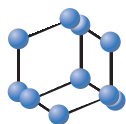
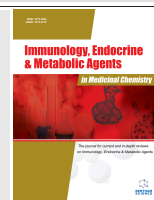


RESEARCH ARTICLE

BENTHAM
SCIENCE

Therapeutic Apheresis in Metabolic Syndrome



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Abstract: Background: The metabolic syndrome unites three pathologies of the person – obesity, arterial hypertension and diabetes. In recent years the progressing of such distribution covering from 2.5% to 3.8% of the population with increase twice each 10-15 years is noted. Even at maintenance of level of sugar at diabetes accumulation of the secondary metabolites breaking small vessels isn't excluded. At the same time many life-endangering complications develop.

Objective: To identify the possibilities of plasmapheresis in the prevention and treatment of complications of metabolic syndrome.

Method: Analysis of the world literature data on complications of metabolic syndrome and methods of their treatment.

Results: At metabolic syndrome the frequency of strokes and myocardial infarctions there is twice more often than in population. For 5-9 years the general life expectancy decreases. Disorders of microcirculation at diabetes lead to a retinopathy with total loss of sight, a nephropathy from the outcome in a renal failure, to polyneuropathy and diabetic foot syndrome with high risk of high level amputations of the lower extremities. At the same time medicamentous therapy is not able to prevent such complications and almost only way of removal of these pathological metabolites is therapeutic apheresis, mainly the plasmapheresis. Data from our own studies confirm the effectiveness of such tactics.

Conclusion: Plasmapheresis has to be applied not only to the correction of already critical conditions, but also to their prevention.

Keywords: Metabolic syndrome, diabetes, diabetic foot, diabetic nephropathy, retinopathy, plasmapheresis.

1. INTRODUCTION

Metabolic syndrome or insulin resistance factor is clearly associated not only with the impairment of glucose tolerance and development of type II diabetes, but also with dyslipidemia with visceral type of adiposis, hypertension as well as with prothrombotic state. Moreover, metabolic syndrome is the early stage of atherosclerosis development, diabetes mellitus type II, and endothelial

dysfunction [1]. Its prevalence is from 2.5% to 3.8% of population with twofold increase in morbidity each 10-15 years. Among subjects over 70 years old diabetes mellitus appears to occur in 10% of cases. If in the end of the XX century there have been 135 million suffering from diabetes mellitus worldwide, by 2005 the amount will have increased up to 300 million [2, 3].

Accompanied by the accumulation of various pathological products infringing microcirculation and blood flow in the vessels of the heart, brain, kidney, eyes and peripheral arteries. Drug therapy is not always able to eliminate such complications

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and to the forefront apheresis therapy mainly plasmapheresis [4].

With the development of obesity there are a number of interdependent processes. Thus, adipocytes contribute to the fatty acids output from chylomicrons, which, in turn, increases the yield of triglycerides of adipocytes. Chylomicrons affect endothelial cells and their triglycerides are rapidly hydrolyzed into lipoprotein lipase. Developing dislipoproteinemia with accumulation of low density lipoprotein, apo-B, triglycerides, non-esterified fatty acids contributes to the development of insulin resistance, and that closes the vicious circle. At the same time, it must be kept in mind that abdominal obesity is associated with insulin resistance with high risk of metabolic syndrome more, than general obesity [5].

In this case, on the first stage, while maintaining β -cells, overproduction of insulin is also possible to compensate insulin resistance [6]. There are evidences showing that hyperinsulinemia, associated with impaired lipid metabolism, in turn, also contributes both to high triglyceride levels (over 2.5 mmol/liter) and high density lipoproteins decrease with increasing tendency to arterial hypertension. Hyperinsulinemia is also associated with the increased thickness of the arterial wall [7, 8]. Higher levels of cholesterol and triglycerides also create favorable conditions for the development of cholelithiasis [9].

Obesity also contributes to the accumulation of "nonfat" tissues lipids, leading to its degeneration. This refers to the development of fatty liver and even of liver cirrhosis [10-13]. Free fatty acids along with triglycerides, accumulate in the parenchymal cells of various organs, including cardiomyocytes, hepatocytes, β -cells of the pancreas, that results in chronic dysfunction of beta-cells [14].

In patients with cardiovascular diseases, coronary artery disease and myocardial infarction there is an increased level of "1 plasminogen activator inhibitor" (PAI-1). In syndrome of insulin resistance associated with obesity this level also increases because PAI-1 is formed and secreted from adipocytes, - mostly by visceral rather than subcutaneous ones. Level of PAI-1 is also increased in patients with Cushing's syndrome and receiving glucocorticosteroids [15].

It is remarkable that the disorders of vascular reactivity and appearance of biochemical markers of endothelial cell activation (endothelin-1, von Willebrand factor, soluble cell adhesion molecules and endothelial cell-cell adhesion) occur very early in individuals at risk of developing diabetes type II, even at the stage of normal glucose tolerance and absence of insulin resistance [16].

In those with the "central" type of obesity, high levels of total cholesterol, triglycerides and very low density lipoproteins, high blood pressure the risk of vascular lesions arises even in the phase of "pre-diabetic" (less than 6.1 mmol/l) glucose level [17]. At the same time, as in pre-diabetic phase and when diabetes is being diagnosed, it is often possible to identify the presence of coronary heart disease already [8]. The study of 5522 diabetic patients, aged 55 years old and older, revealed a clear correlation between the metabolic syndrome and thromboembolism of the deep veins as well as of the lung vessels with a frequency of 0.30-0.40 for the 5-year observation period [18].

In metabolic syndrome the risk and frequency of ischemic strokes increases. At the same time, in such cases there are about 60% of patients with metabolic syndrome, while there are about 20% of such patients among the other neurologic patients. Women, suffering from a metabolic syndrome, are especially subjected to ischemic strokes [19, 20]. The same can be told about risk of coronary heart disease, especially in the senior age group which increases twofold in men and fivefold in women, suffering from metabolic syndrome [21].

On the other hand, in metabolic syndrome men tend more often to develop hypogonadism with sexual and erectile dysfunctions [22-25].

Microcirculatory disorders in diabetes are aggravated by higher blood viscosity due to an increase in fibrinogen, fibronectin, von Willebrand factor and C-reactive protein [26].

Nowadays, the prevalence of metabolic syndrome takes on the character of an epidemics, especially when it starts in childhood, which further leads to the earlier development of atherosclerosis [6, 12]. S.W. Ryder (2007) [27] also reports that in the United States 1/3 of adults suffer from obesity, and for the last 20-30 years there is a 2-3 fold increase in the number of children who are overweight. The higher risk of cardiovascular

disease in diabetes mellitus type II is associated with the accumulation of low-density lipoprotein and triglycerides due to lower high-density lipoproteins, which is the anti-atherogenic factor [28].

One of the causes of VLDL hyperproduction is both insulin resistance and reduction of lipoprotein lipase activity against the raised glucose [29]. After coronary bypass operations in patients with hyperglycemia and insulin resistance more intense progression of atherosclerotic lesions of the coronary vessels is observed [30]. Studies have shown a direct correlation of the insulin-dependence level with the increase of peripheral vascular resistance, blood pressure and decrease of blood flow of the peripheral vessels [31]. A significant relationship between the impaired glucose tolerance and vascular dementia has also been found [32]. Diabetes mellitus type II at age of 55 reduces the expected individual life span for about 5 years [33].

However, diabetic patients can develop severe cardiomyopathy associated mostly with disorders of microcirculation in the myocardium than with atheromatous narrowing of the coronary arteries. It has a non-specific functional and morphological changes including: cardiomyocyte hypertrophy, interstitial fibrosis, arteriolar thickening, capillary microaneurysms associated with their network decrease, disturbances of left ventricular diastolic and then systolic function.

The development of such diabetic cardiomyopathy appears multifactorial. Pathogenetic mechanisms include greater density and stiffness with loss of elasticity due to ventricular myocardial fibrosis, microvascular damages, disorders of energy metabolism in the myocardium, structural abnormalities of collagen, contractile proteins and cardiac muscle sarcolemma [34]. At the same time the prevalence of left ventricular diastolic dysfunction can reach 85% [35].

In this syndrome there are more pronounced rises in blood pressure and vascular resistance during stress than in the control group. This hyperreactivity is a marker for future hypertension in normotensive yet, but hyperinsulinemic obese patients. Diabetes mellitus type II and hypertension are often linked. At the age of 45 years, about 40% of these patients have hypertension, and in 75 years – already 60%. Hypertension, in

turn, increases the risk of cardiovascular disease, retinopathy and microalbuminuria in diabetes mellitus type II [36].

It is interesting to note that 53-80% of patients with hemochromatosis develop diabetes type II. Iron is capable of catalyzing free radical stress while free radicals and lipid peroxidation plays a certain role in the etiology of this form of diabetes. Special studies have confirmed the role of iron in the delay the development of diabetes type II [37]. Patients with cystic fibrosis are also predisposed to the development of both diabetes type I and type II. The glucose production by the liver is more intense, as well as in diabetes type II [38].

There is a definite relationship of insulin and triglyceride levels. In patients with diabetes mellitus who are treated without insulin, blood triglyceride concentration increases. Insulin helps reduce triglyceride levels. Most insulin dependent diabetic patients are insulin resistant and may have a compensatory chronic hyperinsulinemia, which increases the production of triglyceride-containing lipoproteins.

These changes may reflect the balance of many activities – from the increasing number of Non-Esterified Fatty Acids (NEFA) prior to the initiation of the intrahepatic processes of Very Low Density Lipoproteins (VLDL) production. Removal of the latter is performed by lipoprotein lipase, which activity also increases blood levels of insulin. However, the degradation triglycerides products are atherogenic, so the growth of such degradation intensity in diabetic patients increases the risk of atherosclerosis. Under these conditions, lipemia after a fatty meal increases the activity both of hepatic lipase and cholesterol esters. These factors also contribute to the formation of small LDL particles – the major atherogenic agents [39, 40].

In recent years it has been shown that TNF- α also affects the metabolism of lipids and glucose. Adipose tissue is an important source of endogenous TNF- α out-turn and the expression of such cytokine increases with obesity, which in turn contributes to the development of insulin resistance in diabetes type II [41]. Elevated levels of ketone bodies promote greater intensity of lipid peroxidation and hydroxyl radicals in the vascular endothelium and in erythrocytes in diabetes type I,

which contributes to the development of vascular complications. Obesity is associated with metabolic lesions in different tissues. In particular, the maintenance of the endotoxin (lipopoly-saccharide) allocated in intestines, that triggers a number of pro-inflammatory and oxidative processes. In this case a kind of "metabolic endotoxemia" occurs [42]. There is a communication of a metabolic syndrome with gout at which the increased level of uric acid promotes also other metabolic disorders with higher mortality [43]. There is a distinct correlation between the metabolic syndrome and psoriasis [44, 45].

Thus, the presence of both immune and metabolic changes in this form of diabetes makes it reasonable to use apheresis therapy at all stages of the disease. Attempts to use drugs against hypercholesterolemia can lead to a number of adverse complications. So, clofibrate effectively reduced content of atherogenic lipids, but in patients with diabetes it increased mortality from non-cardiac diseases. In particular, there was a 68% mortality increased from tumor diseases [46]. Moreover, during the statins treatment of patients with type II diabetes the content of antiatherogenic HDL has decreased more significantly and triglycerides concentration increased to compare with the patients without diabetes [47].

The fact that the diet, drug therapy, insulin allow to keep blood sugar levels, but it does not prevent its oscillation, which leads to a variety of secondary metabolic disorders, mainly vascular. At the same time, one of the reasons of the angiopathy in diabetes is the increase of platelet aggregation, which depends not only on the magnitude of the concentration of sugar in the blood, but from some other pathological products, affecting platelet membrane [48].

Prolonged hyperglycemia leads to glycation of proteins. Glycation of collagen can provoke atherogenesis by receipt of lipoproteins into the extracellular matrix, making it more susceptible to oxidative modification. The end products of the process of proteins glycation promote migration of monocytes and macrophages expression, which is an important mechanism for development of the early stages of atherogenesis. Nonenzymatic glycation end products are one of the toxic factors that determine the development of vascular complications in diabetes. Among them is pyraline,

arising from the interaction of glucose with amino groups of proteins. One of the consequences of its effects is the suppression of phagocytic activity, predisposing to infectious complications, also characteristic to diabetes [49].

Recent studies show that diabetes develops "oxidative stress." Due to the reduction of antioxidant status production of free radicals increases, enzymatic disorders that largely determine the secondary organ complications from diabetes [50]. Even with a normal level of LOW DENSITY LIPO-PROTEIN (LDL) there may be detectable markers of oxidation, such as antibodies to oxidized LDL and LDL-containing immune complexes, which seems a predisposing factor for the development of coronary artery lesions [51].

Observed in the clinic faster progression of coronary artery disease in diabetic patients is largely determined by the higher oxidative modification of lipoproteins on the background of the intensification of lipid peroxidation. However, attempts to improve the condition of vessels using long-term administration of antioxidants (vitamin E) did not lead to the desired result [52].

In diabetes, superoxide production by monocytes increases, which is probably due to hypertriglyceridemia. Susceptible to oxidative modification lipoproteins become immunogenic, resulting in the formation of circulating immune complexes lipoproteins promoting the progression of atherosclerosis as a result of formation of "foam cell" – macrophages engulfing these immune complexes, and catalytic atherogenic immune mechanisms in the walls of the arteries. In addition, there is a relationship of diabetes with increasing tendency to thrombosis in the field of atheromatous lesions. In diabetes, adhesiveness and aggregation of platelets increase, as well as different levels of coagulation factors and tissue plasminogen inhibitors anticoagulant, which does potentially contribute procoagulant state [53].

Occlusive vascular diseases with disorders of both central and peripheral circulations are almost constant and rather severe satellites of diabetes. According to the U.S. National Commission for diabetes, these patients is 25 times more likely to go blind, 17 times more likely to suffer from kidney disease, 5 times more often affected limb gangrene, 2 times more likely – heart disease, and life expectancy is 30% shorter.

Diabetic foot syndrome is the most frequent problem at patients with type 2 diabetes. The syndrome of "diabetic foot" occurs at 15% from 200 million patients with diabetes around the world. In the countries of the West more than 60% of not traumatic amputations are higher - or below a knee is carried out at patients with diabetes [54]. Rather big spread of diabetes is available in the Arab countries where the number of such patients reaches 20,5 million, and the frequency of development of diabetic foot up to 25-31% [55]. At the same time amputation below a knee has been carried out in 72% and above a knee – at 27% of patients with diabetes [56]. In North America frequency of diabetic foot reaches 13.0% (USA) and 14,8% (Canada), and in Belgium – 16.6% [57]. According to data of the International Working Group on Diabetic foot 72,8% have a small risk of development of diabetic foot, but the high risk at the same time is 17,5% [58].

In the USA where about 16 million people have diabetes, 50-60 thousand amputations of extremities are annually produced. And such tendency accrues. So, if in 2005 in the USA there were 1.6 million amputated, then by 2050 their doubling up to 3.6 ml of people is expected [59]. In the cohort research performed in Turku (Finland) during 1998-2002 the rate of amputations both above- and below the knee, in case of the occlusion diseases of arteries of the lower extremities is 24,1 on 100 000 population for 1 year. In the same research covering France, need of amputations of the lower extremities arose at 15,353 people among whom 7,955 had diabetes. In the latter case the rate of amputations was 378 on 100.000 of population. At the same time need of amputations was 12 times higher in patients with diabetes, than in other cases. And, in 40% of cases amputation was performed in patients, previously having no signs of arterial blood circulation disorders of the lower extremities; so, the main reason for the amputation was diabetes and polyneuropathy [60].

Often there is the development of "diabetic" gangrene of the distal segments of the lower extremities. There are subjective complaints of body aches and muscle pain. In the pathogenesis of these disorders the deposition of sorbitol in the peripheral nerves plays a key role along with the activation of the so-called graft polyol that reduces intraneural blood flow and leads to chronic

hypoxia with functional and structural changes in the nerve trunks. There are also conditions for segmental demyelination of the nerve fibers associated with slowing-down of the neural excitation speed.

The formed trophic ulcers, as a rule, don't tend to healing, progress and inevitably lead to amputation not only feet, but also shins, and is frequent also hips. At the same time more than a half of such patients within the next 5 years have a need of amputation and a contralateral extremity.

Accession of an infection and gangrene is often resulted at the same time in need of amputation [61-64]. Septic complications at the same time are also a frequent cause of death after operations [65].

In the presence of diabetic ulcers of the lower extremities the risk of mortality within 5 years fluctuates from 43% to 55% and reaches 74% for the patients, who have already undergone amputations. Cardiovascular diseases at the same time are the main reasons for death [66]. And, in the next 10 months mortality in the patients who have already undergone high amputations is much higher, than after the sparing amputations [67].

Repeated amputation was required in 34% of the amputated patients. Annual mortality in this group (210 patients) was 52%, and the general mortality for this period was 80% [68]. The need of repeated amputation arose from 23% to 60.7% of patients in the next 3 years. And, reamputation of a counterlateral extremity was carried out more often than the ipsilateral one [69]. From 3565 patients within a year repeated amputation was required in 26%, and more than 30% of them have died. The general costs of treatment of such patients in the USA have made 4.3 billion dollars [70]. In total in the USA for 2007 17.5 million patients with diabetes have been registered, and the general costs of their treatment have made 174 billion dollars [71].

Necrotic processes of the lower extremities in patients with diabetes can be limited to hypodermic cellulose, development of the deeper tissues and even muscular necrosis. In such cases the need of high amputation arises from 7.3% to 20.9% and even 53.2%, respectively [72]. High amputations were necessary even after the sparing

amputations of foot in cases of activation of soft tissues inflammation or osteomyelitis [73].

Operations for revascularization (peripheral angioplasty or artificial vascular prosthesis) allow to postpone amputations in the syndrome of diabetic foot, however, when it is impossible or isn't effective, indications for amputation arise much more often [74]. In such cases high amputations were necessary in 13.4% of patients, and later in 86.2% of cases they have been carried out after peripheral angioplasty, to 21.1% - after vascular shunting and to 59.2% - in group of patients who hadn't undergone operations for revascularization. At the same time, restenosis have developed in 16.7% of patients, thromboses of shunts – in 6.4% and a recurrence of ulcers – in 12.6% of patients. Critical ischemia of the counterlateral extremity has developed in 39.9% of patients and high amputation was required in 6.7% of them. For the four-year period of observations 49.82% of these patients have died, mainly because of coronary insufficiency [75]. It should be noted that operations of revascularization are more effective in non-diabetic occlusion vessels damages of the lower extremities [76].

The risk of coronary lesions in diabetes is 10-20 times higher and lethal outcome after myocardial infarction in these patients is 2 times higher than those without diabetes [77, 78]. Coronary balloon angioplasty in patients with diabetes carries a greater risk of restenosis and mortality [79]. The increased risk of shunts occlusion increases the need for reoperation of the coronary vessels [80]. Diabetic patients also can have cerebral circulatory disorders, progressing as the disease develops.

Diabetic retinopathy results in irreversible loss of vision. Diabetes generally is the leading cause of blindness among working-age population. In the United States the number of newly blinded patients with diabetic retinopathy increased by 8,000 people, and in Germany as a result of diabetic retinopathy blindness rate reaches 2.01 per 100,000 of population [81]. The changes of the retina at different time from the onset of diabetes are found in 98.8% of cases [82].

At the same time there is also proliferation of vessels according to the chorio-vitreous type of the vitreous body neovascularization discovered as one of the manifestations of proliferative diabetic

retinopathy [83]. In these patients, significantly more than in the control groups autoantibodies to phosphatidyl-ethanolamine were detected [84]. Besides, in these cases the content Vascular Endothelial Growth Factor (VEGF) increases in the intraocular liquid, which in addition to stimulating angiogenesis promotes the increased vascular permeability for plasma proteins output and extra-vasal organization of the fibrin gel. The role of VEGF is considered to be the key in the pathogenesis of diabetic retinopathy [85].

Such patients are advised to take systematic courses of plasmapheresis 2 times a year, which will delay the progression of diabetic retinopathy. Plasmapheresis allows 40.5% of patients to reduce the number of retinal hemorrhages, 85% of patients improve visual acuity with the disappearance of "fog" and "flies" before the eyes, in 14% of patients on 5-7⁰ expand the field of view on the background of improving microcirculation of bulbar conjunctiva with the disappearance of "sludge" syndrome, increase of blood flow and restore its continuity, reduce perivascular edema, a significant reduction in levels of cholesterol, triglycerides, fibrinogen.

Proximal diabetic neuropathy, accompanied by severe pain due to inflammatory lesions of the nerves in patients with insulin dependent diabetes mellitus type II at age over 50. Severe pain is not always amenable to steroid and cytostatic therapy [86]. This symmetrical sensory neuropathy associated with a range of structural changes in the peripheral nerves, including axonal degeneration, demyelination para-nodal with loss of myelinated fibers. The latter is possible due to the withering away of the distal axons as a result of phosphorylation of proteins [87].

Upcoming polyneuropathy is accompanied by disturbances of both motor and sensory nerve fibers, as well as elements of the autonomic system. Motor neuropathy is a cause of muscle weakness, atrophy and paresis. Sensory neuropathy leads to weaken of the "watchdog" sensitivity to pain, compression and of thermal damage. Therefore minor injuries remain unnoticed. The patient does not respond to prolonged compression, even footwear that breaks the power of individual sections of the lower limb. Autonomic dysfunction is accompanied by a condition similar to sympathectomy with functional disorders of

microcirculation. All the above mentioned greatly increases the risk of trophic ulcers and gangrene of the foot sections [88]. There is an evidence of a positive effect of plasmapheresis in trophic ulcers of the shins that developed due to the varicose veins dilatation or necrotizing vasculitis.

Diabetic microangiopathy is characterized by impaired capillary basement membrane structure, deposition of LDL in the vascular wall and proliferation of smooth muscle cells there. Related neuropathy contributes to narrowing of arterioles and precapillaries with increasing blood flow through the artery-venous shunts, which further depletes nutrition and gas exchange of peripheral tissues. This is accompanied by increased blood circulation in the skin with its increased surface temperature. Therefore, along with the reduction in sensitivity due to neuropathy there may be a feeling of the heat and burning of the skin and feet, night pain.

There is quite a clear relationship of diabetes and atherosclerosis. When this occurs it causes the formation of autoantibodies (anti-endothelial and "sclerotic") and circulating immune complexes, accumulation of complement and its C3 fraction. If diabetes is accompanied by hypertension the described immunological disorders develop more rapidly and promote atherosclerotic lesions of both peripheral and coronary vessels. At the same time, these immunological changes precede the clinical vascular manifestations [89].

It should be taken into account that one of the pathogenic mechanisms of atherosclerosis development is considered to be low density lipoprotein oxidation, transforming them into a form that is available for capture by macrophages followed by the last generation of cytokines and other biologically active molecules which attract T-cells to increase their adhesion to the endothelium. Hyperglycemia, increasing the prooxidant status, thus, activates atherogenesis with an increased risk of vascular lesions. According to the pathological studies, coronary atherosclerosis in diabetic patients is found 1.7 times more frequently in men and 2.7 times more common in women, cerebral vascular lesions in 2.7 and 3.8 times more likely, and vascular pathology of the lower limbs are in 4 and 6.4 times more, respectively [90]. Diabetics are 2-5 times more likely to die from atherosclerosis than nondiabetics. However, extremely

long atherosclerotic vascular changes occur before the first symptoms of their involvement.

Vascular endothelium in diabetes has a smaller capacity for the vasodilators synthesis and produces more vasoconstrictors and procoagulants. These features exacerbate vascular disorders in diabetes – retinopathy, neuropathy and ischemia. In particular, the vascular endothelium in type II diabetes is less potent of NO synthesis, which promotes local vasoconstriction [91]. Circulatory disorders due to the vascular lumen narrowing are aggravated by the increase of the thrombosis predisposition. The leading role in this process in case of diabetes belongs to the platelet activation along with the release of microparticles and procoagulants. This mechanism plays an important role in the pathogenesis of diabetic nephropathy [92].

There is a certain correlation of metabolic syndrome with psoriasis [44, 45].

Thus, apheresis therapy is pathogenetically justified to treat these secondary vascular disorders in diabetes and metabolic syndrome.

Due to plasmapheresis the aggregation blood cells inducers are removed (fibronectin, von Willebrand factor, fibrinogen, thrombospondin) [93]. Gavrilov *et al.* [94] described the recovery of microcirculatory disorders after courses of plasmapheresis with increasing pain-free walking distance, healing of venous ulcers or amputations suspended with gangrene of the toes. Treatment of nonhealing venous ulcers of "diabetic foot" proved effective also using cascade plasmapheresis (re-apheresis) [95, 96].

It is also supported by our own experience [97, 98]. There were 130 subjects observed having occlusal atherosclerotic conditions of the lower limbs arteries of various geneses and stage of manifestation. Plasmapheresis therapy course (4 sessions of membrane plasmapheresis with laser radiation of the blood) was performed in 34 subjects who had no indications or ability to provide operative revascularization of the lower limbs due to different reasons. In 14 subjects with decompensation of the lower limbs blood circulation, being unable to undergo reconstructive surgeries, plasmapheresis allowed avoiding amputations in 6 of them (43%); 4 (28.5%) of them had to undergo minor amputations and the other 4 subjects had to undergo high

amputations (28.5%). At the same time, in 96 matched subjects the conservative therapy allowed keeping the limbs just in 22 (23%); minor amputations accounted for 11 subjects (11.5%) and 63 subjects (65.5%) had to undergo high amputations of the lower limbs.

There were also 19 subjects with diabetic foot syndrome associated with dramatic ischemia and toes necrosis who had undergone plasmapheresis therapies (4-5 sessions), which allowed eliminating trophic conditions; in case of necrotic process having emerged 6 subjects underwent necrectomy on the level of the demarcation line without mutilating high amputations of the lower limbs. In case of new ischemic and necrosis foci the repeated plasmapheresis therapies also enabled to be limited by the same minor amounts of the necrotized tissues removal.

It can be illustrated by the photographs of the foot initial condition, showing necroses and inflammation irradiating to the adjacent parts of the foot. After plasmapheresis therapy with laser radiation of the blood the microcirculation improved, inflammation subsided, which allowed removing only distal sections of the I, II and III toes of the right foot followed by complete healing (Figs. 1 and 2).



Fig. (1). Patient D, age of 50 years. Diabetic foot. View of foot before an initiation of treatment.

Diabetic nephropathy is left on one of the first places among the causes of ESRD. About half of the diabetic patients in Europe and the U.S. are undergoing hemodialysis. It is the direct toxicity

AFTER COURSE OF MEMBRANE PLASMAPHERESIS



Fig. (2). After course of plasmapheresis and resection of phalanges of 1-2-3 fingers only.

of the elevated glucose concentrations for the nephron structures associated with concomitant lipid disorders (frequent lipid deposits in the kidneys) and subsequent sclerotic changes of mesangium cells, together with deposits of circulating immune complexes that underlies renal parenchymal lesions in diabetes.

In the recent years, attention is paid to the role of "vascular endothelial growth factor" as multi-functional cytokine also known as vascular permeability factor in the development of the micro- and macrovascular diabetic complications, particularly diabetic retinopathy and nephropathy [99]. While the immune complex glomerulo-nephritis is characteristic for diabetes mellitus type I, atherosclerotic nephro-angiosclerosis is typical for diabetes type II.

Due to the increase in vascular permeability in nephropathy the earliest sign of this kind of pathology development is the detection of microalbuminuria (concentration – 30-200 mg/l, or with excretion rate 20-200 micrograms/min), which can be detected in 29-41% of diabetics with the disease duration over 5-7 years [100]. 70% of diabetics also suffer from microalbuminuria and hypertension, which strengthens the relationship between diabetes and nephropathy. In the United States, except for one million patients with diabetes type I and 13 million patients with diabetes mellitus type II, there are still about 6 million people who have this form of diabetes remaining undiagnosed. This is due to not yet

streamlined screening diagnosis of microalbuminuria preceding proteinuria, so it seems reasonable to be measured by radioimmunoassay or enzyme immunoassay techniques capable to measure the levels of 30-200 mg/l [101].

In patients with hyperinsulinemia in diabetes mellitus type II there is a greater risk of developing Alzheimer's disease (7.5% versus 1.4% in those with normal insulin) [102]. Perhaps this is due to the stimulating effect of glycoproteins on the development of neuritic plaques characteristic for Alzheimer's disease [103].

Diabetes mellitus type II is found 10-20 times more often than the insulin dependent diabetes. Cardiovascular diseases – coronary and peripheral vascular disease, stroke are the most common causes of death and morbidity in these patients [17]. Given the high prevalence of type II diabetes and the severity of its complications, it becomes clear that in 2002 in the U.S. has spent more than \$ 90 billion to treat it [27].

In diabetes type II there are marked metabolic changes in these patients being prone to obesity. At the same time the increased concentration of TNF- α , excreted by fat cells when their amount is increased due to the obesity, predisposes the development of insulin resistance [104].

Not only insulin resistance and increased hepatic glucose production, but also β -cells dysfunction plays the key role in the pathogenesis of NIDDM. To some extent it is the hyperglycemia that contributes to the progressive dysfunction of β -cells. Accumulation of lipids and fatty acids in the islets also leads to accelerated apoptosis of β -cells, exacerbating the insulin secretion failure and inability to compensate the insulin resistance. This process is also affected by oxidative stress characteristic for diabetes. It is possible that the reason for this may be the autoantibodies to β -cells found in some patients with diabetes type II [105].

In type II diabetes the islet cells start to secrete amyloid polypeptides, or amylin, which is secreted as well as insulin. Besides, apolipoprotein E (apoE) and heparan sulfate proteoglycan (perlecan) are also secreted. These components are deposited in the structure of the pancreatic islet tissue, which contributes to gradual displacement of β -cells and reduction of insulin secretion. Amyloid deposition is enhanced by apoE and perlekan.

These amyloid deposits in the pancreatic islets are increasing with age and are found in 90% of patients with diabetes mellitus type II and this factor plays the main role in the development of β -cell failure [106].

Assessment of the immune status shows changes of predominantly humoral component associated with the appearance of different special antibodies. Antibodies to insulin also play a pathogenic and sanogenic role, neutralizing its excess in the body in diabetes type II, which can lead even to an insulin deficiency.

Autoantibodies to the islet cell cytoplasm and glutamic acid decarboxylase are also identified in non-insulin dependent diabetes type II. These patients have marked hyperglycemia, and after a long, sometimes up to several years, use of oral hypoglycemic agents may become insulin-dependent. Thus, these options can be regarded as a slowly progressing form of diabetes type I – so-called latent (1.5 type) or latent autoimmune diabetes of adults. The presence of antibodies to glutamic acid decarboxylase is the most sensitive and specific marker for future insulin dependence in patients with latent diabetes [107]. Therefore performing apheresis therapy in diabetes type II may to some extent contribute to the prevention and its eventual transition to diabetes type I.

There is a separate problem of gestational diabetes, occurring in 2-8% of pregnant women mainly having some metabolic disturbances. It is accompanied by the development of hypertension without proteinuria and preeclampsia, but with a higher frequency of caesarean section. The child often develops macrosomia (overweight), hyperbilirubinemia, and polycythemia, as well as hypoglycemia in the next few hours after birth [108]. It was first described by J.B. O'Sullivan and C.M. Mahan [109] in a group of 752 pregnant in Boston when excessive growth of glucose concentration was detected during 3-4-hour "sugar curve" test.

Even a normal pregnancy is accompanied by some hyperinsulinemia and progressive suppression of insulin sensitivity. In addition, many women apparently have had undiagnosed and not manifested type I or type II diabetes revealed only during the pregnancy. However, between 24 and 28 weeks of pregnancy there may be tolerance

disorders to carbohydrates even in previously healthy women. The risk of this gestational diabetes in pregnant women may increase in elder pregnant women, in case of obesity, of unexplained death of a newborn or diabetes diagnosed in the previous pregnancy [110].

Pathogenetic mechanisms of gestational diabetes mellitus development are associated with decreased insulin sensitivity of the tissues and an equivalent increase of its secretion due to the influence of hormones such as lactogen and progesterone together with cortisol and prolactin. Besides, disorders of lipid metabolism associated with increased concentration of free fatty acids and ketone bodies are also of significance. This type of disorders promotes the development of insulin dependent diabetes mellitus later in life in 50% of these women, particularly prone to obesity [111].

In case of gestational diabetes found in the III trimester of pregnancy, especially when it is persistent during 6 months after the birth, there is a high risk of insulin resistance development as well as diabetes type II 11-26 months after the delivery [112]. Hyperglycemia in gestational diabetes may be the cause of reducing the number of nephrons in the fetus, which is manifested in the development of kidney diseases later in life after birth. Such correlation was confirmed in special experiments on animals [113].

Furthermore, pre-gestational diabetes in pregnant women is 2-5 times more likely to lead to birth defects in fetal development. Special studies *in vitro* and *in vivo* have shown that elevated blood glucose levels contributed to the increase of the mutation frequency in embryos [114]. This diabetic embryopathy is the main reason for the higher perinatal mortality and neonatal morbidity of newborns of mothers with diabetes.

Fine *et al.* [115] have experimentally demonstrated the occurrence of genetic disorders in hyperglycemia pregnant animals. There were more incidences of congenital malformations in the fetus with gestational diabetes than in the general population. These defects can occur before the 7th week of pregnancy. They include such severe deformities, as micro- and even anencephaly, spinal canal hernia, hydrocephalus, heart malformations. Besides hyper- and hypoglycemia, hyper-

ketonemia, hyperinsulinemia, these processes are affected by the intracellular accumulation of glutathione in the conditions of oxidative stress during fetal organogenesis [116]. During the gestational diabetes there is accumulation of low-phosphorylated insulin like growth factor and the related protein-1, which interferes with the development of the fetus and leads to the body weight reduction [117]. In diabetes destructive, sclerotic and necrotic processes develop in the placenta, leading to placental insufficiency.

In addition, fatty acid, content of which increases in the blood of a pregnant woman with gestational diabetes, penetrate into the blood circulation and accumulate in fetal membranes of skeletal muscle cells, which in later life of the child becomes a predisposing factor of insulin resistance syndrome development [118].

In pregnant women with diabetes late toxicosis (with prevalence of hypertensive forms) develops more often. Diabetic microangiopathy promotes more severe preeclampsia [119]. Elevated levels of glucose in the fetus stimulate diuresis that promotes polyhydramnios, which poses a threat of pregnancy termination, weakness labor contractions, bleeding and fetal hypoxia.

There is a higher frequency of urogenital infections occurrence and activation as pyelonephritis, cervicitis, and vaginitis develop. It is fraught with intrauterine infection of the fetus when ingested and aspiration of the infected amniotic fluid, being infected in its passage through the birth canal, and accompanied by the onset of pneumonia with a long and persistent cough, conjunctivitis, pustular skin lesions, upto the development of septic complications.

In the presence of diabetes in pregnant women, regardless of its form, the fetus develops diabetic fetopathy. When the body weight and the size of some organs (liver, heart, and spleen) tend to increase the development of functional systems slows down. Weight of the brain in the fetus is decreased due to degenerative changes of nerve and glial cells. And in the first days of life there are especially frequent neurological disorders – such as irritability and hypotonia, upto the development of cerebral palsy. In later life mental lag and physical disabilities, delayed speech and tongue-tied are often found. Neonatal respiratory

distress syndrome and bronchopulmonary dysplasia are the most common findings [120].

These findings allow justifying the preventive courses of plasmapheresis in pregnant women when gestational diabetes is found in order to reduce the risk of the process spreading on the fetus and to prevent the disease left untreated in women after the childbirth.

Therefore apheresis therapy becomes not only indicated in very advanced complications of diabetes, but also in its very early period, including when the level of glucose is not achieved the "diabetic" level. Indeed, numerous studies indicate the favorable results of this treatment, its corrective influence on carbohydrate and lipid metabolism, coagulation factors in patients with diabetes, especially in conjunction with CHD [121]. Plasmapheresis can significantly reduce cholesterol levels (from 353.8 ± 60.1 to 154.3 ± 32.6 mg%), triglycerides (from 428.0 ± 142.6 to 178.3 ± 141.6 mg%), fibrinogen (from 432.9 ± 97.4 to 255.5 ± 52.4 mg%) with a reduced risk of possible acute vascular complications with $41.17 \pm 7.17\%$ to $11.7 \pm 4.6\%$ [122]. Enabling courses of plasma-pheresis in a secondary dyslipidemia in diabetes allowed more significantly reduce cholesterol to 4.03 ± 0.38 mmol / l ($p = 0.025$), low-density lipoprotein to 2.78 ± 0.28 ($p = 0.017$) and athero-genic coefficient to 3.31 ± 0.63 ($p = 0.028$). This improves the sensitivity to drugs, including hypoglycemic ones [123].

Methods of direct extracorporeal adsorption of fibrinogen and lipoprotein are also used [124-126]. Methods of cascade plasmapheresis are also perspective, given its greater efficiency and selectivity [127].

Plasmapheresis in diabetes reduces thirst, polyuria, pruritus, hyperglycemia, and glycosuria, improves blood rheology and microcirculation, and, most importantly, improves the sensitivity of cellular insulin receptors. Plasmapheresis is indicated in patients with an advanced picture of the disease in order to prevent a number of secondary complications of diabetes [128].

Thus, the presence of both immune and metabolic shifts in this form of diabetes makes the use of apheresis therapy reasonable in all stages of the disease development. Plasmapheresis is almost the only way of correction of these complications

– elimination of secondary metabolic disorders. Only by means of plasma exchange it is possible to remove the numerous damaging factors, such as CEC, glycoproteins, lipids, uric acid, endothelin, antibodies to insulin and others [129]. The plasma exchange at diabetes leads to reduction of thirst, a polyuria, skin itch, decrease in level of a glycemia, glucosuria, improvement of a rheology of blood and microcirculation, and that is especially important, to increase in sensitivity of cellular receptors to insulin [130].

And indeed, numerous works indicate favorable results of such treatment, its corrective influence on carbohydrate, lipidic exchange, and coagulative factors in patients with diabetes, especially in combination with ischemic heart disease [126]. By means of a plasmapheresis inductors of blood cells aggregation (fibronectin, Villebrand's factor, fibrinogen, thrombospondin) are removed [131]. At the same time the sensitivity to medicines including anti-hyperglycemics improves [123].

Gavrilov *et al.* [94] described restoration of microcirculation disorders after plasmapheresis courses with increase of pain-free walking distance, healing of trophic ulcers or delay of amputations in case of toes gangrenes. It confirms also our own experience of membrane plasmapheresis in diabetic angiopathy when in most cases it was possible to stop necrosis progression or to limit it only to toes phalanxes' resections [97].

Treatment of poorly healing trophic ulcers in "diabetic foot" appeared effective by means of cascade plasma exchange as well (rheopheresis) [95, 127]. Rheosorption in processing of plasma through special affine sepharose columns allowed significant reducing of concentration of fibrinogen, fibrin and other products of degradation that dramatically improved microcirculation in diabetic foot syndrome [73].

Unlike drug therapy (alprostadiol, pentoxifylline), plasmapheresis promotes more considerable decrease in aggregation of erythrocytes and platelets due to removal of inductors of their aggregation (a fibronectin, von Willebrand's factor, fibrinogen, thrombospondin) [131].

Thus, the provided findings indicate the relevance of the "diabetic foot" problem and the perspective of apheresis therapy methods, mainly

plasmapheresis, in treatment of this severe vascular pathology diabetic patients.

Results of the treatment of patients with “diabetic foot”.

Operations	Without Plasmapheresis N = 96	With Plasmapheresis N = 34
Without amputations	23.0%	76.4%
Small amputations	11.5%	11.8%
High level amputations	65.5%	11.8%

CONCLUSION

The provided findings show real dangers and serious complications of metabolic syndrome, which not always can be prevented by drug therapy. The accumulating large molecular secondary metabolites aren't removed by kidneys and damage the vessels endothelium, defining the further development of microcirculation disorders with ischemia of various tissues and organs. Only timely removal of them by means of plasmapheresis is capable to prevent irreversible damages of the latter.

Sufficiently high cost of plasmapheresis may stop its use, although in our country (Russia), it is much lower than in Europe or America. It is mainly provided due to more sparing plasmapheresis technique when only 30% of the circulating plasma is removed during one procedure instead of 100% of it, which enables to replace this volume by “water” only (isotonic solution of sodium chloride). Nevertheless, during all the set of four plasmapheresis procedures, performed every other day, up to 1-1.5 of the circulating plasma volume is removed. Such procedures are tolerated much better, takes about 1.5 and in half an hour of rest and observation the patient can go home. Risks of allergic reactions and viral diseases transmission is excluded, which otherwise is always possible when donor's blood components are used.

Well-established Russian plasma filters such as “Rosa” and development of simple and safe single needle methods and devices for membrane plasmapheresis such as “Hemofenix” (“Trackpore Technology” Company) makes these important tasks quite realistic in almost all hospitals even on municipal levels. Possibility to perform such procedures in out-patient settings opens perspectives

of their broader application in clinical practice. It is especially important, considering the increasing incidence of metabolic syndrome and diabetes in population.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Not applicable.

HUMAN AND ANIMAL RIGHTS

No Animals/Humans were used for studies that are the basis of this research.

CONSENT FOR PUBLICATION

Not applicable.

CONFLICT OF INTEREST

The author declares no conflict of interest, financial or otherwise.

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