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Research Article

The effect of methylethylpyridinol hydrochloride on the levels of α-tocopherol and transforming growth factor β-1 in patients with chronic kidney disease and type 2 diabetes mellitus

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Abstract

Introduction: Chronic kidney disease (CKD) is one of the most common complications of diabetes mellitus (DM) associated with oxidative stress developing with hyperglycaemia. Excess activity of the transforming growth factor β-1 (TGF-β1) signaling pathway has been identified as a key contributor to fibrosis in the development of CKD in the context of type 2 DM.

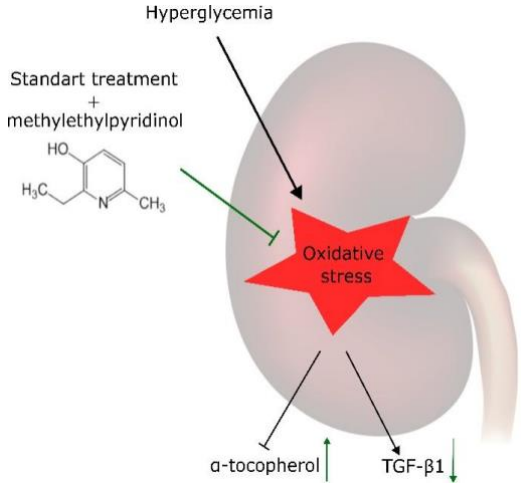
The aim of the research was to assess the levels of α-tocopherol and TGF-β1 in individuals with CKD and type 2 DM who were undergoing standard treatment and treatment with methylethylpyridinol hydrochloride.

Materials and Methods: The study involved 60 participants with CKD and type 2 DM. The distribution of patients was carried out depending on the therapy received: the first group (n=30) used sugar-reducing agents, hypotensive, hypolipidemic and antiaggregant drugs, the second group (n=30) received methylethylpyridinol hydrochloride (10 mg once daily for 14 days) in addition to the main scheme of therapy.

Results and Discussion: Before the initiation of inpatient treatment, all study group patients showed a 1.7-fold reduction in α-tocopherol levels. Simultaneously, the level of TGF-β1 increased by 6.1 times compared to the control group. During basic treatment, the concentration of α-tocopherol increased by 1.1 times, and the TGF-β1 level in blood serum decreased by 1.3 times compared with pre-treatment indicators. The combined treatment regimen using methylethylpyridinol hydrochloride led to a 1.4-fold increase in α-tocopherol level and a 1.6-fold reduction in TGF-β1 level.

Conclusion: Treatment with methylethylpyridinol hydrochloride has shown a significant antioxidant and anti-inflammatory effect that exceeds that of standard therapies.

Graphical Abstract



Keywords

methylethylpyridinol hydrochloride; oxidative stress; type 2 diabetes mellitus; transforming growth factor β-1; chronic kidney disease; α-tocopherol

Introduction

Chronic kidney disease (CKD) is a condition characterized by a gradual decline in kidney function, damage to the renal tubules, oxidative stress, and inflammation (Reiss et al. 2024). CKD is one of the major complications of diabetes mellitus (DM). DM is a disease manifested by impaired carbohydrate metabolism. The combination of DM and CKD leads to a particularly marked increase in the risk of cardiovascular disease (Swamy et al. 2021). Oxidative stress mediated by hyperglycaemia plays a major role in the pathogenesis of renal pathology in diabetes. Oxidative stress is a state of excessive activity of free radicals in relation to the body's antioxidant defense mechanisms (Atukeren 2018).

During prolonged hyperglycaemia, there occurs glycosylation of various proteins that make up the basal membrane of blood vessels and the renal tubular apparatus. This process results in damage to the glomerular apparatus of the kidneys, damage and release of cytokines, growth factors and other biologically active substances. These compounds stimulate the production of reactive oxygen species (ROS), which are mainly formed in the respiratory chain of electron transfer in mitochondria. Oxidative stress is caused by excessive formation of ROS, which, in turn, will activate lipid peroxide oxidation (LPO), a constituent of renal cell membranes. Due to LPO activation, perforations in renal tubular cells and their death occur (Dong and Tong 2025).

The antioxidant system (AOS) is essential for protecting against free radical damage that can occur during LPO. The AOS comprises both enzymatic and non-enzymatic components. Among the non-enzymatic antioxidants, α-tocopherol plays a critical role. Due to its compact structure, this component effectively protects cell membrane phospholipids by preventing the oxidation of their unsaturated fatty acid residues. Additionally, α-tocopherol has the ability to neutralize lipid peroxides and other oxygen-based radicals (Kaye et al. 2025). In addition to its antioxidant properties, α-tocopherol has 'non-oxidative' functions consisting of direct effects on various groups of genes involved in important cellular processes such as cell cycle regulation, proliferation and cell death signalling, as well as xenobiotic detoxification and reduction of inflammation (Azzi 2019). However, it should be noted that in case of excessive formation of ROS and, as a consequence, increased free radical-induced oxidation, AOS has low efficiency.

TGF-β1, which is produced by most types of kidney cells and also by infiltrating leukocytes and macrophages, is a multi-functional cytokine. Excessive activation of the TGF-β1 signaling pathway has been identified as a key factor in the development of fibrosis in CKD against a background of type 2 diabetes (Peng et al. 2022). This cytokine plays an important role in regulating a variety of biological processes, including stimulating tissue fibrosis, regulating cell

division, controlling apoptosis, affecting cell differentiation, activating autophagy mechanisms, and significantly influencing the body's immune response (Tang et al. 2021). The mechanism of direct effects of TGF-β1 on fibroblast-type cells in the kidney, such as mesangial cells and fibroblasts, has been most extensively studied. TGF-β1 has a direct effect on these cells, promoting their proliferation, migration, activation, and the production of molecules that are involved in the formation of fibrous tissue. These molecules include collagen, fibronectin, and plasminogen activator inhibitor-1. In addition, TGF-β1 may indirectly stimulate the repair and/or development of fibrous tissue through other mechanisms (Tang et al. 2021).

In the light of the above, it is crucial to develop new methods for the correction of CKD symptoms in patients with type 2 DM. These methods should be aimed at reducing the severity of oxidative and inflammatory stress. One potential approach may be the utilization of 3-hydroxypyridine derivatives. Among these, methylethylpyridinol hydrochloride has been identified as a promising candidate. Based on some research, this medication has been shown to enhance insulin sensitivity and improve glucose tolerance. Furthermore, it possesses antihypoxic and neuroprotective characteristics (Volchegorskiĭ et al. 2017). Other studies demonstrate that methylethylpyridinol hydrochloride can reduce the severity of oxidative stress due to its structure and properties that allow it to neutralise ROS (Popov et al. 2021a).

The aim of this research is to investigate the levels of α-tocopherol and transforming growth factor β-1 in patients with chronic kidney disease combined with type 2 diabetes, using standard treatment approaches and the addition of methylethylpyridinol hydrochloride to the treatment regimen.

Materials and Methods

Participants

The research involved 60 individuals with CKD that had developed in the context of type 2 diabetes mellitus. The sample was composed of 18 men (30%) and 42 women (70%). All patients were on inpatient treatment in endocrinological departments of Voronezh City Emergency Care Hospital #10 and Voronezh Regional Clinical Center for Public Health and Medical Prevention, the average age of whom was 65.3±7.9 years. Clinical and anthropometric parameters of the studied groups of patients are presented in Table 1. Patients who were on inpatient treatment had decompensated forms of type 2 DM, with complaints of sleep disturbance, which required correction of the therapeutic regimen. The average duration of clinical manifestations of DM was 10.4±4.8 years. The diagnosis of type 2 DM and CKD was made in accordance with current clinical guidelines. Patients were excluded from the study if they had type 1 DM, viral hepatitis, acute infections, acute myocardial infarction, malignancies, acute cerebrovascular accidents, or stages 1-5 of CKD. The most common comorbidities reported were arterial hypertension (diagnosed in 100% of patients), diabetic retinopathy in the preproliferative stage (diagnosed also in 100% of patients), obesity (diagnosed in 69% of cases), and chronic heart failure (diagnosed in 66% of participants).

Ethical approval for this study was granted by the Ethics Committee of Voronezh State Medical University named after N.N. Burdenko' of the Ministry of Health of the Russian Federation (Minutes No. 4 of 29.09.2016). All patients gave informed consent to participate in the experiment after careful explanation of the objectives, methods and potential risks of the study.

Table 1. The baseline clinical characteristics of patients in group 1, who received the standard treatment, and patients in group 2, who received combination therapy with methylethylpyridinol hydrochloride

Indicator	Group 1 (n=30)	Group 2 (n=30)
Gender, male/female	8/22	10/20
Age, years	64.1±7.9	66.5±7.8
Mean duration of diabetes, years	9.1±4.4	11.6±5.1
Weight, kg	97±5.1	96.2±8.2
Body mass index	31.6±1.1	32.4±1.6
Stages of CKD C2, n/% C3a, n/% C3b, n%	 3 (10%) 20 (67%) 7 (23%)	 0 20 (67%) 10 (33 %)

Design of the study

This clinical trial is a randomized, open-label, controlled trial conducted in strict adherence to the principles of evidence-based medicine.

The participants were randomly divided into two groups (Table 2). Group 1, consisting of 30 individuals, received the standard treatment, which included medications for lowering blood sugar levels (biguanides, sulfonylureas, and dipeptidyl peptidase-4 inhibitors), blood pressure-lowering drugs (angiotensin-converting enzyme inhibitors and beta-blockers), cholesterol-lowering agents (statins), and blood-thinning medications (acetylsalicylic acid). Group 2, also receiving the standard treatment, was given methylethylpyridinol hydrochloride at a dose of 10 mg intramuscularly, in a 2 mL solution, once daily, in the morning for a period of 14 days. A control group of 65 individuals with normal biochemical and hematological parameters was also included.

Research methods

The subject of this study was the serum of patients who had undergone treatment at the hospital. The blood samples were obtained using the "vacutainer" method in the morning, prior to breakfast, from the ulnar vein.

The concentration of α-tocopherol was determined using the photometric method of measuring the chromogenic complex formed between Fe^{2+} ions and ortho-phenanthroline, using a Hitachi U1900 spectrophotometer (Japan) set at 510 nanometers. The level of TGF-β1 in serum was quantified by enzyme immunoassay, using a kit provided by RayBiotech (USA).

Statistical data analysis

The statistical data were processed using the following criteria: Kolmogorov-Smirnov, Mann-Whitney, Student's t-test, and the calculation of quantitative variables such as the mean, standard error of the mean, and standard deviation. The analysis was conducted using SPSS 23.0. The statistical significance was determined at $p<0.05$.

Table 2. Prescribed medications to study participants

Indicator	Group 1 (n=30)	%	Group 2 (n=30)	%
Hypoglycaemic drugs	Biguanides (metformin - 500-1500 mg once in the evening)	100%	Biguanides (metformin - 500-1500 mg once in the evening)	100%
	Sulphonylurea drugs (Gliclazide - 30-90 mg once daily)	13.3%	Sulphonylurea drugs (Gliclazide - 30-90 mg once daily)	10%
	Dipeptidyl peptidase-4 inhibitors (Vildagliptin - 50-100 mg 1-2 times per day, Alogliptin - 12.5-25 mg once daily)	80%	Dipeptidyl peptidase-4 inhibitors (Vildagliptin - 50-100 mg 1-2 times per day, Alogliptin - 12.5-25 mg once daily)	83%
Antihypertensive drugs	ACE inhibitors (Enalapril -5-20 mg 1-2 times per day, Lisinopril 5-20 mg once daily)	100%	ACE inhibitors (Enalapril -5-20 mg 1-2 times per day, Lisinopril 5-20 mg once daily)	100%
	β-adrenoblockers (Bisoprolol - 2.5-10 mg once daily, Metoprolol succinate - 50-100 mg once daily)	46%	β-adrenoblockers (Bisoprolol - 2.5-10 mg once daily, Metoprolol succinate - 50-100 mg once daily)	40%
Hypolipidaemic drugs	Statins (Atorvastatin - 20-40 mg once daily)	100%	Statins (Atorvastatin - 20-40 mg once daily)	100%
Diuretics	Thiazide diuretics (Indapamide 2.5 mg once daily)	100%	Thiazide diuretics (Indapamide 2.5 mg once daily)	100%
Antiaggregant drugs	Acetylsalicylic acid 50-100 mg once daily at bedtime	100%	Acetylsalicylic acid 50-100 mg once daily at bedtime	100%
Methylethylpyridinol hydrochloride	-		10 mg of methylethylpyridinol hydrochloride, intramuscularly, 2 ml of solution, once a day, in the morning	100%

Results and Discussion

As is well known, hyperglycemia can lead to the development of oxidative stress in the body, which in turn triggers an inflammatory response. This process involves the aggregation of immune cells and the production of various inflammatory mediators, such as cytokines and growth factors, which are involved in the development of kidney disease. ROS can damage various biological molecules in the cells of the renal tissue, directly leading to pathological

changes in glomeruli, tubules, and interstitial space. This can result in a decrease in levels of important proteins like nephrin and podocin, as well as podocyte hypertrophy and apoptosis. The development of oxidative stress and inflammation can also lead to platelet adhesion and activation on endothelial cells. This causes endothelial dysfunction and the production of fibronectin and collagen, leading to the accumulation of extracellular matrix and eventually glomerulosclerosis. Ultimately, oxidative stress contributes to the progression of glomerular damage, tubulointerstitial fibrosis, and decreased renal function, ultimately leading to kidney failure (Jin et al. 2023).

α-tocopherol is a key antioxidant in the lipid system, which protects cells from oxidative damage. It has been established that α-tocopherol can increase the expression of various proteins, such as heat shock proteins 70 and superoxide dismutase, which play a key role in neutralizing ROS. This, in turn, leads to a reduction in the peroxidation of proteins and lipids in the renal cell membrane (Monami et al. 2021). In our study, we found a 1.7-fold decrease in α-tocopherol concentration ($p<0.05$, Fig. 1) in patients of all groups before inpatient treatment compared to the control group. This may be due to the increased consumption of this active metabolite in the neutralisation of the forms of ROS excessively formed during the pathogenesis of CKD (Popov et al. 2021b). Elevated levels of oxidative stress markers, such as LPO products, are observed in the blood cells and plasma of patients with CKD. This indicates that polyunsaturated fatty acids and cholesterol are not adequately protected from oxidative stress. Additionally, there is evidence of increased susceptibility of plasma lipids to oxidative stress damage in this condition, which is supported by increased levels of active carbonyl groups in plasma proteins formed from LPO, also known as advanced lipid oxidation end products. Furthermore, the antioxidant capacity of vitamin E may be reduced in CKD patients due to disruptions in vitamin C status or overall redox balance. This could lead to inadequate protection against oxidative stress, exacerbating the effects of CKD on lipid metabolism and contributing to further ROS-induced damage. Additionally, secondary malnutrition associated with CKD may affect the intake of antioxidants, trace elements, and fat-soluble vitamins like vitamin E (Galli et al. 2022). Basic therapy had no significant impact on the level of α-tocopherol in patients' blood serum. However, when combined with methylethylpyridinol hydrochloride treatment, the concentration of α-tocopherol increased by 1.4-fold ($p < 0.05$), indicating that the drug slows free radical-induced oxidation by its antioxidant properties. This is manifested by a decrease in α-tocopherol consumption to neutralize ROS (Pelle et al. 2022). For methylethylpyridinol, there is evidence of its ability to reduce LPO activity and activate the antioxidant system of the body. The drug exhibits a pronounced capacity for direct interaction with various radicals, suppression of the Fenton reaction through chelation of metals of variable valence, modulation of the ratio of prostacyclin to thromboxane A2, and inhibition of leukotriene synthesis (Korneeva et al. 2025). Methylethylpyridinol may also have a beneficial effect on the cellular energy metabolism by increasing the bioavailability of succinate. This substance is used, among other purposes, as an antioxidant and angioprotective agent in the treatment of diabetic retinopathy (Peresypkina et al. 2019).

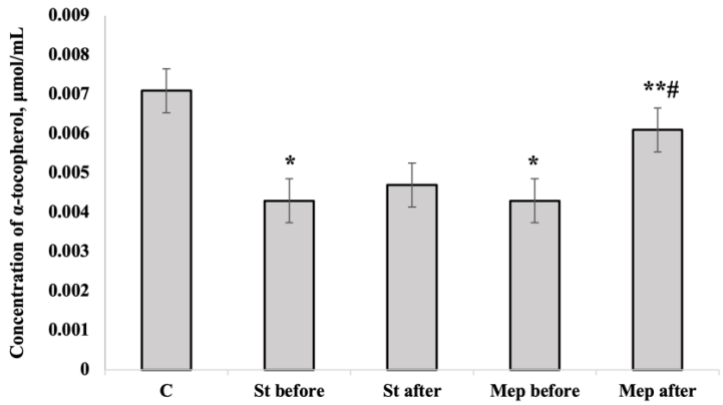


Figure 1. Serum α-tocopherol levels in participants of the control group (C), patients with chronic kidney disease treated with standard therapy (St before and St after), and patients treated with a combination therapy including methylethylpyridinol hydrochloride (Mep before and Mep after). ***Note*:** * – $p<0.05$ between pre-treatment and control group; ** – $p<0.05$ between post-treatment and pre-treatment data; # – $p<0.05$ between changes in parameters during combination therapy with methylethylpyridinol hydrochloride and changes in parameters during standard treatment.

Oxidative stress developing in CKD leads to the activation of mitogen-activated protein kinases and stimulates the synthesis of a number of cytokines that trigger the process of fibrosis. TGF-β1 is one of the most important factors induced under conditions of impaired redox

homeostasis, regulating fibrotic and inflammatory processes. Maintaining TGF-β1 levels within the normal range is crucial for the proper functioning of most tissues. However, an elevation in the expression of this protein is associated with inflammatory stress, which is a frequent occurrence in conditions such as pulmonary fibrosis, spinal muscular atrophy, and kidney disease (Gu et al. 2020). Our data show that in the first and second groups of patients before treatment the concentration of TGF-β1 in blood serum was increased 6.1 and 6.3 times ($p<0.05$) compared to the control values (Fig. 2). The observed differences indicate a significant strengthening of fibrotic processes in CKD developing against the background of type 2 DM. The mechanisms of fibrosis in CKD are regulated by TGF-β1 and are a complex, multifactorial process. This includes increased expression of the extracellular matrix, reduction of its degradation, increased formation of cross-links between collagen and elastin, and activation of dedifferentiation of proximal tubule and endothelial cells. TGF-β1 also promotes production of chemokines, such as tumor necrosis factor-α (TNF-α) and inducible nitric oxide synthase. These chemokines stimulate the production of additional TGF-β1, leading to a positive feedback loop (Zhao.et al. 2020). These results align with previous research, which suggests a rise in TGF-β1 concentrations in individuals with diverse CKD diagnoses, including diabetic nephropathy, IgA nephropathy, focal segmental glomerulosclerosis, sickle cell glomerulonephritis, and lupus nephritis (Gu et al. 2020).

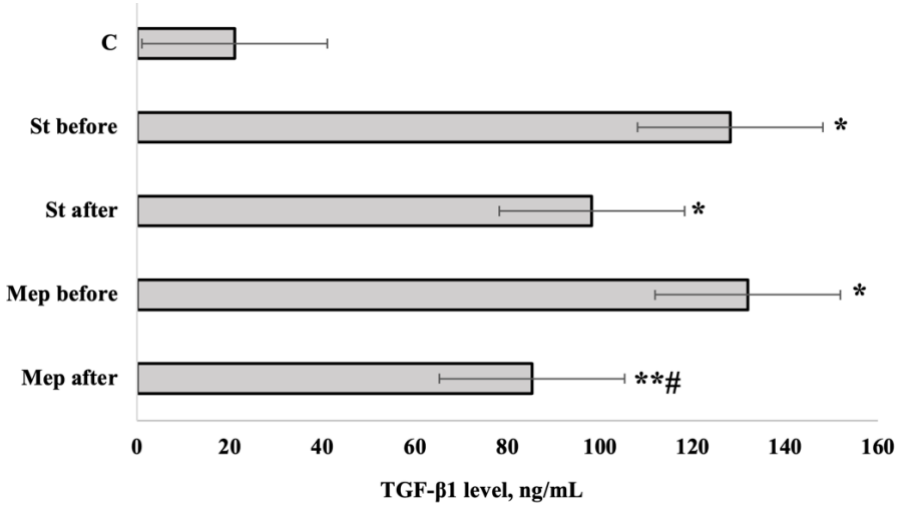


Figure 2. Concentration of transforming growth factor β-1 in serum of the control group (C), patients with chronic kidney disease treated with standard therapy (St before and St after), and patients treated with a combination therapy including methylethylpyridinol hydrochloride (Mep before and Mep after). ***Note:*** * – $p<0.05$ between pre-treatment and control group; ** – $p<0.05$ between post-treatment and pre-treatment data; # – $p<0.05$ between changes in parameters during combination therapy with methylethylpyridinol hydrochloride and changes in parameters during standard treatment.

During the standard treatment, the level of TGF-β1 in the serum of patients decreased 1.3 times ($p<0.05$), compared to the pre-treatment values. The incorporation of methylethylpyridinol hydrochloride into the treatment regimen resulted in a more pronounced reduction in TGF-β1 levels compared to the baseline. Thus, in the second group of patients the content of this factor decreased 1.6 times ($p<0.05$). It has been observed that the effects of combined therapy are associated with the antioxidant and anti-inflammatory properties of methylethylpyridinol hydrochloride. There is evidence that TGF-β1 and other markers associated with fibrosis become activated under conditions of oxidative stress. ROS can directly stimulate the activation of fibroblasts, which are cells responsible for producing extracellular matrix proteins, such as collagen, fibronectin, and elastin. Additionally, ROS can stimulate the release of mediators that promote fibroblast activity and extracellular matrix formation, including TGF-β1. ROS also inhibits the activity of matrix metalloproteinases, enzymes that degrade extracellular matrix proteins (Ghafouri-Fard et al. 2024). There is evidence that antioxidants may function as potential regulators of the TGF-β signaling pathway in the development of fibrosis in various organs. Guanxin V reduced ROS levels by normalizing mitochondrial metabolism and decreased TGF-β1-mediated activity and myocardial fibrosis (Liang et al. 2022). Oleanolic acid, due to its antioxidant effects, has been shown to reduce the expression of TGF-β and related receptors in diabetic rats. Losartan, in addition to its antihypertensive effects, has also been shown to increase the antioxidant capacity of thiol-containing compounds and reduce the oxidative stress index. This compound also has an antifibrotic effect mediated through TGF-β receptor inhibition.

Melatonin, a potent antioxidant hormone, protects against renal fibrosis caused by elevated glucose levels by inhibiting TGF-β expression (Ghafouri-Fard et al. 2024). Therefore, an improvement in oxidative status and a reduction in TGF-β1 activation due to the use of methylethylpyridinol may represent a promising avenue for the treatment of CKD.

Conclusion

The results suggest an increased efficacy of the combination therapy with methylethylpyridinol hydrochloride compared to the standard treatment. Combination treatment with methylethylpyridinol hydrochloride at a dose of 10 mg intramuscularly once daily for 14 days has a powerful antioxidant impact, mitigating the severity of free radical-induced oxidation and restoring α-tocopherol levels in individuals with CKD and type 2 DM.

The incorporation of methylethylpyridinol hydrochloride into standard therapy resulted in a substantially more pronounced shift in the control of TGF-β1 levels in comparison with standard treatment. This findings reflect the enhanced anti-inflammatory and antioxidant potential of combined therapy in CKD. Consequently, the utilisation of methylethylpyridinol hydrochloride may represent a promising therapeutic approach in CKD in the context of type 2 DM.

Additional Information

Conflict of interest

The authors declare the absence of a conflict of interests.

Funding

The authors have no funding to report.

Ethics statement

Ethical approval for this study was granted by the Ethics Committee of Voronezh State Medical University named after N.N. Burdenko' of the Ministry of Health of the Russian Federation (Minutes No. 4 of 29.09.2016).

Data availability

All of the data that support the findings of this study are available in the main text.

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