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Diabetes & its Complications

Clinical and Pharmacological basis for the Use of Telmisartan in Patients with Diabetic Neuropathy

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ABSTRACT

Statement of the problem: *Diabetes mellitus (DM) is the most common cause of diabetic neuropathy (DNP) comprises a heterogeneous group of disorders that can cause neuronal dysfunction throughout the human body. The incidence of diabetes and its complications is increasing to staggering proportions. In 2014 the WHO estimated an overall prevalence of 422 million (8,5%). The incidence of diabetic neuropathy approaches 50% in most diabetic populations; there is no treatment, and its consequences in the form of foot ulceration and amputation.*

The recent studies suggest that the renin angiotensin aldosterone system (RAAS) plays a vital role in regulating glucose metabolism and blood pressure. In the same time the metabolic abnormalities associated with diabetes lead to activation RAAS, which might promote the formation of reactive oxygen species to lead the endothelial and neuronal dysfunctions. Furthermore, TNFα is part of the response of the organism to hypertension and is originally described as one of the central mediators of inflammation trough the activation of transcription factor NFκB an important factor in the control of cell proliferation, differentiation, and apoptosis.

Methodology & Theoretical Orientation: *The study population consists of 15 individuals diagnosed with DM complicated by DNP. The enrolled subjects will take Telmisartan during 6 weeks. At the start of the trial and on completion of the six weeks period TNFα level and C-peptide as well as evaluation of severity of DPN will be determined.*

Findings: *Telmisartan by reducing of plasma TNFa level improves moderately conditions of DM patients with DNP. Namely, the symptoms of neuropathy are relatively reduced; Telmisartan has visible TNFα modulatory effects but do not change C-peptide level properly.*

Conclusion & Significance: *Our results confirm hypothesis that TNFα may play a substantial role in the development and progression of DM as well as in pathogenesis of DPN. Telmisartan moderately ameliorates symptoms of DPN patients by visible modulatory impact on TNFα. So, we have results for further research to compare Telmisartan with other RAAS inhibitors for final clinical and pharmacological analysis of RAAS inhibitors application in diabetic neuropathy.*

Keywords
Telmisartan, Diabetes Mellitus, Diabetic Neuropathy, Renin Angiotensin Aldosterone System, Tumor Necrosis Factor alpha, peroxisome proliferator-activated receptor gamma.

Introduction
Diabetes mellitus (DM) is the main problem of public health worldwide. DM patients have a high risk to develop microvascular complications such as retinopathy, and neuropathy and macrovascular complications of cardiovascular disease (CVD), stroke and peripheral arterial disease but the most frequently established problem is diabetic peripheral neuropathy (DPN) [1].

The incidence of diabetes and its complications is increasing to staggering proportions. In 2014 the WHO estimated an overall prevalence of 422 million (8,5%). In 2015, an expected 1.6 million deaths were directly caused by diabetes [2]. It is estimated there will be 552 million people with diabetes until 2030. [3] The incidence of diabetic neuropathy approaches 50% in most diabetic populations; there is no treatment, and its consequences in the form of foot ulceration and amputation are financially punishing for health care providers [4].

The treatment of DN still remains unresolved. There are currently no FDA-approved therapies for DN and only 3 approved therapies for painful DN. But unfortunately no treatment results in complete resolution of the underlying pathophysiological abnormalities and treatment of DN is an unmet need in clinical practice [5-8]. Nowadays the optimal therapy involves: blood glucose level control, anticonvulsants, antidepressants and opioid administration, though it does not change pathogenic pattern. In addition of that patients have high need for meticulous foot hygiene, appropriate footwear, and mobility support as needed. [9-11].

DN includes a heterogeneous group of disorders that can cause neuronal dysfunction throughout the human body [12]. In about one fifth of patients, painful diabetic peripheral neuropathy (DPN) predominates, and has a significant negative impact on health-related quality of life and general function [13]. Foot problems from underlying DPN are a major cause for developing ulcers, Charcot foot abnormalities, injuries, infections, and lower extremity amputation and this is a lifetime risk for patients with DM [14]. Other manifestations include small-fiber neuropathy, autonomic neuropathy, diabetic amyotrophy, radiculopathy, mononeuritis multiplex, mononeuropathy, and treatment-induced neuropathy [15].

Generally, two mechanisms have been suggested to be involved in the pathogenesis of DPN. The first mechanism is the activation of the RAAS in the presence of hyperglycemia with increased tissue level of Ang II. Ang II stimulates NAD (P) oxidase which enhances oxidative stress and vascular damage and leading to DPN [16]. The other mechanism is disturbance in the metabolism and vasculature of nerve tissue in the presence of excessive uptake of glucose [17].

The recent studies suggest that RAAS plays a vital role in regulating glucose metabolism and blood pressure, electrolyte and fluid homeostasis. The genes of RAAS have important roles in glucose metabolism and regulation of blood pressure. Activation of RAAS leads to elevated levels of the main vasoconstrictor peptide of the angiotensin II (Ang II). Ang II affects glucose homeostasis and is involved in the pathogenesis of DM through inhibition of insulin signal transduction, reduction of glucose uptake, resistance to insulin, and destroying the beta cells of pancreas by inducing oxidative stress [3].

Consequently, RAAS is associated with DM and its complications of retinopathy, neuropathy and cardiovascular disease (CVD) [18]. In the same time the metabolic abnormalities associated with diabetic patients hyperglycemia lead to activation RAAS, which might promote the formation of reactive oxygen species to lead the endothelial dysfunctions, thrombosis, inflammation and vascular remodelling [19,20]. Namely, activation of the RAAS and enhanced production of Ang II has an inhibitory effect on insulin signal transduction pathway. The Ang II prevents insulin receptor substrate-1 (IRS-1) phosphorylation with the subsequent decrease in phosphatidylinositol 3 kinase and also it reduces glucose uptake through GLUT4 that resulted in insulin resistance. Further, Ang II increases reactive oxygen species, which leads to damaging the pancreatic β-cells and may indirectly impair insulin secretion from the pancreas through vasoconstriction and reduction in islet blood flow. Chronic exposure to high levels of glucose and fat induces oxidative stress, inflammation and apoptosis with participation of Ang II through AT1R in β-cells of pancreas.

All these effects resulted in the development of DM [21]. The other component of the RAAS, aldosterone, decreases the insulin secretion from β-cells in a mechanism involves oxidative stress [22]. In other hand TNFa is part of the response of the organism to hypertension. TNFα was originally described as one of the central mediators of immunity and inflammation trough the activation of transcription factor NFκB an important factor in the control of cell proliferation, differentiation, and apoptosis through the induction of variety of genes [23]. Moreover, local accumulation of glucose and its metabolite, succinate, through activation of a G-protein coupled receptor (CPR91) triggers the cell to cell signaling that results in prorenin and renin release from juxtaglomerular cells in early diabetes [4].

Moreover, the damage of peripheral nerve in diabetes could be attributed to polyol accumulation, advanced glycation end-products and oxidative stress [16]. Formation of advanced glycosylated end products (AGEs) in DM appears to play a crucial role in the pathogenesis of microvascular complications and maybe in the "metabolic memory" observed in large studies. It has been proposed that the pathophysiological cascades triggered by AGEs have a dominant, hyperglycemia-independent role in the onset of the microvascular complications of diabetes [24].

Furthermore, Onset of insulin resistance is often accompanied by obesity, in particular visceral obesity. Resistance of dysfunctional fat cells to the antilipolytic effects of insulin leads to chronic elevations in plasma free fatty acid (FFA) levels. This, in turn, induces insulin resistance in the liver and skeletal muscle, resulting in reduced glucose uptake and increased gluconeogenesis. Dysfunctional fat cells also produce excessive amounts of cytokines (e.g., tumor necrosis factor-α [TNF-α], interleukin [IL]-6, and resistin) that further induce insulin resistance, inflammation, and atherosclerosis and that secrete reduced amounts of insulin-sensitizing cytokines such as adiponectin [25].

As the list of clinical studies explain the peroxisome proliferator-activated receptor (PPAR) family of nuclear receptors and the winged-helix-forkhead box class O (FOXO) family of factors are two key families of transcription factors that regulate glucose homeostasis and insulin responsiveness In the adipose and muscle tissues [26]. The three peroxisome proliferator–activated receptor (PPAR) isoforms PPARα, -γ, and -δ are nuclear receptors activated by fatty acids and fatty acid–derived eicosanoids. In general, PPARα regulates genes involved in fatty acid uptake and oxidation, inflammation, and vascular function, whereas PPARγ regulates genes involved in growth and differentiation of adipocytes, as well as fatty acid uptake and storage, inflammation, and glucose homeostasis. PPARδ regulates genes involved in fatty acid metabolism, inflammation, and macrophage lipid homeostasis. [25,27].

As geneticak research results identifaid, PPARγ was the first gene reproducibly associated with T2DM [28,29]. PPARγ activation can regulate gene expression for genes involeved in metabolism of glucose and lipids, insulin's sensitivity, cell growth and differentiation [30,31]. Rare inactivating mutations of the gene encoding PPARγ are associated with insulin resistance type 2 diabetes, and hypertension, whereas a rare gain of function mutation causes extreme obesity [27]. PPARγ is also expressed in immune/inflammatory cells (monocytes and macrophages), which could contribute to its anti-inflammatory activity [33,33]. Consequently, PPARγ has been the focus of intense research during the past decade because ligands for this receptor have emerged as potent insulin sensitizers used in the treatment of T2DM [34].

Finally it is also very important to identify that C-peptide deficiency is an important contributing factor to the characteristic functional and structural abnormalities of the peripheral nerves [35]. C-peptide binds to cell membranes, resulting in stimulation of endothelial nitric oxide synthase (eNOS) and Na+, K+-ATPase [36].

A number of different therapeutic approaches that target the various pathogenetic mechanisms of DNP have been the subject of clinical trials, to impact favorably the underlying pathophysiological aberrations encountered in DPN by targeting different elements in the pathways leading to neurovascular dysfunction [37]. It has been demonstrated that the inhibition of RAAS by ACE inhibitors (ACE I) or AT1R blockers prevents the adverse effects of Ang II on glucose metabolism and insulin resistance [21]. Results of a meta-analysis indicated that the treatment of nondiabetic individuals with ACE I and ARB decreased the risk of T2DM [12]. Decreased production of Ang II and aldosterone or inhibition of both receptors of AT1R and mineralocorticoid has been improved insulin sensitivity in both in vivo and in vitro studies [22].

In according the research study on the rats, Telmisartan (AT1R blocker) has a potential neuro-protective effect on peripheral DN; this is mediated through its anti-inflammatory effects and its dual properties as an angiotensin receptor blocker, and a partial peroxisome proliferator activator receptor-g ligand [38,39].

In consequence, further optimization of the DNP treatment will become feasible. It can be assumed that Telmisartan administration will significantly improve patients' condition by modulating TNFα activation and correspondingly, reduce severity of neuropathy, extent and number of complications. Quality of life will improve and consequently mortality rate and health care expenditures will decrease.

Research Goals and Objectives

Research goal: Assessment of Telmisartan efficacy in clinical management of diabetes mellitus, complicated with peripheral neuropathy.

We hypothesized that administration of Telmisartan in patients with DPN during 6 weeks would ameliorate the symptoms of DPN trough blocking of AT1R and consequently inhibition of TNF-α level, as well as by activation PPARG which would contribute to the prevention of DPN induced complication in patients with Diabetes Mellitus.

Methods

Participants

Total 15 patients (over 18 years of age) with Diabetes Mellitus complicated by DPN who fulfilled inclusion criteria were randomized enrolled in this study and were informed of study requirements from internal medicine department #2 of Tbilisi State Medical University Hospital. The following exclusion criteria were applied to select the participants; (1) Subjects on ACE inhibitors and other RAAS inhibitors; (2) Subjects with the history of myocardial infarction, cardiovascular surgical intervention, acute coronary syndrome, atrial fibrillation, dysrhythmia, severe cardiac ischemia; (3) Subjects with renal failure (creatinine level over 1.5mg.dL); (4) Subjects with hyperkalemia over 0.5 mmol/L. We used trial Termination Criteria for Patients, in Accordance with GCP (Good Clinical Practice) Standards.

Methods applied

Each lab test was conducted at 9.00 am. Blood HbA1c was measured using "Ge Tein BioMedical inc" Immune chromatography diagnostic test kits and medical devices; but for assessment of fasting C-peptide and Plasma TNF-α level we have used immunoassay method using AccuBind ELIZA kits ("Monobind inc") and "Immun Diagnostik" TNF-α ELISA kits respectively. The results have been analyzed by the reader-"Urit Medical 600". We have evaluated severity of DPN in patients by revised neuropathy disability score (NDS) [40] which includes assessment of the following parameters: (a) Vibration perception threshold (128Hz); (b) Temperature perception; (c) Pin prink testing; (d) Achilles tendon reflex; The maximum score for the modified NDS is 10 (0 if normal; 1 if abnormal for a-c and if the reflex present (score=0), present with reinforcement (score=1) or absent (score-=2) for d) indicating a complete loss of all sensory modalities and absent reflexes. A score of six or more has been found to indicate an increased risk of foot ulceration. Also we used additionally Monofilament sensory testing and added max 2 score (0 if normal; 1 if abnormal for each foot).

Study design

This study was randomized, open-label, within-participants of clinical trail and was conducted according to the study protocol involving human subjects was approved by ethnic committee of Tbilisi State medical University. At the beginning of the trial the study protocols and benefits of study were explained to each participant. The written informed agreement was signed by all of participants. On the first day, before medical consultation patients passed trough lab investigation to perform blood HbAc, serum TNFα and fasting C-peptide tests. During the medical consultation the subjects with DPN were detailed examined through: (a) the general inspection of the feet and patient's foot wear; (b) vascular asses of the feet, and assessment of the heart rate and blood pressure (c) neurological assessment by the above mentioned methods (see 2.2). All participants took the same Telmisartan during first 4 weeks in dose 40mg and in dose 80mg daily following two weeks keeping their own original treatment schedule. At the end of trail all of patients did serum TNF-α and fasting C-peptide tests and passed trough clinical investigation to evaluate DPN symptoms. During this 6 weeks patients are filtered trough GCP criteria monitor by study implementation team (Figure 1).

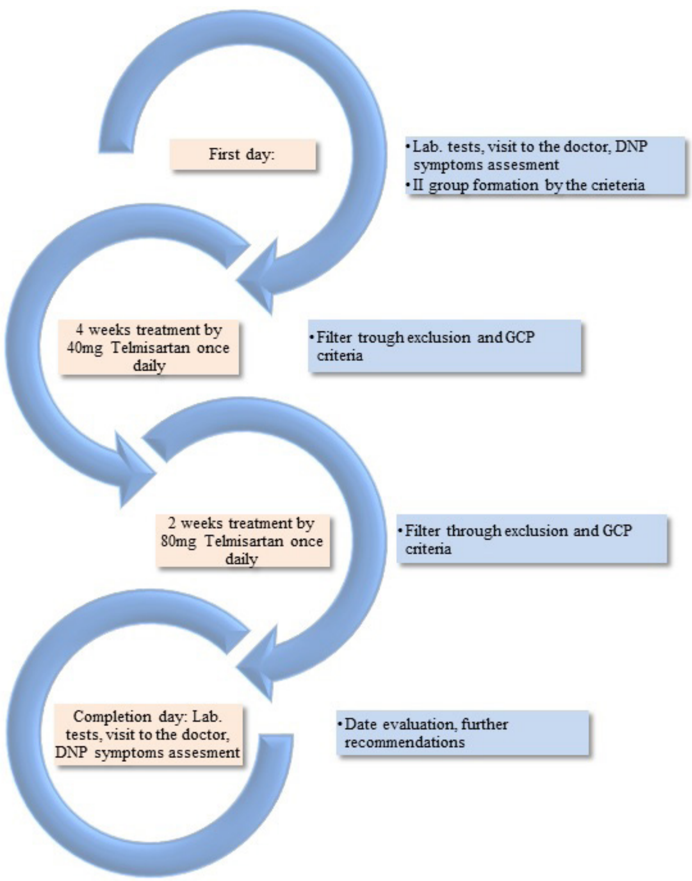

Figure 1: Study design. Participants pass through the same steps during 6 weeks clinical trial period.

Results

Of 15 subjects (mean age 63.6 and mean body weight 87.7), suffered from DPN, which consisted mild pain in 73% (n=11), severe in 6% (n=1) and painless in 20% (n=3) were evaluated. The majority of patients 73% (n=11) were diagnosed more than 10 years ago. Of the 5 patients, 36% have had diagnosed for 4 years or less. Patients were Caucasians and over half were male (60%); all of subjects in this study had co-morbidity: hypertension (no hyperlipidemia) (53%), hyperlipidemia with hypertension (67%) and obesity (53%). All of patients were evaluated for HbA1c at the beginning. The mean of HbA1c was 7.69%. Of the 15 patients 33% (n=5) have HbA1c of 7.0% or less, and 20% (n=3) of the patients had HbA1c greater than 9.0% (Table 1). Because one of patient violated terms and conditions laid down in the protocol the termination criteria filter excludes him from study. 14 patients completed pilot phase of clinical trials.

Characteristics		Participants, n (%)
Men		9 (60)
Women		6 (40)
Mean age, years		63.6
Mean body weight (kg)		87.7
Race/ethnicity		Caucasians
Smoking status	Smokers	5 (33)
	Nonsmokers	10 (67)
	T2DM insulin dependent	1 (6)
	T2DM alone (no hypertension or hyperlipidemia)	1 (6)
	T2DM + hypertension (no hyperlipidemia)	8 (53)
	T2DM + hyperlipidemia +hypertension	10 (67)
	Obesity	8(53)
HbA1c start level	Mean	7.69
	HbA1c 7% or lesser	5 (33) •
	HbA1c 9% or greater	3 (20)
Comorbidity	None	0
	Depression	3 (20)
	DNP	15 (100)
	Total NDS ≥6	8(53)
	Total NDS<6	7(47)
	Total NDS=8	5(33)
	Painless DNP	3(20)
	Mild pain DNP	11 (67)
	Severe pain DNP	1 (13)
	Retinopathy	10 (67)
	Chronic kidney disease	2 (13)

Table 1: Baseline characteristics of study participants (and Group II_ n=15). • Percentages may not total to 100 because of rounding.

The plasma TNF-α level was high (μ=34.8 pg/ml) in patients with NDS =8 (n=5). After 6 weeks Telmisartan treatment the serum TNF-α level was changed 24.5 ± 9.9pg/ml vs 16.8 ± 3.0pg/ml as shown in Figure 2. The baseline of serum TNF-α μ=24.5 pg/ml significantly changed in study participants after Aliskiren treatment μ=16.8 pg/ml. The serum TNF-α levels of patients with DNP before and after Telmisartan application was changed by ≤40% (n=11) and by >40% (n-3); P –value is <0.00001 ($p<0.05$).

In the same time the fasting C-peptide level was changed 2.7 ±

1.5 ng/ml vs. 2.5 ± 0.85 ng/ml after 6 weeks Telmisartan treatment as indicated in Figure 3. In the most patients of group the fasting insulin C- peptide levels before and after Telmisartan application was modified by ≤ 20% (n=10) and in some patients by >20% (n-4); P-value is 0.103, therefore the result is not significant at $p<0.05$;

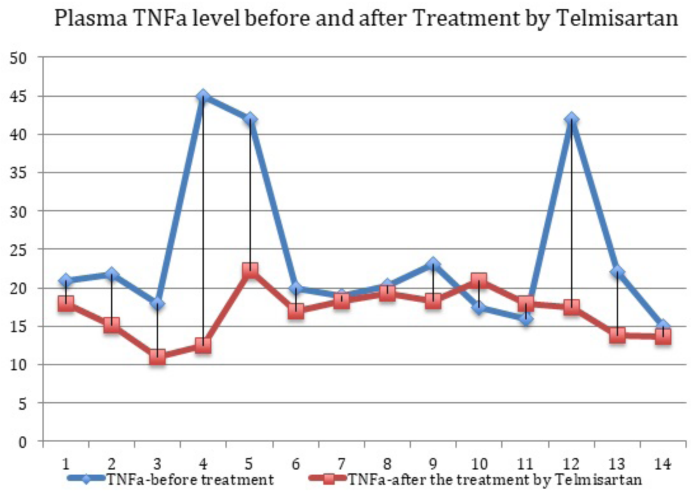

Figure 2: Plasma TNF- α level profiles of Telmisatan treatment during the study period in participants with DNP (n=14); The blue line is plasma TNF- α level (μ=24,5 pg/ml) before treatment, red line indicates how Telmisartan reduces plasma TNF- α level (μ=16.8 pg/ml) after 6 weeks treatment.

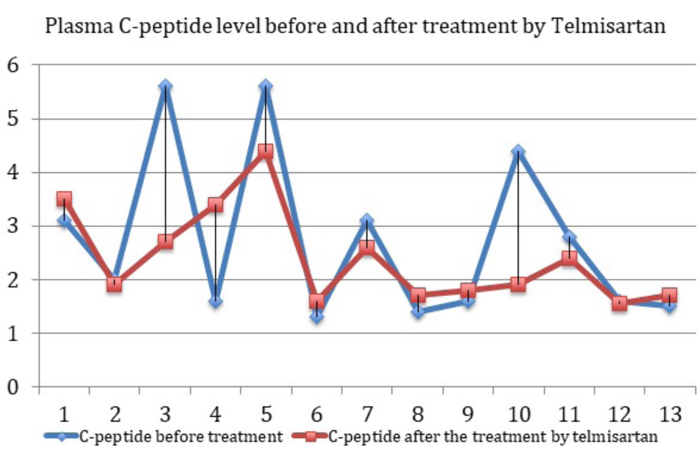

Figure 3: Fasting insulin C-peptide level profiles of Telmisartan treatment during the study period in participants with DNP (n=14); The blue line is fasting C-peptide (μ=2.7ng/ml) before treatment, red line indicates how Telmisartan regulates plasma C-peptide level (μ=2.5ng/ml) in each patients (n=14) after 6 weeks treatment.

Consequently, DNP symptoms are improved moderately in participants. At the beginning of study in 47% (n=7) we have detected the score <6 and 53% (n=8) patients we have found the score ≥6 (Table 1). After Telmisartan treatment DNP symptoms improved in 54% (4 from 8) and the NDS reduced fewer than 6.

Discussion

The main and original finding of this study was to show effects of Telmisartan in DPN patients by inhibition of TNF-α, inflammatory cytokine involved in the pathogenesis of neuronal dysfunction and T2DM formation [41,42]. We demonstrated that the administration of Telmisartan change the serum TNF-α and moderately ameliorate DPN symptoms. The level of serum TNF-α is reduced in patients with high TNFα after 6 weeks Telmisartan treatment. Recent study indicates that Telmisartan reduces inflammatory cytokines level by inhibiting of Ag II effect in ineriferral cells [43]. In the same time Telmisartan by activation of PPAR-γ inhibits NF-kB signaling pathway, therefore the inflammatory cytokines such as TNFa formations as well as and apoptotic mediators gene expression are decreased; moreover the oxidative stress elements such as reactive oxygen species and nitric oxide levels are reduced also. In contrast, antioxidants level is increased. Net effect of mentioned changes leads to amelioration of neuroinflammation [44]. Furthermore, by activating of $PPAR^{\gamma}$ it regulates lipid and glucose metabolism [38,39,45]. As a result of this action Telmisartan inhibits oxidative stress and reduces free radicals [44-47]. PPARG ligands can reduce the expression of pro inflammatory genes, decrease TNFa production and increase adiponectine expression [26,30-34].

On the other hand as it is known TNF-α is the main pro-inflammatory cytokine critically involved in the development of insulin resistance and pathogenesis of T2DM [48,49]. Therefore, we proposed that Telmisartan, by inhibiting of serum TNF-α level should improve pancreatic β-cells function, as well as insulin receptors sensitivity and by this way should regulate fasting C-peptide level. But as our clinical research resalts show after 6 weeks Telmisartan treatment, the level of fasting C-peptide not normalized properly in evaluated patients. We propose that the reason of this results maybe the following, as recent study suggest, RAAS blockers prevent insulin resistance in some, but not all T2DM patients indicating inter-individual variability [12]. In the other hand formation of C-peptide takes place in the endoplasmic reticulum of pancreatic β-cells. The endoplasmic reticulum stress, which can be expressed, by the TNFα, sRAGE, IL-1- β and IFN-γ is one of the cause of C-peptide deficiency. As it is mentioned Telmisaetan regulates angiotensin II induced TNFa formation, therefore the other ligands formed in DPN patients can leads to ER stress and concequnctly C-peptide formation destruction [50].

Also, many clinical research studies results illustratrate that TNF-α produced by the activated macrophages and monocytes plays an important role in pathogenesis of DPN trough the demyelination of nerve fibers, disorganization of lamellar and axonal structures and decreased expression of myelin basic protein (MBP) in the nerve tissues [41]. In addition of that TNF-α, produced by adipocytes and/or peripheral tissues maybe cause of DNP trough generation ROS [42]. By our study we correspond to the already done clinical studies that the TNF-α high serum level and abnormal fasting C-peptide level are involved in DNP formation [41,42,51]. Telmisartan by modulation of only TNF-α level moderately improves the symptoms of DNP.

Finally, the recent clinical study indicates moderate effects of Telmisartan in DM with complication recognized to its anti-diabetic, renoprotective, antioxidant, anti-inflammatory, and anti-apoptotic effects trough the inhibition of AT1R and activation

PPARγ [52]. In our study there was positive correlation between DPN symptoms and TNF-α level. The study results prove Telmisartan above mentioned effects linked with reducing plasma TNF-α, in DM patients.

It can be assumed that Telmisartan administration will improve moderatly patients' condition by modulating TNF-α activation and correspondingly, reduce symptmes of neuropathy in some patients and extent and number of complications.

Conclusion

Our results may demonstrate of TNF-α and Angiotensin II implication for organ-specific complication pathogenesis of DM as well as in DPN.

Findings

Telmisartan by reducing of plasma TNFa level improves moderately conditions of DM patients with DNP. Namely, the symptoms of neuropathy are relatively reduced; Telmisartan has visible TNFα modulatory effects but do not change C-peptide level properly.

Conclusion & Significance

Our results confirm hypothesis that TNFα may play a substantial role in the development and progression of DM as well as in pathogenesis of DPN. Telmisartan moderately ameliorates symptoms of DPN patients by visible modulatory impact on TNFα. So, we have results for further research to compare Telmisartan with other RAAS inhibitors for final clinical and pharmacological analysis of RAAS inhibitors application in diabetic neuropathy.

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