers in the United Kingdom is estimated at more than £225 million.[141] In the United States, the total annual cost of diabetic peripheral neuropathy and its complications was estimated to be between $4.6 and $13.7 billion.[142] A growing number of cost-effectiveness studies are demonstrating that HBOT could benefit many patients and health care budgets through improved clinical efficacy and cost-efficiency in the treatment of specific conditions, especially nonhealing diabetic ulceration of the lower limbs, particularly based on a long-term perspective.[142-144]

Hyperbaric Oxygen Therapy Side Effects

Hyperbaric oxygen therapy remains among the safest therapies used today.[145] Nevertheless, there are side effects associated with HBOT that are self-limiting and potentially could be avoided with adequate risk assessment. One of the most common side effects are middle ear barotrauma, sinus and paranasal barotrauma, an increase in both systolic and diastolic blood pressure, claustrophobia, and hypoglycemia in patients with DM.[145,146] However, clinically relevant hypoglycemia during HBOT is not common. Hyperbaric oxygen therapy may induce oxygen toxicity, most commonly as CNS seizure, arterial gas embolism, and pulmonary barotrauma.[147,148] An oxygen toxicity seizure is relatively rare at typical clinical treatment pressures (2-3 ATA).[145] Ocular side effects such as hyperoxic myopia (reversible), cataracts, and retrolental fibroplasia are rare but should be monitored. Adjustment of the treatment protocol to decrease maximum pressure and provide additional air brakes, and pretreatment screening may be undertaken to avoid HBOT side effects.

Conclusions

The dramatic increase in the incidence of DM and accompanied diseases, such as HT, led to a subsequent increase in the number of patients with associated vascular complications. The pathophysiology of DM and associated vascular complications is complex, and its treatment requires a multidisciplinary approach. Hence, DM complications have become widespread and are a public health-care problem. As DM vasculopathy is rarely localized, but predominantly diffuse and extended to microcirculation, these characteristics frequently limit the

performance of invasive procedures. One of the noninvasive therapies used to treat vascular complications and ischemic wounds caused by DM is HBOT.[87] Hyperbaric oxygen therapy triggers many molecular mechanisms that may lead to positive therapeutic effects in DM treatment, mainly by exerting a positive influence on glucose and lipid metabolism, anti-inflammatory, and antiatherogenic effects.[101,102,124,137] The improvement in patients with DM after HBOT significantly contributes to reduced vascular complications.

The article reviewed the molecular mechanisms and practical issues of HBOT. Despite its maybe less-frequent use in DM treatment, this therapeutic procedure with coadministered drugs (statins, acetylsalicylic acid, NO-donors) significantly improves quality of life in selected groups of patients. Future studies related to the determination of both frequency and dose of HBOT with the maximum efficiency and minimum side effects during the treatment of micro- and macrovascular complications of patients with DM are desirable due to the therapeutic potential of HBOT. We could expect very soon that equipment modernization and technology innovations should enable safe and widespread HBOT use with less side effects. The administration of HBOT on selected body parts or its use at the patient's home may be the future perspective of HBOT.

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