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Targeting AGEs pathway in delayed diabetic wound healing

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Abstract

Introduction: Diabetic complications as peripheral neuropathy and delayed wound healing affect patient's quality of life and may lead to amputation. Several mechanisms are involved in mediating these complications including accumulation of Advanced Glycation End Products (AGEs) and the subsequent state of inflammation which were investigated in the current study. Methos: A wound of fixed size was induced in STZ-diabetic rats and the effect of diabetes and treatment with glimepiride, α-lipoic acid and pyridoxamine on the levels of glucose, insulin, HbA1c, AGEs, RAGE, sRAGE, TNF-α and adiponectin were investigated. Also the latency time in the hotplate test and wound healing were quantified at different time points. Results: Our results have shown that STZ induced a condition of diabetes (elevated glucose, HbA1c, and reduced insulin), enhanced AGEs signaling (elevated AGEs, RAGE, and reduced sRAGE) and inflammation (elevated TNF-α and reduced adiponectin), accompanied by hyperalgesia and delayed wound healing, while all treatments were able to ameliorate most of these effects. Conclusion: These results confirm the involvement of AGEs signaling in mediating diabetic complications and suggest their possible use in the standard therapy for diabetic patients.

Keywords: *AGEs, Glimepiride, α-lipoic acid, Pyridoxamine, Diabetic, Wound*

1. Introduction

High levels of Advanced Glycation End Products (AGEs) are formed in healthy older adults and those with chronic diseases, including degenerative diseases of aging, cardiovascular diseases, Alzheimer's disease and diabetic complications (Luevano-Contreras and Chapman-Novakofski, 2010). Hyperglycaemia induces the formation of AGEs, release of proinflammatory molecules and free radicals that contribute to diabetic complications (Elseweidy *et al*., 2013). Binding of AGEs with RAGE is associated with release of pro-inflammatory molecules and free radicals that mediate diabetic complications (Ahmed, 2005) and RAGE signaling is implicated in several chronic diseases as diabetes, atherosclerosis, Alzheimer's disease (Lin *et al*., 2009). AGEs may also cause direct damage of protein structures and extracellular matrix (Ahmed, 2005). Soluble RAGE (sRAGE) acts as a decoy receptor that decreases AGE binding (Devangelio *et al*., 2007). Therefore, AGEs, RAGE and sRAGE are involved in diabetic complications (Norata *et al*., 2009). The prevalence of

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diabetes worldwide is expected to reach 4.4% in 2030 (Wild *et al*., 2004). Neuropathy is a common complication of diabetes that affects the quality of life (Davies *et al*., 2006; and Benbow *et al*., 1998) and is associated with pain, decreased motility and amputation (Edwards *et al*., 2008). Patients with diabetic peripheral neuropathy have impaired gait pattern (Menz *et al*., 2004) due to the vascular insufficiency, nerve damage and ulceration in lower extremity associated with plantar pressures and foot deformity (Noor *et al*., 2015). Insult to foot caused by trauma at the affected site goes unnoticeable to patient due to loss of sensation (Noor *et al*., 2015). In addition, diabetes is associated with impaired / delayed wound healing (Al-Mulla *et al*., 2011) which might be attributed to defect in resolution of inflammation and enhancement in TNF-α / NF-κB activity (Al-Mulla *et al*., 2011). Despite the widespread prevalence of diabetic neuropathy, treatment options are lacking except for strict glycemic control (Harati, 2007). Interestingly, it was previously shown that restriction of dietary AGEs has positive effects on wound healing, insulin resistance and cardiovascular diseases (Luevano-Contreras and Chapman-Novakofski, 2010).

The current study aims to investigate the effect of modulation of AGEs signaling (by α-lipoic acid (Juranek *et al*., 2015; and Leu *et al*., 2013) and pyridoxamine (Takatori *et al*., 2004; and Voziyan *et al*., 2003) on wound healing in diabetic rats in comparison to the standard antidiabetic drug glimepiride (Nakamura *et al*., 2014).

2. Materials and methods

2.1. Animals

Adult male albino rats (150-200 g) purchased from National Research Centre (Cairo, Egypt) were used in the present study. Rats were housed in clear polypropylene cages (four rats per cage) and kept on a light–dark cycle of equal duration and were fed normal chow diet and water ad libitum. Experimental design and animal handling procedures were approved by the Ethical Committee for Animal Handling at Zagazig University (ECAHZU) (P1-5-2014).

2.2. Drugs and chemicals

Streptozocin (STZ) was purchased from Sigma-Aldrich (Dorset, UK), glimepiride, α-lipoic acid and pyridoxamine were purchased from Sigma pharmaceuticals (Egypt).

2.3. Study protocol

Diabetes was induced in rats by single intraperitoneal injection of streptozotocin 50 mg / kg dissolved in ice cold distilled water immediately before use (Mwafy and Yassin, 2011; and Hassan *et al*., 2014). Animals were divided into five groups ($n = 8$): Control, diabetic, diabetic treated with glimepiride (0.5 mg / kg) (Schaalan *et al*., 2009), diabetic treated with α-lipoic acid (35 mg / kg) (Feng *et al*., 2013) and diabetic treated with pyridoxamine (180 mg / kg) (Elseweidy *et al*., 2013). All drugs were dissolved in dimethyl sulphoxide (DMSO) and treatment started two weeks after diabetes induction and continued for eight weeks.

2.4. Hot plate test

Response of animals in the hotplate test (Gardmark *et al*., 1998) was measured after 2, 4, 6 and 8 weeks of treatment.

2.5. Wound induction

A wound of standard area (2 mm $\times$ 5 mm) was induced on the dorsal surface of the right dorsal hind limb on the first day of the fifth week and the size was measured every four days (starting from next day of wound induction) to check for the healing process (Lau *et al*., 2009).

2.6. Biochemical analysis

Serum glucose was determined by glucose meter (Bionime GmBH). At the end of the study, blood was collected from the retro-orbital plexus and serum was used for the detection of: insulin (Millipore kit), HbA1c (BioSystems kit), AGEs (MyBioSource kit), RAGE (RayBio kit), sRAGE (Aviscera Bioscience kit), adiponectin (Chemicon kit) and TNF-α (Quantikine kit) according to the manufacturers instructions.

2.7. Histopathological examination

After euthanasia, the right foot was rapidly dissected out and fixed in 10% phosphate buffered formalin at room temperature and paraffin-embedded sections were stained with hematoxylin and eosin (H&E) (Takeo *et al*., 1989) and examined under light microscope at magnification power ×1200.

2.8. Statistical analysis

Statistical analysis was carried out using GraphPad Prism 5.0® (Graphpad Software, La Jolla; CA; USA). Results were expressed as the mean ± standard error. One-way ANOVA followed by Tukey's post hoc test at level of significance $p < 0.05$ and Two-way ANOVA followed by Bonferroni post hoc was used.

3. Results

3.1. Effect of diabetes and treatment with glimepiride, α-lipoic acid and pyridoxamine on blood glucose, insulin, glycated hemoglobin (HbA1c) and body weight

STZ injection resulted in a significant increase in blood glucose reaching 402.3 vs 105.6 mg / dl compared to control group, while administration of glimepiride and α–lipoic acid to diabetic animals resulted in significant decrease in blood glucose reaching 118.4 and 313.6 vs 402.3 respectively compared to diabetic group (Figure 1a).

In addition, STZ resulted in a significant decrease in insulin level reaching 3.5 vs 15 uIU / ml compared to control group, while administration of glimepiride to diabetic animals resulted in significant increase in insulin level reaching 17.2 vs 3.5 respectively compared to diabetic group (Figure 1b).

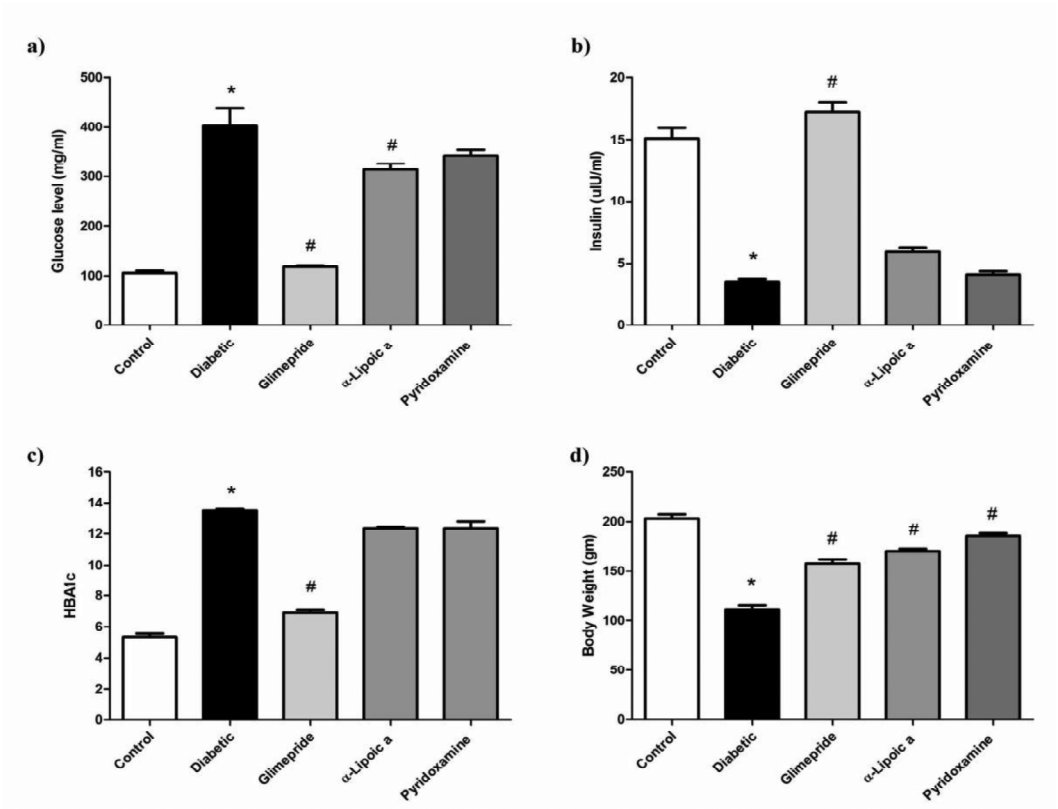

Figure 1: Effect of diabetes induction using STZ and treatment with glimepiride, lipoic acid and pyridoxamine for 8 weeks on: (a) blood glucose, (b) serum insulin, (c) glycated hemoglobin (HbA1c) and (d) body weight

Note: Data are presented as mean ± SEM (n = 6-8); * significantly different from control group, # significantly different from diabetic group at $p < 0.05$ using One Way ANOVA and Tukey's post hoc test.

Figure 1c shows that diabetes resulted in a significant increase in HbA1c reaching 13.5 vs 5.3 compared to control group, while administration of glimepiride to diabetic animals resulted in significant decrease in HbA1c reaching 6.9 vs 13.5 compared to diabetic group.

Diabetes resulted in a significant decrease in body weight reaching 111 vs 203 g compared to control group, while administration of glimepiride, α-lipoic acid and pyridoxamine to diabetic animals resulted in significant increase in body weight reaching 158, 170 and 185 vs 111 g respectively compared to diabetic group (Figure 1d).

3.2. Effect of diabetes and treatment with glimepiride, α-lipoic acid and pyridoxamine on hotplate latency and wound healing

Diabetic group showed a significant decrease in hotplate latency time after 2, 4, 6 and 8 weeks of treatment compared to control group reaching 10.1, 8.1, 7.2 and 7.7 vs 46.5, 43.8, 44.2 and 43.7 sec respectively. Treatment with glimepiride resulted in significant increase in hotplate latency time after 2, 4, 6 and 8 weeks reaching 32.1, 30.1, 31.3 and 34.2 vs 10.1, 8.1, 7.2 and 7.7 sec compared to diabetic group. In addition, treatment with α-lipoic acid and pyridoxamine resulted in a significant increase in the latency time after 6 and 8 weeks reaching 25.5 and 27.5 for α-lipoic acid and 23.2 and 28.2 for pyridoxamine vs 7.2 and 7.7 sec compared to diabetic group (Figure 2a).

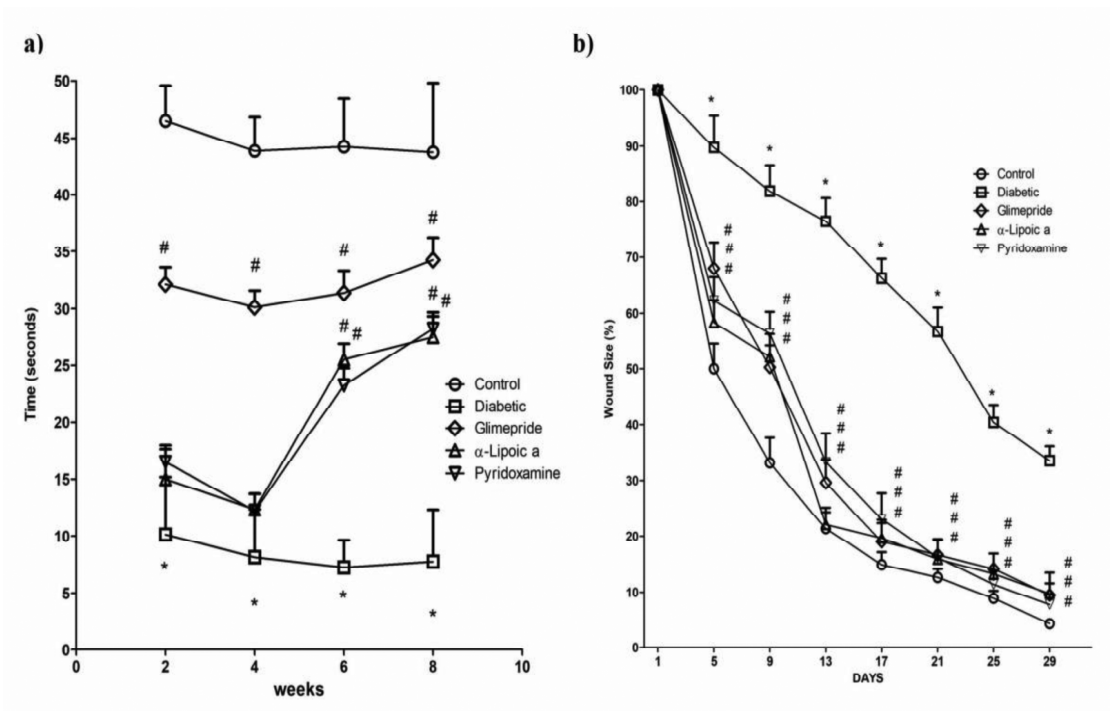

Figure 2: Effect of diabetes induction using STZ and treatment with glimepiride, lipoic acid and pyridoxamine for 8 weeks on: (a) hot plate latency, (b) wound healing

Note: Data are presented as mean ± SEM (n = 6-8); *significantly different from control group, # significantly different from diabetic group at $p < 0.05$ using Two Way ANOVA and bonferroni post hoc test.

Diabetes resulted in delayed wound healing on days 5, 9, 13, 17, 21, 25, 29 as measured by wound size compared to control group reaching 89.7, 81.8, 76.5, 66.2, 56.7, 40.3 and 33.5 vs 50, 33.1, 21.3, 14.8, 12.6, 8.8 and 4.2 respectively. Improvement in wound healing was observed in diabetic animals treated with glimepiride (68, 50.2, 29.6, 19, 16.6, 14.1 and 9.5 respectively), α-lipoic acid (58.3, 52.1, 22.1, 19.6, 15.8, 13.2 and 9.7 respectively), pyridoxamine (62.2, 56.3, 33.2, 23.1, 16.1, 11.3 and 7.7 respectively) on days 5, 9, 13, 17, 21, 25 and 29 compared to diabetic group (89.7, 81.8, 76.5, 66.2, 56.7, 40.3 and 33.5 respectively) (Figure 2b).

3.3. Effect of diabetes and treatment with glimepiride, α-lipoic acid and pyridoxamine on tissue histopathology

Figure (3) shows photomicrograph of rat skin after injury; where normal rat skin was formed of normal epidermis with underlying hair follicles and no inflammatory cells, while, diabetic rat skin after injury showed

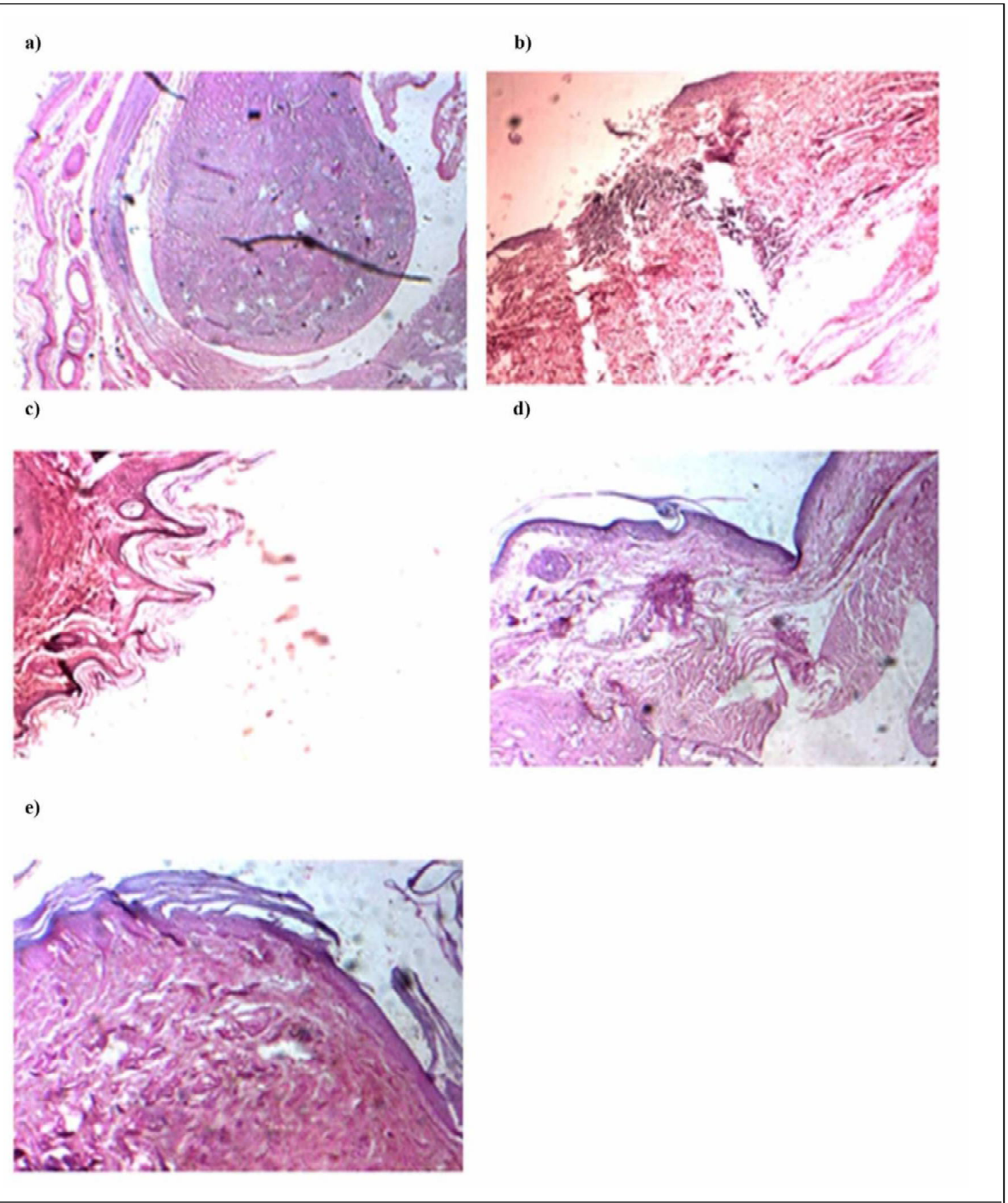

Figure 3: Histopathological changes following diabetes induction using STZ and treatment with glimepiride, lipoic acid and pyridoxamine for 8 weeks using hematoxylin and eosin staining (×1200)

central ulceration of the epidermis with underlying aggregates of inflammatory cells in the dermis. Treatment with glimepiride resulted in increasing hyperplastic epidermis with mild aggregates of inflammatory cells. On the other hand, α-lipoic acid treatment resulted in normal epidermis and dermis with absence of inflammatory cells and formation of granulation tissue. Pyridoxamine showed large area of granulation tissue formed of numerous thin-walled vascular spaces and mild aggregates of inflammatory cells.

3.4. Effect of diabetes and treatment with glimepiride, α-lipoic acid and pyridoxamine on serum AGEs, RAGE and sRAGE, adiponectin and TNF level

In Figure 4a, diabetes resulted in a significant increase in AGEs level reaching 47 vs 9.1 μg / ml compared to control group, while, administration of glimepiride, α-lipoic acid and pyridoxamine to diabetic animals resulted in significant decrease in AGEs level reaching 41.5, 15.5 and 18.8 vs 47 μg / ml compared to diabetic group.

Diabetes resulted in a significant decrease in sRAGE level reaching 28.1 vs 52 ng / ml compared to control group. Treatment with α-lipoic acid and pyridoxamine resulted in significant decrease in sRAGE level reaching 70.4 and 61.3 vs 28.1 ng / ml respectively compared to diabetic group as shown in Figure 4b.

Diabetes induction resulted in a significant increase in RAGE level reaching 172.5 vs 56.9 pg / ml compared to control group. On the other hand, administration of α-lipoic acid and pyridoxamine to diabetic animals resulted in significant decrease in RAGE level reaching 115.4 and 125.4 vs 172.5 pg / ml compared to diabetic group as shown in Figure 4c.

STZ-induced diabetes resulted in a significant decrease in serum adiponectin level reaching 3.6 vs 12.2 ng / ml compared to control group. While, glimepiride, α-lipoic acid and pyridoxamine resulted in significant increase in serum adiponectin level reaching 8.6, 8.4 and 6.3 vs 3.6 ng / ml respectively compared to diabetic

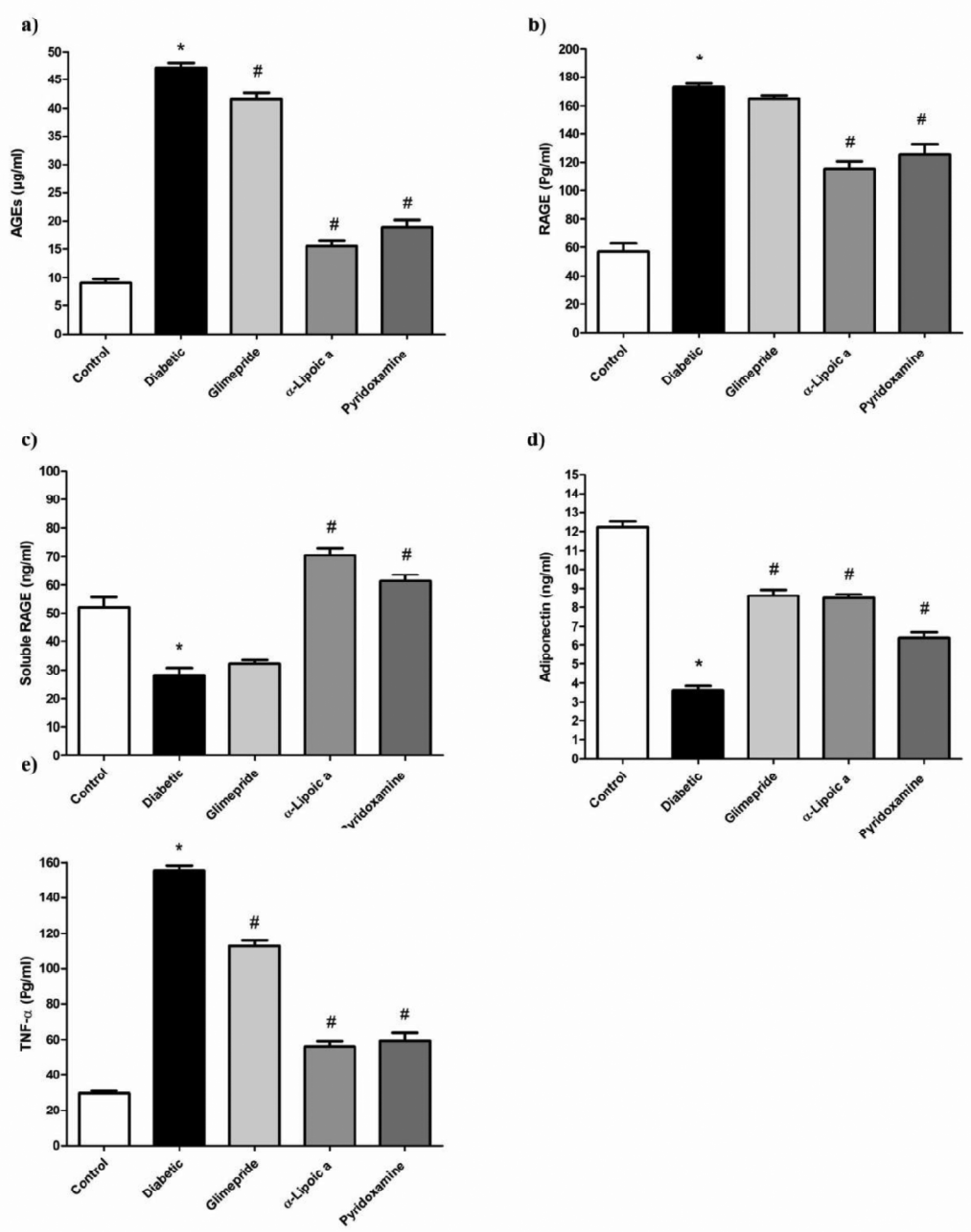

Figure 4: Effect of diabetes induction using STZ and treatment with glimepiride, lipoic acid and pyridoxamine for 8 weeks on: (a) AGEs, (b) sRAGE and (c) RAGE, (d) adiponectin and (e) TNF-α levels

Note: Data are presented as mean ± SEM (n = 6-8); * significantly different from control group, # significantly different from diabetic group at $p < 0.05$ using One Way ANOVA and Tukey's post hoc test.

group (Figure 4d). Diabetes induction increased TNF-α level reaching 155.9 vs 29.5 pg/ml compared to control group, while, administration of glimepiride, α-lipoic acid and pyridoxamine to diabetic animals resulted in significant decrease in TNF-α level reaching 113, 56.2 and 59.2 vs 155.9 pg/ml respectively compared to diabetic group (Figure 4e).

4. Discussion

Diabetes with its complications is the leading global epidemic of the 21st century (Milosevic and Panin, 2019). Patients with diabetic peripheral neuropathy have increased risk of falling due to reduced walking speed, cadence, step length, and less rhythmic acceleration patterns at the head and pelvis (Menz *et al*., 2004). In addition, wound healing in diabetes is frequently impaired (Tong *et al*., 2012) and diabetic foot ulcers are a major cause of non-traumatic lower extremity amputations (Yadav *et al*., 2019).

Hyperglycemia is associated with accumulation of AGEs (Voziyan *et al*., 2003) which are implicated in diabetic complications by protein glycation, increased free radical activity (Ahmed, 2005) activation of NF-κB, production of pro-inflammatory cytokines, and inflammation (Lin *et al*., 2009). RAGE and AGEs play a central role in disordered diabetic wound healing as their expression is increased in wounds developed in diabetic mice and blockade of RAGE using sRAGE accelerated wound healing and reduced cytokine levels (Goova *et al*., 2001).

The present study was designed to explore the potential beneficial effect of agents that affect AGEs signaling on delayed wound healing in STZ diabetic rats.

In the present study, STZ injection induced diabetes as evidenced by the elevation in blood glucose level, HbA1c, and decreased body weight and insulin level. STZ was shown to destroy pancreatic β-cells (Szkudelski, 2001; and Hayashi *et al*., 2006) and to exert diabetogenic effect with similar alterations as observed in our study (Mwafy and Yassin, 2011; Hassan *et al*., 2014; Wei *et al*., 2003; Sharma *et al*., 2006; and Huang *et al*., 2003).

In addition, STZ-treated rats had significantly higher level of TNF-α, AGEs, RAGE and decreased adiponectin and sRAGE levels. Previous studies have shown that STZ-induced diabetes in rats was associated with elevated serum TNF-α (Hassan *et al*., 2014), higher levels of AGEs (Tanaka *et al*., 1999), RAGE (Kislinger *et al*., 2001) and reduced sRAGE levels (Norata *et al*., 2009) and reduced adiponectin (Mahmoud, 2013).

In the current investigation, STZ diabetic rats showed hyperalgesia as evidenced by the reduction in the latency time in the hotplate test as shown previously (Sharma *et al*., 2006; and Ramos *et al*., 2007).

The process of wound healing involve inflammation, epithelialization, angiogenesis, granulation tissue formation and deposition of interstitial matrix (Liu *et al*., 2013). Hyperglycemia and elevated AGEs level were shown to impair diabetic wound healing (Peppa *et al*., 2009). Delayed diabetic wound closure was associated with defect in resolution of inflammation, prolonged inflammatory phase, increased infiltration of inflammatory cells in the basal layer of the epidermis (Bhattacharya *et al*., 2016), enhanced TNF-α / NF-κB activity (Al-Mulla *et al*., 2011), suppressed angiogenesis, oxidative stress (Al-Mulla *et al*., 2011; and Bitar *et al*., 2013) and decreased matrix accumulation (Thomson *et al*., 2010). Our results have demonstrated cellular infiltrations and immature granulation tissue in the diabetic rats. The impairment of cellular infiltrations and decreased granulation tissue formation was previously shown in diabetic wounds (Gutierrez-Fernandez *et al*., 2007).

On the other hand, administration of the antidiabetic drug glimepiride reversed the diabetic effects of STZ as indicated by the reduction in blood glucose level, HbA1c and TNF-α and elevated adiponectin level as previously shown (Mwafy and Yassin, 2011; Huang *et al*., 2003; and Tsunekawa *et al*., 2003). Glimepiride was shown to exert anti-oxidative, anti-inflammatory, angiogenic properties and decreased AGEs (Nakamura *et al*., 2014). These actions were also accompanied by improved wound healing and near normal pain perception.

In addition, administration of α-lipoic acid exerted mild hypoglycemic effect and reduced AGEs, RAGE and TNF-α and increased sRAGE and adiponectin levels. It also improved wound healing and hyperalgesia that was altered by STZ injection. Similar effects of α-lipoic on blood glucose and RAGE level were previously reported (Leu *et al*., 2013). In addition, α-lipoic was shown to exert anti-oxidant (Mendes *et al*., 2014) and anti-inflammatory actions (Feng *et al*., 2013). Topical application of α-lipoic acid was previously shown to accelerate wound healing on diabetic mouse skin and decrease RAGE expression through angiogenesis regulation and anti-inflammatory effects (Chen *et al*., 2012).

In the present study, administration of pyridoxamine decreased AGEs, RAGE, TNF-α and increased sRAGE and adiponectin levels. This was associated with amelioration of hyperalgesia and improved wound healing.

Pyridoxamine was previously shown to exert therapeutic benefits on diabetic nephropathy, histopathological improvements, reduction of TNF-α (Elseweidy *et al.*, 2013), ameliorate hyperalgesia (Jolivalt *et al.*, 2009), neuropathic pain (Jolivalt *et al.*, 2009) through inhibition of AGEs formation (Voziyan *et al.*, 2003).

5. Conclusion

The present study has confirmed the involvement of AGEs signaling and the consequent inflammatory state in delayed diabetic wound healing. In addition, we have shown that α-lipoic acid was able to ameliorate these deleterious effects through its mild hypoglycemic effect, altered AGEs signaling and its anti-inflammatory action, while pyridoxamine exerted similar beneficial effects but without any hypoglycemic effect. Both drugs were nearly as effective as the standard hypoglycemic drug glimepiride.

Both α-lipoic acid and pyridoxamine are already used safely in humans so they could be incorporated in the treatment protocols for diabetes and diabetic complications.

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Conflicts of interest

The authors wish to confirm that there are no known conflicts of interest associated with this publication.

Also the authors confirm that all data were generated in-house and that no paper mill was used.

Author contribution

RA and WB designed the research, NH performed the animal experiments, NH and WB analyzed the data and wrote the manuscript, RA revised the manuscript.

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