Journal of Nephrology & Renal Diseases

Research Article

A SCITECHNOL JOURNAL

Plasmapheresis in diabetic nephropathy prevention and treatment

Voinov V.A. and Voinova Ya.V

***Corresponding author:** Voinov V.A., I.P Pavlov First Saint Petersburg State Medical University, Saint Petersburg, Russia, Phone No: +79119126502 Email: voinof@mail.ru

Received: June 01, 2020 **Accepted:** June 10, 2020 **Published:** July 31, 2020

Introduction:

Diabetic nephropathy is a serious complication of diabetes up to development of terminal renal failure with a high mortality rate. It is important to realize that in its pathogenesis there is accumulation of various pro-inflammatory cytokines, chemokines, adhesion molecules, uric acid and glycated hemoglobin, as well as oxidative stress with increased activity of the renin-angiotensin-aldosterone system. In this case there is thickening of the glomerular basement membrane, mesangial expansion, nodular glomerular sclerosis, and tubulointerstitial fibrosis. Treatment is mainly based on the control of sugar levels and blood pressure and there is practically no validated therapy that can stop the kidney damage progression. Therefore, in all these cases, plasmapheresis is almost the only and pathogenetically justified method of treating and preventing this condition. Only plasmapheresis can remove numerous damaging factors, such as circulating immune complexes (CIC), glycoproteins, lipids, uric acid, endothelin, antibodies to insulin and others.

Methods and Results: A normal level of glycaemia can be maintained, but this does not prevent the accumulation of secondary toxic metabolites that damage the walls of the blood vessels, and there are no medications to prevent the progressive course of these complications. Most of these pathological large-molecular substances, such as circulating immune complexes, glycoproteins, lipids, endothelin, antibodies to insulin and others are not excreted by the kidneys and can only be removed using plasmapheresis, which is essentially the only way to correct these complications - elimination of secondary metabolic disorders. And you need to start this not waiting for the terminal renal failure development, but already at the first signs of the kidney damage. Membrane plasmapheresis on the Russian Hemofenix device with a small volume of filling allows it to be performed even on an outpatient basis, including in children, and that expands the possibilities of its use in almost any medical institution, even of the municipal level. This is especially important, given the huge number of patients in need of this treatment.

Conclusion:

Diabetes mellitus is accompanied by accumulation of a wide variety of pathological metabolites. At the same time, the glomerular basement membrane thickening, mesangial expansion, nodular glomerular sclerosis and tubulointerstitial fibrosis develop, leading to irreversible damage of the kidneys. In this case, the treatment is mainly based on the sugar levels and blood pressure control and there is practically no validated therapy that can stop the progression of the kidney damage.

Key words:

diabetes mellitus, diabetic nephropathy, toxic metabolites, apheresis therapy, plasmapheresis.

Introduction

Diabetes mellitus is a serious systemic epidemic-like disease developing in the United States of America and worldwide [1]. It is 2.5 to 3.8% of population with doubling of the patients' number every 10-15 years. Moreover, the annual increase in the number of such patients reaches 20% [2]. By 2025, their number may have increased to 300 million. Among people over 70 years old diabetes mellitus occurs in 10% of cases [3].

Diabetic nephropathy is one of the most serious complications of diabetes and the leading cause of the terminal stage of kidney damage in the world [4, 5]. The death rate for 5-year period in this case reaches up to 61.7% [6].

Pathogenesis of diabetic nephropathy

The direct toxicity of increased glucose concentrations for nephron structures with concomitant lipid metabolism disorders (frequent lipid deposition in the kidneys) and subsequent sclerotic changes in mesangium cells, together with deposits of circulating immune complexes, underlie renal parenchyma lesions in diabetes. At the same time, there is thickening of the glomerular basement membrane, mesangial expansion, nodular glomerular sclerosis and tubulointerstitial fibrosis [7–9].

Immune disorders also play a role in the immune cells infiltration, mainly macrophages, and complement activation [10]. In addition, there is an increase of the level of the circulating pro-inflammatory cytokines that contribute to the kidney damage progression [11]. Accumulation of uric acid and glycated hemoglobin, as well as oxidative stress with increased activity of the renin-angiotensin-aldosterone system appear significant [12-16]. In this case, intracellular active oxygen accumulates in the vascular mesangium [18, 19].

In recent years, attention has been drawn to the role of "vascular endothelial growth factor" as a multifunctional cytokine, also known as vascular permeability factor. It participates in the development of micro- and macrovascular complications in diabetes and, in particular, diabetic retinopathy and nephropathy [19-22]. There is evidence of various inflammatory cytokines, chemokines, and adhesion molecules accumulation that contribute to the development of diabetic nephropathy [23]. The complement system also plays a role in the diabetic nephropathy pathogenesis [24]. If immunocomplex glomerulonephritis is typical for Type I diabetes, atherosclerotic nephroangiosclerosis – for Type II diabetes.

Arterial hypertension, prevailing in patients with diabetes, also contributes to the progression of endothelial dysfunction [25]. On the other hand, diabetic nephropathy also increases the risk of cardiovascular disease [26]. All this determines the higher death rate

in such patients [27].

There are three mechanisms to develop diabetic nephropathy.

1. Hyperglycemia contributes to the tubulo-glomerular apparatus damage, leading to vasodilation, increased renal blood flow and hyperfiltration. In addition, the tissue concentration of myoinositol in the glomeruli increases, which disrupts cellular metabolism and leads to hemodynamic disorders in the kidneys.
2. Hormonal imbalance. With insulin deficiency, other hormones, such as growth hormone and glucagon, are included in the pathogenesis of diabetic nephropathy. Both of them promote hyperfiltration, which is also a consequence of disturbances in the levels of angiotensin II, catecholamines and prostaglandins.
3. Hemodynamic changes. Hyperglycemia facilitates an increase in extracellular fluid volume, renal hypertrophy, also leading to increased glomerular filtration [28].

Microalbuminemia is traditionally considered the earliest marker of microcirculatory disorders. Protein concentration of 30-200 mg/l, or its excretion at a rate of 20-200 μg/min can be detected in 29-41% of diabetic patients with the disease duration over 5-7 years, which predicts a high risk of developing a progressive stage of the kidney damage [29, 30]. 70% of diabetic patients with microalbuminuria also suffer from arterial hypertension, which strengthens this association of diabetes and nephropathy.

In the United States, in addition to 1 million patients with Type I diabetes and 13 million patients with Type II diabetes, there are approximately 6 million people who remain undiagnosed with this form of diabetes. This is due to still not established screening diagnosis of microalbuminuria preceding proteinuria, therefore, it seems appropriate to measure it by radioimmune or enzyme immunoassay methods that can measure levels of 30-200 mg / l [28].

Diabetic Nephropathy Treatment

The treatment is mainly based on the sugar level and blood pressure control and there is practically no validated therapy that can stop the kidney damage progression [31].

For the cause of the kidney damage is the accumulation of large molecular toxic products not excreted by the kidneys, plasmapheresis is a pathogenetically justified method of treatment and prevention of progressive kidney damage [32-34]. Indeed, the use of plasmapheresis on the background of immunosuppressants allows faster stabilization of the renal function with cessation of renal failure progression. At the same time, removal of very massive plasma volume is required - up to 2-2.5 L (1 CPV), starting with three such procedures every other day, and then after 2-3 procedures - every 2 weeks [35-36].

Apheresis therapy is essentially the only way to correct these complications i.e. secondary metabolic disorders [37]. Only plasmapheresis can remove numerous damaging factors such as CIC, glycoproteins, lipids, uric acid, endothelin, antibodies to insulin and others [32, 38, 39]. Diabetes is very dangerous during pregnancy and plasmapheresis helps eliminate complications including nephropathy [40]. Plasmapheresis in diabetes mellitus leads to decreased thirst, polyuria, skin itching, glycemia, and glucosuria, improvement in the blood rheology and microcirculation, and, most importantly, increased sensitivity of cellular receptors to insulin [41]. In cases of recurrent IgA nephropathy after the kidney transplantation an early and intense plasmapheresis is able to stop this process [35, 36]. Particularly, diabetic ketoacidosis is also an indication to use plasmapheresis [42].

Conclusion

Diabetes mellitus is accompanied by accumulation of a wide variety of pathological metabolites. At the same time, the glomerular basement membrane thickening, mesangial expansion, nodular glomerular sclerosis and tubulointerstitial fibrosis develop, leading to irreversible damage of the kidneys. In this case, the treatment is mainly based on the sugar levels and blood pressure control and there is practically no validated therapy that can stop the progression of the kidney damage. The large size of these molecules does not allow them to be excreted by the kidneys; therefore, the only pathogenetically justified method of treatment is apheresis therapy, mainly plasmapheresis. Its use is also advisable at the first signs of the kidney damage to prevent their irreversible disorders. Moreover, considering the inevitable complications development, apheresis treatment is to be started right after diagnosing diabetes.

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Author Affiliation

Top

I.P Pavlov First Saint Petersburg State Medical University, Saint Petersburg, Russia.