Research Article ISSN 2639-9326

Diabetes & its Complications

Clinical and Pharmacological Basis for the Use of Aliskiren in Diabetes Mellitus Patients with Peripheral Neuropathy

Archvadze Anna Sh[1], Kistauri Alexandre[1*], Gongadze Nikoloz[2] and Chirakadze Ketevan[2]

[1]*Department of internal medicine, University Hospital, Tbilisi State Medical University, Tbilisi, Georgia.*

[2]*Department of Medical Pharmacology, Tbilisi State Medical University, 33 Vazha-Pshavela ave, 0177, Tbilisi, Georgia.*

[*]Correspondence:
Kistauri Alexandre, Department of internal medicine, University Hospital, Tbilisi State Medical University, Tbilisi, Georgia, Tel: +599 559183; E-mail: a_kistauri@yahoo.de.

Received: 06 March 2018; **Accepted:** 02 April 2018

Citation: Archvadze Anna Sh, Kistauri Alexandre, Gongadze Nikoloz, et al. Clinical and Pharmacological Basis for the Use of Aliskiren in Diabetes Mellitus Patients with Peripheral Neuropathy. Diabetes Complications. 2018; 2(2): 1-6.

ABSTRACT

Statement of the problem: *Diabetes mellitus is a challenging problem in modern medicine. Over 347 million people worldwide suffer from diabetes. Polyneuropathy is the most common complication of diabetes mellitus (60-70% of patients). Its treatment still remains unresolved. The optimal therapy involves: blood glucose level control, anticonvulsants, antidepressants and opioid administration, though it does not change pathogenic pattern. It has been identified that tumor necrosis factor alpha (TNF-α) and renin-angiotensin aldosterone system (RAAS) play a significant role in Type I and Type II diabetes development The data collected in the present-day scientific literature indicate the essential pathogenic role of TNF-α in the development of diabetic neuropathy (DNP). In our study we use Aliskiren (renin inhibitor) to study modulatory impact on TNF-α.*

Methodology & Theoretical Orientation: *The study population consists of 15 individuals diagnosed with diabetes mellitus (T2DM) with DNP. The enrolled subjects take Aliskiren during 6 weeks. At the start of the trial and on completion of the six weeks period TNF-α level and C-peptide will be determined.*

Findings: *Aliskiren improves conditions of T2DM patients with DNP. Namely, the symptoms of neuropathy are reduced, the blood TNF-α level is reduced and C-peptide level is increased.*

Conclusion & Significance: *Our results confirm hypothesis that TNF-α may play a substantial role in the development and progression of type 2 diabetes mellitus as well as in pathogenesis of diabetic neuropathy. Aliskiren has modulatory impact on TNF-α, so we have results for clinical and pharmacological analysis of Aliskiren application in diabetic neuropathy.*

Keywords

Aliskiren, Diabetes mellitus, Diabetic neuropathy, Renin angiotensin Aldosterone System, Tumor necrosis factor alpha.

Introduction

Diabetes mellitus is a challenging problem in modern medicine. It has multi-component pathogenesis, varied clinical manifestations, and is characterized by diverse mechanisms of development, clinical course and complications. In Type I diabetes, the immune system attacks and affects insulin-producing beta cells in the pancreas. It is characterized by the formation of autoantibodies, progressive immune cell infiltration in Langerhans islets, followed by insulin-producing beta-cell destruction [1]. It is believed that Cytokine production may be the major factor in beta-cell death involving interleukin1 (II-1), interferonγ (INF γ) and tumor necrosis alpha (TNF-α) [2,3] belonging to inflammatory cytokines produced by T cells during this process. It has been identified that TNF-α and renin-angiotensin system play a significant role in the development of Type II diabetes through the resistance formation to insulin [4-5]. TNF-α mainly produced in adipocytes and/or peripheral tissues induces tissue-specific inflammation through the involvement of generation of ROS and activation of various transcriptional mediated pathways. One of the results of such effects is formation of insulin resistance through serine

phosphorylation that leads to the development of T2DM [6]. The data collected in the present-day scientific literature indicate the essential pathogenic role of TNFα in the development of diabetic neuropathy (DNP) [7]. The clinical and electrophysiological study recommend that "Tumor necrosis factor-α is a novel biomarker for peripheral neuropathy in type II diabetes mellitus" [8]. Infliximab, an agent currently in clinical use, is effective in targeting TNF-α action and expression and amelioration of diabetic neuropathy in mice [9].

Different inflammatory mediators involved in DNP development and all regulating MAPK (mitogen activated protein kinase, activated by renin) engaged in their synthesis should be noted. Aliskiren is MAPK suppressing agent and correspondingly, reduces inflammatory cytokines including TNFα activation [10]. Aliskiren regulates inflammation by reducing MAPK and Nuclear Factor B (NF-k B) activation in kidneys [11]. It is noteworthy that Aliskiren serves as TNF-α activation modulator [12].In addition of that the recent clinical studies indicates significant effects of Aliskiren treatment in diabetic nephropathy (DN) in rats, which could be attributed to its anti-diabetic, renoprotective, antioxidant, anti-inflammatory, and anti-apoptotic effects. Aliskiren normalized streptozotocin-induced hyperglycemia in rats, increased insulin level both in vivo and in vitro [13].

Aliskiren as a direct renin inhibitor is non-peptide molecule marked by high affinity and specificity to human renin. It inhibits enzyme-renin by binding to its catalytic center and blocks renin-angiotensin system at its activation stage, respectively, angiotensin I, angiotensin II and aldosterone levels as well as hemodynamic and inflammatory effects induced by them decrease. It can become a reasonable therapeutic choice to treat a wide range of clinical conditions like stable coronary syndrome, cardiovascular and cardio-renal diseases, diabetes and peripheral artery diseases [14]. Among contraindications individual hypersensitivity to the medication should be noted. Among side/adverse effects low incidence of angio-edema, diarrhea, cough and others were reported [15].

Number of studies should note that in diabetic nephropathy C-peptide through Gi (G inhibitory) protein mechanism protects cells of the proximal renal tubule from TNF-α conditioned apoptosis [16]. Presently, clinical studies are being conducted on diabetic angiopathy treatment with Aliskiren in Type I diabetic patients. Aliskiren effect on the immune system functioning as TNF-α activation modulator is also of particular interest. With this respect recent study on rats showed that Aliskiren does not impair immune system, on the contrary, it has the ability to impede immuno-suppression conditioned nephrotic syndrome development [17]. Actually anti-TNF-α treatment induces immune tolerance selective to syngeneic beta cells. In addition to these curative effects on T1D anti-TNF-α treatment fixed in vivo insulin signaling resulting in restoration of insulin sensitivity [18].

Furthermore, the effects of the Renin Angiotensin System (RAS) on insulin secretion are mediated by a reduction in pancreatic blood flow and induction of islet fibrosis, oxidative stress as well as inflammation; whereas both impaired skeletal muscle function and adipose tissue dysfunction may underlie RAS-induced insulin resistance [19-20]. In the same time the metabolic abnormalities associated with diabetes lead to activation of the Renin-Angiotensin-Aldosterone System (RAAS), which might promote the formation of reactive oxygen species to lead the endothelial dysfunctions [21].

Over 347 million people worldwide suffer from diabetes [22]. In 2012 1.5 million people died from diabetes [23,24]. By WHO estimations, based on mortality rate statistics, in 2030 diabetes will come in 7-th among leading causes of death globally [25]. Polyneuropathy is the most common complication of diabetes mellitus (60-70% of patients) [26]. Its treatment still remains unresolved. The optimal therapy involves: blood glucose level control, anticonvulsants, antidepressants and opioid administration, though it does not change pathogenic pattern [27,28].

As it is above mentioned the literature source suggests that the various mechanisms associated with elevation of TNF-α can be cause of the inflammatory damages leads to formation of insulin resistance, pancreatic β-cell apoptosis, as well as formation of DNP in patients with T2DM [7,11,29-31]. In consequence, further optimization of the syndrome treatment by inhibition of TNF-α will become feasible.

Research goals and objectives

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

We hypothesized that administration of Aliskiren in patients with DNP during 6 weeks would ameliorate the symptoms of DNP trough inhibition of TNF-α level, which would contribute to the prevention of DNP induced complication in patients with Diabetes Mellitus.

Methods

Participants

Total 15 patients (over 18 years of age) with type 2 Diabetes Mellitus complicated by DNP 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 ARB; (2) Subjects with the history of myocardial infarction, cardiovascular surgical intervention, acutecoronary 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 DNP in patients by revised neuropathy disability score (NDS) [32] 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 trial 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 through lab investigation to perform blood HbAc, serum TNFα and fasting C-peptide tests. During the medical consultation the subjects with DNP 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 Aliskiren during first 4 weeks in dose 150mg and in dose 300mg 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 through clinical investigation to evaluate DPN symptoms. During these 6 weeks patients are filtered through GCP criteria monitor by study implementation team (Figure 1).

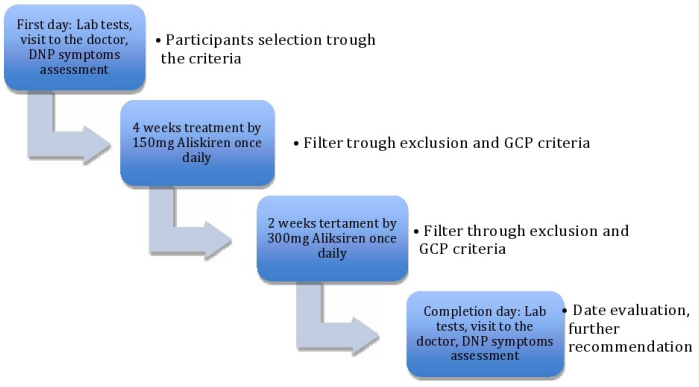

Figure 1: Study design. Participants pass through the same steps during 6 weeks clinical trial period.

Results

Of 15 subjects (mean age 63.3), suffered from DNP, which consisted mild pain in 67% (n=10), severe in 13% (n=2) and painless in 20% (n=3) were evaluated. The majority of patients 64% (n=9) were diagnosed less than 10 years ago. Of the 5 patients, 36% have had diagnosed for 15 years or more. Patients were Caucasians and over half were male (60%); all of subjects in this study had co-morbidity: hypertension (no hyperlipidemia) (26%), hyperlipidemia (no hypertension) (1%) and obesity (73%). All of patients were evaluated for HbA1c at the beginning. The mean of HbA1c was 6.8%. Of the 15 patients 46% (n=7) have HbA1c of 7.0% or less, and 53% (n=8) 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.

		Participants, n (%)
Characteristics	Men	9 (60)
	Women	6 (40)
	Mean age, years	63.3
	Mean body weight (kg)	78.6
	Race/ethnicity	Caucasians
Smoking status	Nonsmokers	10 (67)
	T2DM alone (no hypertension or hyperlipidemia)	0
	T2DM + hypertension (no hyperlipidemia)	4 (26)
	T2DM + hyperlipidemia (no hypertension)	1 (6)
	Obesity	11(73)
HbA1c start level	Mean	6.8
	HbA1c 7% or lesser	7 (46)•
	HbA1c 9% or greater	8 (53)
Comorbidity	None	0
	Depression	4 (26)
	DNP	15 (100)
	Total NDS ≥6	12(80)
	Total NDS<6	3(20)
	Painless DNP	3(20)
	Mild pain DNP	10 (67)
	Severe pain DNP	2 (13)
	Retinopathy	2 (13)
	Chronic kidney disease	1 (6)

Table 1: Baseline characteristics of study participants (n=15).

The plasma TNF-α level was high (μ=25.1 pg/ml) in patients with NDS ≥ 6 (n=12). After 6 weeks Aliskiren treatment the serum TNF-α level was changed 25.1±7.3 pg/ml vs 17.4 ± 2.9 pg/ml as shown in Figure 2. The baseline of serum TNF-αμ=25.1 pg/ml significantly changed in study participants after Aliskiren treatment μ=17 pg/ml. The serum TNF-α levels of patients with DNP before and after Aliskiren application was changed by ≤ 45% (n=12) and by >45% (n-2); p=0.0122 (<0.05);

In the same time the fasting C-peptide level was changed 2.3 ± 0.7 ng/ml vs. 2.9 ± 0.8 ng/ml after 6 weeks Aliskiren treatment as indicated in Figure 3. In the most patients of group the fasting insulin C- peptide levels before and after Aliskiren application was modified by ≤ 45% (n=11) and in some patients by >45% (n-3); p=0.039 (<0.05);

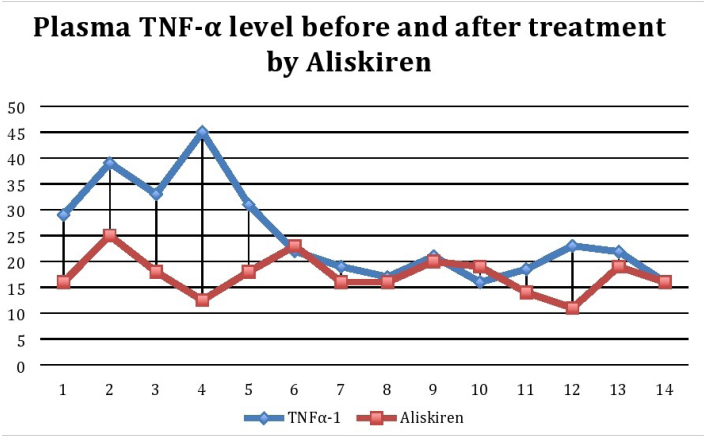

Figure 2: Plasma TNF-α level profile of Aliskiren treatment during the study period in participants with DNP (n=14); The blue line is plasma TNF-αLevel (μ=20,1pg/ml) before treatment, red line indicates how Aliskiren reduces plasma TNF-α level (μ=17.4pg/ml) after 6 weeks treatment.

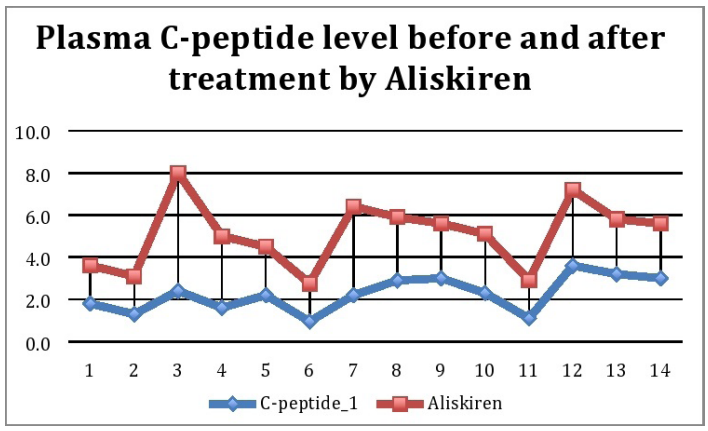

Figure 3: Fasting insulin C-peptide level profiles of Aliskiren treatment during the study period in participants with DNP (n=14); The blue line is fasting C-peptide (μ=2.3ng/ml) before treatment, red line indicates how A Aliskiren regulates plasma C-peptide level (μ=2.9ng/ml) in each patients (n=14) after 6 weeks treatment.

Consequently, DNP symptoms are improved in participants also. At the beginning of study in 20% (n=3) we have detected the NDS score <6 and 73% (n=11) patients we have found the NDS score ≥ 6 (Table 1). After Aliskiren treatment DNP symptoms improved in 85% (12 from 14) and the NDS reduced above 6.

Discussion

The main and original finding of this study was to show effects of Aliskiren in DNP patients by inhibition of TNF-α, inflammatory cytokine involved in the pathogenesis of neuronal dysfunction and T2DM formation [4,29]. We demonstrated that the administration of Aliskiren change the serum TNF-α and C-peptide levels as well as ameliorate DNP symptoms. The level of serum TNF-α is reduced in patients with high TNFα after 6 weeks Aliskiren treatment. The TNF-α inhibitory role of Asliskiren has been showed also in the recent study identified attenuated effect of Aliskiren in chronic constriction injury induced neuropathic pain and elevated TNF-α level in rats [30]. Aliskiren reduces inflammatory cytokine TNF-α activity by reducing of MPAK and NF-kB activation in the neurons as it is found in recent research [10,11]. In addition of that Aliskiren inhibits also TNF-α activated renin, which leads MAPK induced tissues damages [33].

In the same time after 6 weeks Aliskiren treatment, the level of fasting C-peptide normalized in evaluated patients. As last evidences explain TNF-α is the main pro-inflammatory cytokine critically involved in the development of insulin resistance and pathogenesis of T2DM [4,30]. We can propose that Aliskiren, by inhibiting of serum TNF-α level improves pancreatic β-cells function, in addition of that by inhibiting of serum TNF-α, it improves insulin receptors sensitivity and by this way reduce fasting C-peptide high level.

On the other hand clinical research studies results shows 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 [29]. Also, TNF-α, produced by adipocytes and/or peripheral tissues maybe cause of DNP trough generation ROS [31]. 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 [16,29,31]. Aliskiren by modulation of the both parameters level improves the symptoms of DNP.

Moreover, recent studies results that the RAAS effects on insulin secretion as well as insulin resistance trough the formation of reactive oxygen species and leadsT2DM and its cardiovascular and renal complications [19,20,34]. Therefore, still now, clinical studies tray to find association of RAAS genes with DM and its complication of retinopathy, neuropathy and cardiovascular disease [21]. In this regard we have results indicated that the inhibition of RAAS by Aliskiren trough renin inhibition plays significant role in improvement of symptoms of DNP and ameliorates insulin C-peptide level. But it is still controversial, the dual role of RAAS in different states of pain. Consequently RAAS inhibitors modulate pain by inhibiting the inflammatory cytokines, such as TNF-α [35]. On the contrary clinical studies have shown pain-inducing action of RAAS inhibitors [35].

Finally, the recent clinical study indicates significant effects of Aliskiren in DM patients with complication recognized to its anti-diabetic, renoprotective, antioxidant, anti-inflammatory, and anti-apoptotic effects [13]. in our study there was positive correlation between DNP symptoms and TNF-α level. The study results prove Aliskiren's above mentioned effects linked with reducing plasma

TNF-α, and improving insulin C-peptide level in T2DM patients. All of these changes lead to the improvement of DNP symptoms in our patients. In the same time correlation between NDS score, HBA1c and co-morbidity of patients were not statistically significant, indicating that above mentioned factors were not proven to increase DNP.

Results of our study are to be seen in the contexts of some limitation. First, we have evaluated DNP in T2DM patients only. Our date will be more validated with the same results in T1DM patients. Second, study results are not filtered by other RAAS drugs to identify Aliskiren efficacy.

Conclusion, rennin inhibition by Aliskiren abrogates TNF-α mediated stimulation of DNP in Patients' with T2DM. The data may constitute a focus for future studies aimed of evaluation of the TNF-α inhibitory effect of Aliskiren and Telmisartan (ARB) to specify mechanism of anti TNF-α effect of Aliskiren.

Conclusions

Our results may demonstrate of TNF-α and renin implication for organ-specific complication pathogenesis of diabetes mellitus type 2 as well as in DNP.

Findings

Aliskiren administration significantly improves patients' condition by modulating TNF-α activation and correspondingly, reduce severity of neuropathy, extent and number of complications.

Conclusion & Significance

Our results confirm hypothesis that TNFα may play a substantial role in the development and progression of type 2 diabetes mellitus as well as in pathogenesis of diabetic neuropathy. Aliskiren has modulatory impact on TNF-α, so we have results for clinical and pharmacological analysis of Aliskiren application in diabetic neuropathy.

Acknowledgments

We thank all the supervisors and patients for participation of this study.

Findings

This research study plan was approved by the degree #647/03 22.10.2015 of the rector of the Tbilisi State Medical University in the framework of PhD program. No grant financing is provided for this clinical study.

References

1. Lee LF, Xu B, Michie SA, et al. The role of TNF-alpha in the pathogenesis of type 1 diabetes in the nonobese diabetic mouse: analysis of dendritic cell maturation. Proc Natil Acad Sci USA. 2005; 102: 15995-6000.
2. Kawasaki E, Abiru N, Eguchi K. Prevention of type 1 diabetes: from the view point of beta cell damage. Diabetes Res Clin Pract. 2004; 55: S27-S32.
3. Ichinose K, Kawasaki E, Eguchi K. Recent advancement of understanding pathogenesis of type 1 diabetes and potential relevance to diabetic nephropathy. Am J Nephrol 2007; 27: 554-564.
4. Borst SE. The role of TNF-alpha in insulin resistance. Endocrine. 2004; 23: 177-182.
5. Underwood PC, Adler GK. The renin angiotensin aldosterone system and insulin resistance in humans. Curr Hypertens Rep. 2013; 15: 59-70.
6. Akash MSH, Rehman K, Liaqat A. Tumor Necrosis Factor-Alpha: Role in Development of Insulin Resistance and Pathogenesis of Type 2 Diabetes Mellitus. J Cell Biochem. 2018; 119: 105-110.
7. Xia Li, Ju Zhu, Na Liu, et al. TNF-Alpha in Peripheral Neuropathy Patients with Impaired Glucose Regulation. J Diabetes Res. 2017; 2017: 7024024.
8. Mohja A. Ei-Badawy, Dina AB, et al. Tumor necrosis factor-α is a novel biomarker for peripheral neuropathy in type II diabetes mellitus. Egyptian Rheumatology & Rehabilitation. 2017; 44: 8390.
9. Yamakawa I, Kojima H, Terashima T, et al. Inactivation of TNF {alpha} Ameliorates Diabetic Neuropathy in Mice. Am J Physiol Endocrinol Metab. 301: 844-852.
10. Seto SW, Krishna SM, Moran CS, et al. Aliskiren limits abdominal aortic aneurysm, ventricular hypertrophy and atherosclerosis in an apolipoprotein E deficient mouse model. Clin Sci (Lond). 2014; 127: 123-134.
11. Satyanarayana Medicherla, Scott Wadsworth, Breda Cullen, et al. p38 MAPK inhibition reduces diabetes-induced impairment of wound healing. Dove Medical Press Limited. 2009; 2: 91-100.
12. Del Fiorentino A, Ciancbetti S, Celi A, et al. Aliskiren, a renin inhibitor, dawnregulates TNF-α induced tissue factor expression in HUVECS. J Renin Angiotensin-Aldosteron System. 2010; 11: 243-247.
13. Mahfoz AM, El-Latif HA, Ahmed LA, et al. Anti-diabetic and renoprotective effects of aliskiren in streptozotocin-induced diabetic nephropathy in female rats. Naunyn Schmiedebergs Arch Pharmacol. 2016; 389: 1315-1324.
14. Graziano Riccioni, Nicola Vitulano, Nicolantonio D'Orazio, at al. Aliskiren, the first approved renin inhibitor: Clinical application and safety in the treatment of hypertension. J Advances in Therapy. 2009; 26: 700-710.
15. http://www.pharma.us.novartis.com/product/pi/pdf/tekturna.pdf
16. Nawal M. Al-Rasheed, Gary B. Willars, Nigel J. Brunskill. C-Peptide Signals via Gαi to Protect against TNF-α–Mediated Apoptosis of Opossum Kidney Proximal Tubular Cells. Department of Nephrology, Leicester General Hospital, Gwendolen Road, Leicester LE5 4PW, UK. Journal of American Society of nephrology.
17. Naif O Al-Harbi, Faisal Imam, Mohammed M Al-Harbi, et al. Treatment with Aliskiren ameliorates tacrolimus-induced nephrotoxicity in rats. J Renin Angiotensin Aldosterone Syst. 2015; 16: 1329-1336.
18. Marina Kaulmanda, Manoj Bhasin, Zubeir Awdeh, et al. The

Role of TNF-α in Mice with Type 1- and 2- Diabetes. PLOS. 2012; 7: e33254.
19. Goossens GH. The renin-angiotensin system in the pathophysiology of type 2 diabetes. Obes Facts. 2012; 5: 611-624.
20. Antonio Robeiro-Oliveira, Jr. Anelise Impelizeire Noguera, Regina Maria Pereira, et al. The renin–angiotensin system and diabetes: An update. Vasc Health Risk Manag. 2008; 4: 787-803.
21. Rahimi Z, Moradi M, Nasri H. A systematic review of the role of renin angiotensin aldosterone system genes in diabetes mellitus, diabetic retinopathy and diabetic neuropathy. J Res Med Sci. 2014; 19: 1090-1098.
22. Danaei G, Finucane MM, Lu Y, et al. National, regional, and global trends in fasting plasma glucose and diabetes prevalence since 1980: systematic analysis of health examination surveys and epidemiological studies with 370 country-years and 2.7 million participants. Lancet, 2011, 378(9785):31–40.
23. Health statistics and information systems. Cause-specific mortality. Estimates for 2000-2012.
24. Mathers CD, Loncar D. Projections of global mortality and burden of disease from 2002 to 2030. PLoS Med. 2006; 3: e442.
25. Roglic G, Unwin N, Bennett PH, et al. The burden of mortality attributable to diabetes: realistic estimates for the year 2000. Diabetes Care. 2005; 28: 2130-2135.
26. Global status report on noncommunicable diseases 2010. Geneva, World Health Organization, 2011.
27. www.who.int
28. American Academy of Neurology AAN. Treatment of Painful Diabetic Neuropathyaan. Summary of Evidence-based Guideline for Clinicians. 2011.
29. Shi X, Chen Y, Nadeem L, at al. Beneficial effect of TNF-α inhibition on diabetic peripheral neuropathy. J Neuroinflammation. 2013; 10: 69.
30. Amteshwar S Jaggi. Neuropathic pain-attenuating potential of aliskiren in chronic constriction injury model in rats. Journal of Renin-Angiotensin-Aldosterone System. 2013; 14: 116-123.
31. Purwata TE. High TNF-alpha plasma levels and macrophages iNOS and TNF-alpha expression as risk factors for painful diabetic neuropathy. J Pain Res. 2011; 4: 169-175.
32. National Health and Medical Research Council. Prevention, identification and management of foot complications in diabetes. 2011.
33. Todorov V, Vilki S, Muller M, et al. Tumor Necrosis Factor-α Activates NFκB to Inhibit Renin Transcription by Targeting cAMP-responsive Element. The American Society for Biochemistry and Molecular Biology. 2004; 279: 1458-1467.
34. Hayashi T, Takai S, Yamashita C. Impact of the renin-angiotensin-aldosterone-system on cardiovascular and renal complications in diabetes mellitus. Curr Vasc Pharmacol. 2010; 8: 189-197.
35. Bali A, Singh N, Jaggi AS. Renin-angiotensin system in pain: existing in a double life?. J Renin Angiotensin Aldosterone Syst. 2014; 15: 329-340.