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Efficiency of Endothelial Dysfunction Correction with Methylethylpyridinol in Patients with Type 1 Diabetes Mellitus

Evgeniy Sergeevich Krutikov, MD[1]
Viktoriya Andreevna Zhitova, MD[1]
Larisa Viktorovna Yagenich, PhD[2]

[1] Department of Internal Medicine Propedeutics, S. I. Georgievskiy Medical Academy, V. I. Vernadskiy Crimean Federal University, Simferopol, Russia.

[2] Foreign Language Department, Foreign Philology Institute, Taurida Academy, V. I. Vernadskiy Crimean Federal University, Simferopol, Russia.

Correspondence:
Viktoriya Andreevna Zhitova, MD
Vishnevaya st., Molodezhnoe,
Simferopolskiy district, Russia 297501
phone: +7 978 8350018
e-mail: viki.jitowa@yandex.ru

Objective: This study evaluated the effectiveness of methylethylpyridinol and sulodexide therapy in correcting endothelial dysfunction in patients with type 1 diabetes.

Material & methods: The study included 89 patients with type 1 diabetes divided into 2 groups: group 1 received sulodexide therapy, while group 2 received methylethylpyridinol therapy.

Results: The parameters of endothelial dysfunction, hemostasis and renal function were determined before and after the course of therapy. Results of the study demonstrated the treatment with sulodexide to have led to decrease in the concentration of vascular endothelial growth factor, and normalization of endothelial dysfunction and renal function. Similar changes were noted in patients treated with methylethylpyridinol. The use of sulodexide had a positive effect on decreasing the endothelial dysfunction activity; in addition, methylethylpyridinol increased the antithrombin III activity.

Conclusion: Methylethylpyridinol helps improve the endothelial status and normalize the indicators of hemostasis and microcirculation.

Keywords: diabetes mellitus, endothelial dysfunction, vascular endothelial growth factor, methylethylpyridinol, sulodexide.

Introduction

Some recent researches including large multicentre ones, DCCT from 1993 and UKPDS from 1998 [1,2] have been focused on the exclusive role of chronic hyperglycemia in the process of diabetic microangiopathy development. Hyperglycemia provokes an increase in aldose reductase activity, stimulates glucose oxidation along the polyol pathway and accumulation of final glycation products, aggravates the severity of oxidative stress, and increases blood viscosity and prothrombotic activity [3-5]. These changes lead to damage to endotheliocytes and development of endothelial dysfunction (ED). It is characterized by impairment of the vascular tone regulation and intercellular interaction, aggravates imbalance of the factors of coagulation and anticoagulation systems towards hypercoagulability, and contributes to a decrease in the activity of fibrinolytic properties of blood serum [6,7].

During the whole life, endotheliocytes synthesize a moderate amount of vascular endothelial growth factor (VEGF), which is necessary to ensure endothelial migration, differentiation, and cell survival. The term VEGF unites a whole group of signal proteins that are stimulants of angiogenesis in pathologic conditions (inadequate blood supply and chronic hypoxia).

In patients with diabetes mellitus (DM), hyperproduction of VEGF by endotheliocytes is a protective reaction, indicating an active process of damaging vascular wall and development of microvascular complications (primarily retinopathy and nephropathy) [8-10]. Therefore, more attention has recently been paid to maintaining an adequate level of vascular endothelial re-

generation factors and slowing the progression levels of diabetic microangiopathies [3]. These concepts have raised interest in searching and investigating the agents that are acting simultaneously on ED, rheology and hemodynamics in the vessels of the microcirculatory bed.

For several years, endocrinologists and nephrologists have used sulodexide medication for correction of ED and microcirculatory disorders, owing to its complex pharmacological effect as an anticoagulant, antiadhesive, fibrinolytic, angioprotective, antithrombotic and hypolipidemic agent.

Sulodexide also contributes to restoration of the structural integrity and function of endothelial cells and normalization of the negative charge of the endothelial basal membrane. However, the high cost of the drug prevents its use for the prevention and correction of ED in the vast majority of DM patients. Therefore, there is particular interest in the investigation of the domestic preparation methylethylpyridinol and its effectiveness. Methylethylpyridinol has a number of therapeutic effects including angioprotective, antiplatelet, fibrinolytic and antioxidant.

The aim of this study was to investigate the efficacy of methylethylpyridinol and sulodexide in correcting ED in patients with type 1 DM.

Material and Methods

The study included 89 patients (37 men and 52 women) with type 1 DM according to the WHO diabetes diagnostic criteria from 1999, with the mean disease duration of 8.4±3.7 years and mean age 27.2±4.3 years. The patients with duration of the disease of 10 years were not included in the investigation.

Thirty-seven (41.6%) patients were in the stage of subcompensation and 52 (58.4%) were in the stage of decompensation. The mean level of glycated hemoglobin (HbA1c) was 9.6±0.8%, which was a very high risk factor for development of diabetic microangiopathy. Forty-eight (53.9%) patients had elevated urine albumin level. Hypertension was recorded in ten (11.2%), nonproliferative diabetic retinopathy in 18 (20.2%) and diabetic polyneuropathy in 12 (13.5%) patients.

Exclusion criteria were uncontrolled arterial hypertension, severe cardiac rhythm disturbances, chronic kidney disease (CKD) stage 3b and higher according to the K/DOQI CKD classification (National Kidney Foundation, 2002), chronic arterial insufficiency (CAI) stage IIb and higher (Fontaine stages, 1954), chronic heart failure (CHF) stage III and higher (New York Heart Association Functional Classification, 1964), acute cerebrovascular impairment (ACVI), myocardial infarction (MI) in history, proliferative retinopathy, and alcohol abuse. Study patients underwent complex work-up and treatment (baseline bolus therapy with insulin, statins and angiotensin-converting-enzyme inhibitor (ACE inhibitor) and angiotensin II receptor blockers, according to the adopted protocols.

Study patients were divided into 2 groups: group 1 including 42 (47.2%) patients administered sulodexide (Vesel Doue F®, Alfa Wassermann, Italy) as add-on therapy at a dose of 600 LE/day intravenous drip in saline solution for the course of 14 injections; and group 2 including 47 (52.8%) patients administered methylethylpyridinol (Cardiosipin®, JSC Biosynthesis, Russia) as add-on therapy at a dose of 600 mg/day intravenous drip in saline solution for the course of 14 injections.

The following parameters were determined in both groups before and after the course of treatment: level of albuminuria by enzyme immunoassay (EIA), von Willebrand factor (vWF) by platelet agglutination in the presence of ristocetin (ristomycin) (SPA Renam, Russia), antithrombin III activity by optic recording technique of paranitroaniline count expressed following thrombin III neutralization with antithrombin (SPA Renam, Russia), and VEGF by EIA in blood serum (LLC Hema, Russia). Desquamated endothelial cell counting in peripheral blood was done by use of J. Hladevec method. Glomerular filtration rate (GFR) was estimated by the CKD-EPI formula.

Control group included 20 age- and sex-matched healthy subjects. All trials (research studies) were carried out on admission to the hospital and in 14 days.

For statistical analysis we used statistical packages Plan Maker Professional 2012 and Statistica 8.0 for Windows. Data were expressed as median and interquartile range (Me, 25% quartile; 75 quartiles). For figure comparison, we used Mann-Whitney U test and McNemar test (to compare 2 sets of associated data). Statistically significant difference was considered to be at $p<0.05$.

Results

Data analysis showed urinary excretion of albumin to be increased by factor 5.2 in type 1 DM patients before treatment as compared to control group: 54.3 [42.8; 61.3] mg/day (p=0.002) in group 1 and 55.7 [43.7; 64.2] mg/day (p=0.001) in group 2. Sixteen (38.1%) group 1 patients and 18 (38.3%) group 2 patients showed GFR index lowering by factor 17% (p=0.027 and p=0.024 in groups 1 and 2, respectively), simultaneously with filtration recovery.

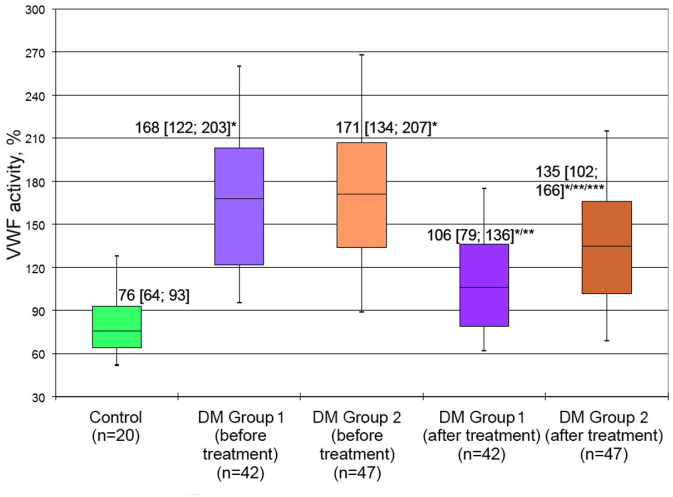
Signs of ED were revealed in randomized patients of both groups. ED was indicated by more than twofold increase of vWF activity as compared with control group (p=0.011 in group 1 and p=0.008 in group 2), of VEGF by more than 5 times (p=0.002 in group 1 and p=0.002 in group 2), and of desquamated endothelial cells in peripheral blood by more than 5 times (p=0.001 in group 1 and p=0.002 in group 2) in comparison with control group.

The activity of antithrombin III, a primary plasma factor of anticoagulation system synthesized by endotheliocytes, was lower in both patient groups as compared with control group: 63 [51; 82]% (p=0.019) and 61[48; 81]% (p=0.014) in groups 1 and 2, respectively, versus 101 [87; 115]% in control group.

After the course of treatment, albumin level in urine decreased by 25% in group 1 and by 24% in group 2: 40.7 [31.9; 54.2] mg/day (p=0.031) and 42.3 [33.7; 57.5] mg/day (p=0.034), respectively, as compared with pre-treatment figures.

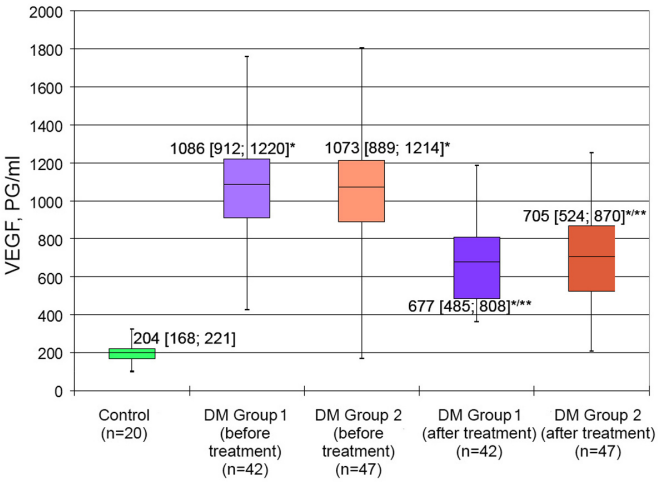
After the course of sulodexide therapy in group 1 and methylethylpyridinol therapy in group 2, GFR index tended to be normal. Reduction in the number of patients with hypo- and/or hyperfiltration was recorded in both groups. Thus, the number of patients with normal GFR index increased to 22 (52.4%) in

Figure 1. von Willebrand factor (vWF) activity before and after the course of treatment.



*p<0.05 – statistically significant difference as compared to control group;
**p<0.05 – statistically significant difference as compared to control group;
***p<0.05 – statistically significant difference as compared to control group.

Figure 2. Changes in vascular endothelial growth factor (VEGF) before and after therapy.



*p<0.05 – statistically significant difference as compared to control group;
**p<0.05 – statistically significant difference as compared to control group.

group 1 and to 25 (53.2%) in group 2. However, McNemar test based on the results after the course of treatment showed no statistically significant changes.

After the course of treatment, group 1 showed a significant decrease in vWF activity as compared to pre-treatment figures (p=0.004). Similar changes were recorded in group 2 (p=0.005). However, these changes were more pronounced in group 1, i.e. vWF activity after the course of treatment was almost normal (p=0.037) as compared with group 2 post-treatment (Fig. 1).

In type 1 DM patients, VEGF index in blood serum after the course of the treatment tended to be normal in both groups 1 and 2 (Fig. 2). In the group of patients treated with sulodexide, VEGF concentration was reduced by almost 38% (p=0.007) as compared to pre-treatment values. In the group of patients treated with methylethylpyridinol, VEGF was reduced by 34% (p=0.001). There were no statistically significant differences between the two groups.

The treatment protocols resulted in a statistically significant reduction in desquamated endothelial cells in both groups. The number of desquamated endothelial cell decreased twofold (p=0.002) in group 1 patients and 1.4-fold in group 2 patients (p=0.005).

After treatment, an increase in the activity of antithrombin III to 73 [59; 94]% (p=0.027 compared with the value before treatment) was recorded in group 1. In group 2, this indicator was 88 [69; 111]% (p=0.018 compared with the value before treatment), which was statistically significantly higher than the results obtained in group 1 after treatment with sulodexide (p=0.022).

Discussion

In type 1 DM patients, ED is detected with high activity of vWF, a sharp increase in the level of VEGF and the number of desquamated endothelial cells. These changes may be primarily explained by inducing the glucose metabolism polyol pathway with persistent hyperglycemia and activation of protein kinase C, accumulation of advanced glycation end-products, lipid peroxidation, etc. Hyperfiltration, increased intracapillary pressure and chronic hypoxia enhance the adverse effects of high VEGF concentrations on microvascular wall. It enhances the activity of ED and desquamation of endothelial cells, and subsequently triggers fibrotic processes and capillary occlusion [11,12].

Thus, in the study patients with type 1 DM, ED indicated initial impaired renal function. The therapy applied had a positive effect on glomerular endothelial function and status in both groups.

Our study results revealed reduction of antithrombin III activity, which may also accelerate the development of diabetic microvascular deterioration by blood rheology in microvasculature. These changes increase the severity of chronic hypoxia and trophic disorders of endothelial cells.

Therapy with sulodexide caused a decrease in VEGF concentration, normalization of ED and renal function. Our findings pointed to a complex therapeutic effect of the drug on the basic pathogenetic mechanisms of diabetic microangiopathy.

Similar changes were observed in patients treated with methylethylpyridinol. However, the latter had greater hemodynamic effects (GFR normalization and decrease of albuminuria). This drug did not only improve endothelial cells and slowed down development of microvascular complications, but also normalized the parameters of hemostasis (pronounced increase in antithrombin III activity as compared with group 1), which could possibly contribute to improvement of the cardiovascular system in patients with diabetes.

Thus, the use of methylethylpyridinol, which has already been recommended as an angioprotector in the treatment of diabetic retinopathy, can be extended to the setting of diabetic

nephropathy. Having angioprotective, antiplatelet, fibrinolytic and anti-oxidant properties, methylethylpyridinol cannot only slow down the development of ED, but can also slightly improve renal function in patients with type 1 DM.

Conclusion

The sulodexide and methylethylpyridinol therapy leads to improvement of endothelial and kidney functions by reducing the activity of vWF, VEGF and number of desquamated endothelial cells, and moderately normalizing the levels of albuminuria. GFR rate was not significantly changed at 14 days. The administration of sulodexide had the greatest positive impact on decrease in the ED activity, while methylethylpyridinol led to further increase in the activity of antithrombin III. The use of methylethylpyridinol contributed not only to improved endothelium status, but also normalized the indicators of hemostasis and microcirculation.

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