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Comparative Study of the Effects of Topically Used Insulin and Simvastatin on Thermal Induced Burn in Diabetic Albino Rats

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Abstract

Background: Diabetic wound healing is a major complication that may be delayed or impaired. This is resulting from abnormalities in inflammatory and oxidative stress responses, impaired growth factors production, angiogenic responses and collagen deposition.

Aim of the Work: The aim of this work was to investigate and compare possible effects of topical insulin and simvastatin on the tissue repair capacity, their anti-inflammatory and anti-oxidant effects.

Material and Methods: Sixty male Wister Albino rats were divided into 5 equal groups, group1 normal burned received vehicle, group 2 diabetic burned received vehicle, group 3 diabetic burned received insulin in vehicle, group 4 diabetic burned received simvastatin in vehicle and group 5 diabetic burned received insulin in saline all applied topically. At certain end recording points (3 rd, 7th, 14th and 21 st days post burning) wound contraction percentage % was calculated and serum tumor necrosis factor- a (TNF-a), blood reduced glutathione and serum malonaldialdehyde (MDA) levels were estimated and dissected burn specimens were prepared for histopathological and immunohistochemical staining for VEGF and a-SMA.

Results: Insulin and simvastatin produced more than satisfactory results evidenced by significant improvement in the whole studied parameters.

Conclusion: Insulin and simvastatin have anti–inflammatory, antioxidant and angiogenic effects improving the healing properties. Although they both in vehicle exhibited similar effectiveness in regard the investigated parameters, they exhibited superiority over insulin in saline.

Key Words: *Diabetic burn – Wound healing – Topical – Insulin – Simvastatin.*

Introduction

DIABETES Mellitus (DM) is a metabolic disorder with hyperglycemia over a prolonged period. It is considered one of the most important health care problems due to its complications **[1]**.

Impaired wound healing is a major complication of diabetes **[2]** and recent studies have reported that reduced lymphangiogenesis and angiogenesis during diabetic wound healing are thought to be a new therapeutic target **[3]** as in diabetic patients there is imbalance in the formation of blood vessels with abnormal pattern of angiogenesis that impairs the healing process and decreased angiogenesis with restriction of the entry of the inflammatory cells to the wound site and reduction of the amount of factors released by these cells **[4]**. It was found that FGF-2 and Platelet Derived Growth Factor (PDGF) have been reduced in diabetic experimental wounds. It was also proved that a high glucose which is topically administrated to wounds of non-diabetic rats inhibits the angiogenic process suggesting the direct role of high glucose in affecting angiogenesis in diabetes **[1,5]**.

Wound healing is an interplay of many steps leading to restoration of the integrity of skin barrier, which includes inflammation, proliferation, cells migration and scar remodeling **[6]**. The impaired healing in diabetes is multifactorial including reduced angiogenesis and lymphangiogenesis **[3]**, decreased fibroblast proliferation and migration, decreased inflammatory changes **[7]**, tissue hypoxia and infection.

Insulin is a natural pancreatic polypeptide hypoglycemic hormone. It regulates energy metabolism, increases DNA replication ,protein synthesis, cellular proliferation, differentiation and growth. Recent studies showed that it plays a role in wound healing process **[8,9]**.

Simvastatin is a member of statins which are HMG-CoA reductase inhibitor used as cholesterol

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lowering agents. In addition to their cholesterol lowering action recent studies suggest their anti-inflammatory, immunomodulatory, angiogenesis and anti-oxidative actions [10]. It reduces the infiltration of polymorph nuclear leukocytes and elevates VEGF secretion in injured arteries in a dose dependent manner [11], it prevents the diffusion of free radicals which are produced under the effect of the oxidative stress through its binding to phospholipids of lipoproteins [12].

Material and Methods

Vehicle preparation:

The study employed liquid crystalline gel like formulation containing a mixture of oleic acid, Tween 80, propylene glycol and distilled water [13]. Fresh formulations were prepared weekly and stored at 4ºC.

Insulin:

(Insulinagypt R 100IU/ml vial) is a product of Medical Union Pharmaceuticals Company (MUP). It was applied to animals topically in two different preparations:

1- In the freshly prepared vehicle (to group 3) by replacing 1ml of distilled water with 100IU of insulin in vehicle.

2- In saline (to group 5) in a dose of 0.1U of regular insulin applied on the burnt area daily [14].

Simvastatin:

It is a pure powder from Hetero Labs Limited (Unit-1) INDIA purchased from October Pharma 6 October City-First Industrial Zone Egypt. It was applied topically to the burnt area dissolved in the freshly prepared vehicle by replacing 2 gram of distilled water with 2 gram of simvastatin, this produced liquid crystalline formula containing 2% w/w of simvastatin [3].

Streptozotocin (STZ):

It is a pure powder purchased from Sigma Aldrich, used to induce diabetes in rats by dissolving the drug in 0.1 mole sodium citrate buffer (pH 4.) which was prepared as following:

1- Dissolve 2.101 gram of citric acid in 100ml distilled water.

2- Dissolve 2.941 gram of tri sodium citrate in 100 ml distilled water.

3- Mix 44.5ml of citric acid with 55.5ml of tri sodium citrate to gain citrate buffer 4.6 pH, then it was injected once i.p. in a dose of 60mg/kg to induce type I diabetes [15,16]; the blood glucose level was checked 3 days later using a blood sample from the tail to detect diabetes.

Animals groups and treatment protocols:

This study was carried out using 60 male Wistar Albino rats weighing 150-200gm., obtained from Tanta University Animal House. Animals were acclimatized for 10 days before induction of diabetes as mentioned before, then each animal was anaesthetized using ether, the dorsal inter-scapular area was shaved using an electrical razor and a deep second degree burn was induced using a metallic solid aluminium bar 2cm of diameter, previously heated in a boiling water [17]. The bar was maintained in direct contact to the shaved area for 15 seconds. The animals then were kept individually in plastic cages; they were fed standard food and water ad libitum through the whole period of the experiment.

Animals were divided into 5 equal groups (12 rats each) as following:

- *Group 1:* Non-diabetic burned received vehicle.
- *Group 2:* Diabetic burned group received vehicle.
- *Group 3:* Diabetic burned group treated with insulin in vehicle.
- *Group 4:* Diabetic burned group treated with simvastatin in vehicle.
- *Group 5:* Diabetic burned group treated with insulin in saline.

All drugs were applied topically daily immediately after induction of burn. At the recording end points 3rd, 7th, 14th and 21st days post-burn; 3 animals from each group were taken and the burned area was measured to calculate wound contraction [18] that expressed as the reduction in percentage (%) of original wound size, by the following formula:

$$\%\ \text{Wound contraction on day X} = \frac{(\text{Area on day 0} - \text{Area on day X})}{\text{Area on day 0}} \times 100$$

These 3 rats were sacrificed and blood was collected by cardiac puncture from each animal and divided into two parts; one was stored and used for detection of reduced glutathione level and the other was centrifuged for obtaining serum and lipid peroxides malondialdehyde (MDA) and tumor necrosis factor- a (TNF-α) levels. A full thickness burned skin with a margin of normal skin from each rat was dissected and immediately fixed in 10% formalin and processed for histopathological examination.

The immunohistochemical analysis:

Staining was performed on formalin-fixed paraffin-embedded specimens for:

- Vascular Endothelial Growth Factor (VEGF) (VEGF ready to use for IHC, 1467-R7) this method is according to **[19]**.
- Anti alpha smooth muscle actin (α-SMA) (asm-1 ready to use for IHC, 113-R7),This method is according to Skalli, Ropraz **[20]**.

Statistical analysis:

Results were analyzed statistically using software Statistical Package for the Social Science (SPSS) for windows, Version 23 (SPSS Inc., USA).

The level of significance was established as 5% by One Way ANOVA followed by Tukey's post-Hoc test. Descriptive statistics were presented as Mean ± Standard Error of mean.

This study was conducted in Pharmacology Department, Faculty of Medicine, Tanta University from October 2016-Febrauary 2017.

Results

All rats that have been injected with STZ showed symptoms of diabetes, the non-diabetic animals showed blood glucose level ranging (132-159mg/dl) while the diabetic animals showed (486-876mg/dl) through the whole period of the experiment. The treated groups either with insulin in vehicle, simvastatin in vehicle or insulin in saline showed significant increase in the wound contraction percentage with no significant difference on comparing the all treated groups to each other (Table 1). There was significant decrease in TNF-α levels when compared to the untreated group, The simvastatin in vehicle treated group showed significant decrease in the 21st day when compared to the other groups (Table 2). The all treated groups showed increase in blood reduced glutathione **[21]** levels, while on comparing the insulin in saline treated group to the other treated groups it showed significant decrease (Table 3). There was significant decrease in serum (MDA) levels, with no significant differences when comparing the all treated groups to each other (Table 4).

Histopathological examination results:

Similar histopathological patterns of the healing process were observed in non-diabetic burned group (group 1) and the all treated groups either with insulin in vehicle (group 3), simvastatin in vehicle (group 4) or insulin in saline (group 5). On the 3rd post burn day group 2 showed total autolysis of both epidermis and dermis with dense inflammatory cells infiltrate Fig. (1A) while the other groups showed inflammatory response, hyperemia, necrosis with absence of the epithelial lining Fig. (1B). On the 7th post burn day, thermal injury with intense inflammatory response was still observed in group 2 with complete destruction of epidermis and dermis Fig. (2A) while the other groups showed diffuse inflammatory response with angiogenesis and fibroblasts that induce collagen deposition (immature granulation tissue) Fig. (2B). on the 14th post burn day, group 1 showed moderate autolysis and immature granulation tissue with no surface epithelium Fig. (3A), while the other groups showed advanced healing process with reduction in the inflammatory reaction and well developed granulation tissue with epithelial surface lining Fig. (3B). on the 21st day post burn, in group 1 there was no evidence of complete healing with tissue debris and thrombosed blood vessels Fig. (4A), while the other groups showed more advanced healing process with dense collagen deposition and complete epithelialization Fig. (4B).

Immune histochemical study:

The software (Image J) (National Institute of Health, Bethesda, Maryland, USA) **[22]** was used to measure the color intensity then data were analyzed by one way analysis of variance (ANOVA) test followed by Post Hoc Tukey's test.

Regarding VEGF the samples showed peak in the expression on the 14th day, which was higher in the diabetic burned treated group with simvastatin in vehicle with significant increase on compared to the other treated groups (Table 5) Fig. (5). Regarding α-SMA the samples showed a peak on the 7th day, which was higher in the diabetic burned treated group with insulin in vehicle with significant increase on comparing to the other treated groups (Table 6) Fig. (6).

Table (1): Comparative statistics of wound contraction percentage among studied groups.

	3rd day	7th day	14th day	21 st day
Group 1	37.5±2.5	57.83±1.88	87.25±0.63	99.93±0.03
Group 2	14.5±2.74 $p1$***	37.33±2.67 $p1$***	57.75±1.88 $p1$***	94.25±0.29 $p1$***
Group 3	38.92±1.34 $p2$***	56.08±2.51 $p2$***	82.75±2.43 $p2$***	99.63±0.07 $p2$***
Group 4	34.75±1.38 $p2$***, $p3$NS	51.08±2.02 $p2$**, $p3$NS	80±1.18 $p2$***, $p3$NS	99.38±0.13 $p2$***, $p3$NS
Group 5	26.33±2.83 $p2$*, $p3$*, $p4$NS	54.67±2.03 $p2$**, $p3$NS, $p4$NS	79.08±0.79 $p2$***, $p3$NS, $p4$NS	98.8±0.38 $p2$***, $p3$NS, $p4$NS

Significant at p-value (<0.05); values expressed as mean ± SEM. N.S: Non-Significant.
*: p<0.05. **: p<0.01. ***: p<0.001.

Table (2): Comparative statistics of TNF-α (pg./ml) serum levels in studied groups.

	3rd day	7th day	14th day	21 st day
Group 1	0.85±0.03	0.73±0.03	0.76±0.02	0.75±0.05
Group 2	1.98±0.03 $p1^{***}$	2.15±0.04 $p1^{***}$	3.25±0.25 $p1^{***}$	2.18±0.2 $p1^{***}$
Group 3	1.15±0.09 $p2^{***}$	0.95±0.02 $p2^{***}$	0.74±0.18 $p2^{***}$	0.97±0.06 $p2^{***}$
Group 4	1.04±0.06 $p2^{***}$, $p3$NS	0.83±0.05 $p2^{***}$, $p3$NS	1.04±0.1 $p2^{***}$, $p3$NS	0.33±0.1 $p2^{***}$, $p3$NS
Group 5	0.93±0.01 $p2^{***}$, $p3$NS, $p4$NS	0.96±0.06 $p2^{***}$, $p3$NS, $p4$NS	1.18±0.1 $p2^{***}$, $p3$NS, v4NS	1.29±0.22 $p2^{***}$, $p3$NS, $p4^{**}$

Significant at p-value (<0.05); values expressed as mean ± SEM. N.S: Non-Significant.
*: p<0.05. **: p<0.01. ***: p<0.001.

Table (3): Comparative statistics of GSH blood levels (nmol/ml) in studied groups.

	3rd day	7th day	14th day	21st day
Group 1	8.89±0.14	8.06±0.16	9.34±0.25	9.3±0.52
Group 2	4.89±0.24 $p1^{***}$	4.16±0.62 $p1^{**}$	5.98±0.34 $p1^{**}$	5.16±0.81 $p1^{**}$
Group 3	10.54±0.62 $p2^{***}$	14.37±0.93 $p2^{***}$	14.67±0.66 $p2^{***}$	14.59±0.91 $p2^{***}$
Group 4	13.17±0.55 $p2^{***}$, $p3^{**}$	17.98±0.75 $p2^{***}$, $p3^{**}$	15.96±0.53 $p2^{***}$, $p3$NS	15.31±0.39 $p2^{***}$, $p3$NS
Group 5	9.04±0.28 $p2^{***}$, $p3$NS, $p4^{***}$	9.83±0.3 $p2^{***}$, $p3^{**}$, $p4^{***}$	9.73±0.25 $p2^{**}$, $p3^{***}$, $p4^{***}$	10.8±0.37 $p2^{***}$, $p3^{**}$, $p4^{**}$

Significant at p-value (<0.05); values expressed as mean ± SEM. N.S: Non-Significant.
*: p<0.05. **: p<0.01. ***: p<0.001.

Table (4): Comparative statistics of MDA serum levels (nmol/ml) in studied groups.

	3rd day	7th day	14th day	21st day
Group 1	6.44±0.25	6.06±0.44	4.42±0.55	5.25±0.35
Group 2	9.13±0.36 $p1^{***}$	8.34±0.49 $p1^{**}$	7.08±0.2 $p1^{***}$	7.21±0.22 $p1^{**}$
Group 3	8.16±0.53 $p2$NS	6.32±0.12 $p2^{*}$	4.59±0.31 $p2^{***}$	3.64±0.21 $p2^{***}$
Group 4	8.3±0.25 $p2$NS, $p3$NS	5.76±0.26 $p2^{**}$, $p3$NS	3.73±0.15 $p2^{***}$, $p3$NS	3.39±0.21 $p2^{***}$, $p3$NS
Group 5	8.92±0.37 $p2$NS, v3NS, $p4$NS	6.36±0.45 $p2^{*}$, $p3$NS, $p4$NS	4.85±0.36 $p2^{**}$, $p3$NS, $p4$NS	4.12±0.13 $p2^{***}$, $p3$NS, $p6$NS

Significant at p-value (<0.05); values expressed as mean ± SEM. N.S: Non-Significant.
*: p<0.05. **: p<0.01. ***: p<0.001.

Table (5): Comparative statistics of the color intensity of VEGF in different studied groups.

	3rd day	7th day	14th day	21st day
Group 1	3.66±0.14	5.53±0.03	9±0.11	5±0.11
Group 2	2.28±0.05 $p1^{***}$	4.57±0.34 $p1^{**}$	7.47±0.11 $p1^{***}$	4.34±0.06 $p1^{***}$
Group 3	5.09±0.13 $p2^{***}$	7.51±0.09 $p2^{***}$	13.04±0.07 $p2^{***}$	6.04±0.07 $p2^{***}$
Group 4	5.30±0.09 $p2^{***}$, $p3$NS	7.88±0.07 $p2^{***}$, $p3$NS	14.03±0.09 $p2^{***}$, $p3^{***}$	8.03±0.09 $p2^{***}$, $p3^{***}$
Group 5	4.98±0.07 $p2^{***}$, $p3$NS, $p4$NS	7.36±0.09 $p2^{***}$, $p3$NS, $p4$NS	12.8±0.13 $p2^{***}$, $p3$NS, $p4^{***}$	5.99±0.09 $p2^{***}$, $p3$NS, $p4^{***}$

Significant at p-value (<0.05); values expressed as mean ± SEM. N.S: Non-Significant.
*: p<0.05. **: p<0.01. ***: p<0.001.

Table (6): Comparative statistics of the color intensity of α-SMA in different studied group.

	3rd day	7th day	14th day	21st day
Group 1	3.61±0.04	14.78±0.14	3.85±0.06	2.22±0.04
Group 2	2.33±0.13 $p1^{***}$	8.33±0.19 $p1^{***}$	3.32±0.1 $p1^{**}$	2.16±0.03 $p1$NS
Group 3	4.82±0.5 $p2^{***}$	17.35±0.55 $p2^{***}$	6.78±0.09 $p2^{***}$	2.69±0.08 $p2^{***}$
Group 4	4.67±0.15 $p2^{***}$, $p3$NS	14.56±0.13 $p2^{***}$, $p3^{***}$	5.24±0.09 $p2^{***}$, $p3^{***}$	2.31±0.06 $p2$NS, $p3^{**}$
Group 5	4.88±0.12 $p2^{***}$, $p3$NS, $p4$NS	16.05±0.12 $p2^{***}$, $p3^{*}$, $p4^{***}$	5.36±0.06 $p2^{***}$, $p3^{***}$, $p4$NS	2.45±0.06 $p2^{**}$, $p3$NS, $p4^{*}$

Significant at p-value (<0.05); values expressed as mean ± SEM. N.S: Non-Significant.
*: p<0.05. **: p<0.01. ***: p<0.001.

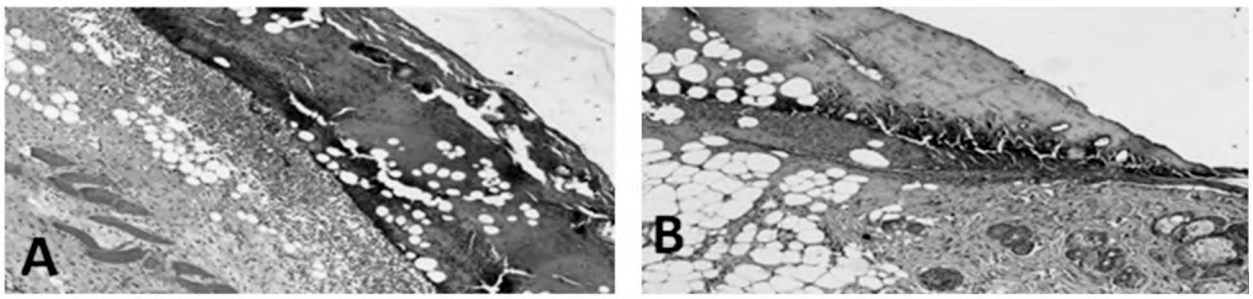

Fig. (1): (A) Deep inflammatory infiltrate, (B) Deep coagulative necrosis and inflammatory infiltrate.

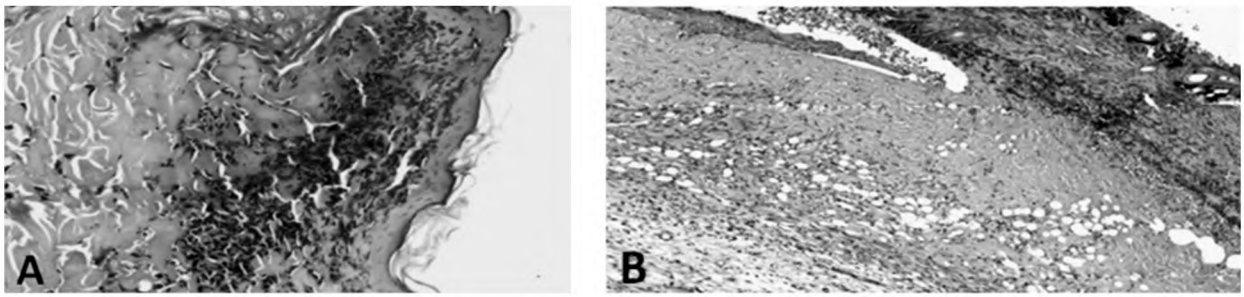

Fig. (2): (A) Intense inflammatory infiltrate, (B) Moderate inflammatory infiltrate, cogulative necrosis and crust.

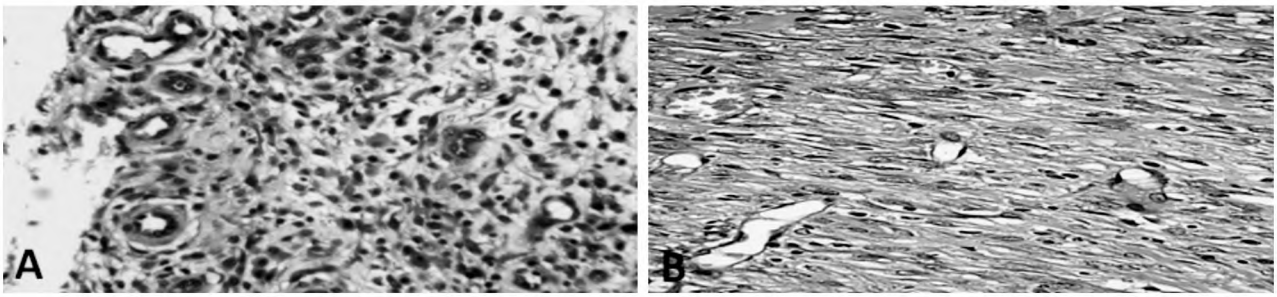

Fig. (3): (A) No epithelium with surface granulation tissue, (B) Developed granulation tissue (fibroblasts and blood capillaries).

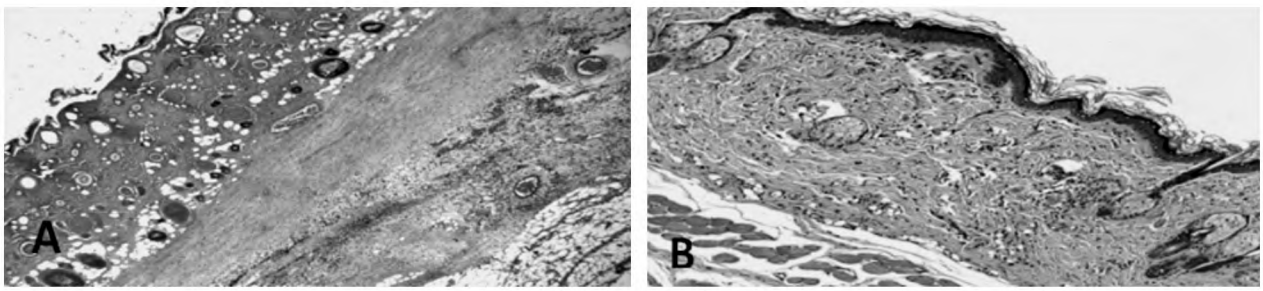

Fig. (4): (A) No evidence of complete healing and dilated thrombosed vessels, (B) Completely healed skin with minimal inflammatory cells.

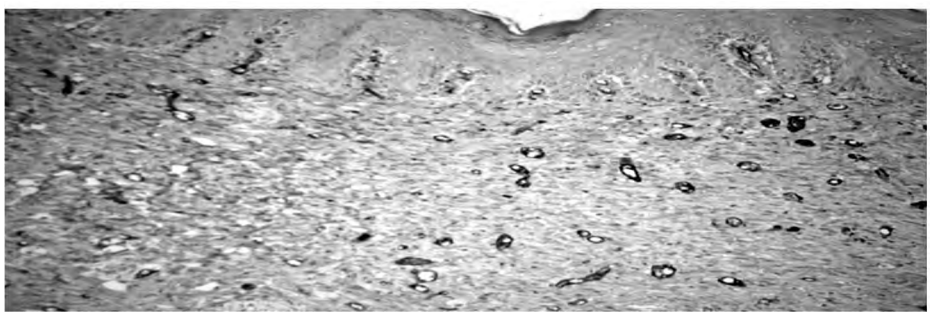

Fig. (5): IHC staining of CEGF showing newly formed blood vessels.

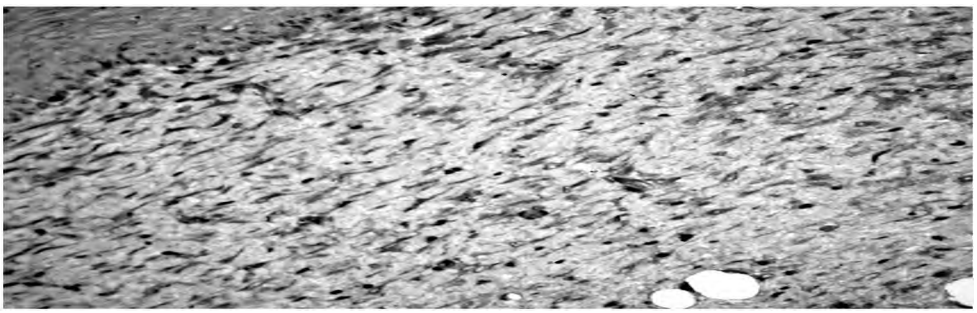

Fig. (6): IHC staining of α-SMA showing fibroblasts.

Discussion

Diabetes is known to impair the healing process by affecting the inflammatory response, blood supply and fibroblast proliferation [23]. Defects in the inflammatory phase affect the subsequent process of fibroblast and collagen synthesis [24].

The microemulsion vehicle was used as a carrier improving the transdermal passage of tested drugs as El-Maghraby [13] has suggested that it has high drug loading capacity and penetration enhancing effect increasing the fluidity of the subcutanes lipids increasing drug permeability.

In the present study the induced deep second degree burn in diabetic rats induced with STZ showed significant decrease in wound contraction percentage, significant increase in serum TNF-α, significant decrease in blood GSH and significant increase in serum MDA levels. Also, marked histopathological changes and decreased detection of VEGF and α-SMA.

The increased TNF-α level impairs fibroblast proliferation, which was proved by invivo inhibition of TNF-α in diabetic mice that increase the number of proliferating fibroblast [25]. The impairment of migration of fibroblasts and keratinocytes was proved to be affected by TNF-α [26].

Recent studies revealed that Reactive Oxygen Species (ROS) are required as defense against invading organisms, and also as essential mediators of intracellular signaling of migration, proliferation and angiogenesis, however excess ROS leading to cell apoptosis [27].

Vascular Endothelial Growth Factor (VEGF) is an angiogenic growth factor that functions as endothelial cell mitogen, chemotactic agent and inducer of vascular permeability. It has unique effects on multiple components of the healing process including angiogenesis, epithelialization and collagen deposition [28].

Lerman, [29] have proved that dermal fibroblasts obtained from diabetic mice have abnormalities even when allowed to grow in an ex-vivo optimized environment, as they show diminished VEGF production as a result of blunted fibroblast response to injury with profound effects on diabetic wound healing.

α-SMA is a major myofibroblasts differentiation marker that regulates the expression of collagen gene, myofibroblasts which express that protein are strongly active compared with retractable protomyofibroblasts [30].

Insulin in vehicle showed a significant increase in the wound contraction percentage, that was in accordance with the results of Lima, Caricilli [23] who reported that topical insulin shortening the time needed for complete epithelialization, increase myofibroblasts expression and collagen deposition and stimulates proliferation of microvascular endothelial cells and with Goren, Müller [31] who proved that TNF-α inhibits the action of insulin and the diabetes-impaired wound healing is related to the failure of resident cells to respond in a proper way to insulin stimulus. Bravi, Armiento [32] demonstrated that insulin decreases the intracellular oxidative stress by elevating GSH/GSSG ratio in the erythrocytes from diabetic patients, and Langston, Circu [33] demonstrated that insulin affects GCLc expression and GSH recovery during oxidative challenge.

The significant decrease of serum MDA was in accordance with the results of Dhall, Silva [34] who reported that the insulin induced decrease in MDA levels indicates decrease in the oxidative stress that has a powerful consequences on the healing process. AbdelKader, Osman [35] have proved in their studies that insulin increases the expression and activation of AKT at the wound site as compared to intact skin which is important for VEGF release through a post-transcriptional mechanism which is important for angiogenesis.

The significant increase of α-SMA in wound area is in agreement with that of Tecilazich, Kafanas **[36]** who showed that diabetic patients treated with insulin suffer from thick skin as a result of excessive accumulation of abnormal collagen fibers that become resistant to be degraded by collagenase.

In the present study, simvastatin in vehicle showed a significant increase in the wound contraction percentage, these results are in agreement with Rego, et al. **[37]** who found that topical application of simvastatin on open diabetic wound, accelerates the healing process through the enhancement of angiogenesis and lymphangiogenesis; it also has a protective effects against infection due to its antibacterial action.

Regarding the serum levels of TNF- α, simvastatin in vehicle showed significant decrease, these results are in agreement with Stojadinovic, Lebrun **[11]** and Farsaei, et al. **[38]** who reported the anti-inflammatory effects of simvastatin are due to the inhibition of Th1-type chemokine receptors on T-cells, inhibition of trans-endothelial migration of leukocytes and inhibition in the production of CRP and pro inflammatory cytokines (IL-6 and TNF-α) and stimulating the production of anti-inflammatory cytokine (IL-10).

Regarding to the oxidative stress, simvastatin in vehicle showed a significant increase in blood GSH levels, and these results were in harmony with Dalcico, et al. **[39]** who showed that simvastatin improved the gingival oxidative stress in experimentally induced periodontitis by re-establishing GSH levels and McFarlane, Muniyappa **[40]** who proved that all statins inhibit the uptake and generation of oxidized-LDL, attenuate vascular and endothelial superoxide anion formation.

It also showed a significant decrease in serum MDA levels, this was in accordance with the result of Jowkar and Namazi **[41]** who proved that it inhibits the activity of oxidant enzymes as reduced nicotinamide adenine dinucleotide phosphate oxidase and myeloperoxidase and up-regulates the activity of antioxidant enzymes such as catalase.

Simvastatin in vehicle showed a significant increase in expression of VEGF, these results were in harmony with that of Nishimoto et al. **[42]** who proved that simvastatin stimulates VEGF expression by HIF-1α up-regulation and RhoA down-regulation in endothelial cells and Bitto, et al. **[43]** who showed that simvastatin improves the altered pattern of VEGF production and secretion in mutant diabetic mice.

It also showed a significant increase in α-SMA, These results were in controversy with Bagnato, et al. **[44]** who suggested that simvastatin administration inhibited myofibroblasts differentiation thus preventing the development of cutaneous and pulmonary fibrosis in systemic sclerosis model.

It was found that the inhibitory effect of simvastatin on TGF-β 1-induced expression of α-SMA was dose dependent. Concentrations of 10 μM inhibit the α-SMA production in keloid fibroblasts without affecting cell viability. Concentrations of 0.1-10 μM were reported to be within physiological relevant levels of the drug **[45]**.

As a conclusion, insulin and simvastatin have anti-inflammatory, antioxidant and angiogenic effects improving the healing properties and could be recommended in the topical treatment of diabetic wounds. Although the treatment with insulin in vehicle exhibited similar effectiveness in regard the investigated parameters with simvastatin in vehicle, they exhibited superiority over insulin in saline denoting that such vehicle could provide good contact and penetration properties.

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دراسة مقارنة عن تآثيرات الإستخدام الموضعى لكلا من الآنسولين والسيمفاستاتين على الحرق الحرارى المستحث فى الجرذان البيضاء المصابة بالسكرى

إلتئام الجروح هى عملية معقدة تتضمن إستجابات مختلفة للعديد من الخلايا لتكوين وتنظيم مراحل الإلتئام من تكوين نسيج إلتهابى وتكاثر خلايا وتوليد آوعية دموية جديدة لإعادة تشكيل نسيج بدلا من الجزء المجروح. ولكن فى المرضى المصابون بداء السكرى يكون هناك خلل فى هذه العملية آما بطول الوقت آو إختلال الترتيب المنظومى للإلتئام نظرا لما يعانيه المريض من إضطراب وعائى وعصبى ومناعى وشذوذ فى التفاعلات الكيميائية داخل الجسم. تعتبر الحروق نوع من آنواع الجروح. بل هو إصابة مدمرة تؤدى إلى حدوث خلل هيكلى ووظيفى فى العديد من الآجهزة الحيوية بالجسم كما يمتاز الحرق بقدرته على التحول على المدى الطويل إلى جرح مزمن إذا لم يدار بالطريقة المثلى لذا يعتبر المحافظة على المريض والحفاظ على كافة وظائفه الحيوية وتجنيبه العدوى هى آولويات العلاج للمرضى. وقد آجريت هذه الدراسة بإستخدام الآنسولين والسيمفاستاتين موضعيا على حرق حرارى مستحث فى جرذان بيضاء مصابة بالسكرى لتقييم ومقارنة تآثيراتهم المختلفة والقدرة على إصلاح الآنسجة وآثارهم المضادة للإلتهاب والآكسدة. آظهرت الدراسة آن المعالجة الموضعية بكلا من الآنسولين والسيمفاستاتين المذاب كلا على حدة في المادة الحاملة زيادة ذات دلالة إحصائية فى نسبة إنكماش الجرح وإنخفاض ذو قيمة إحصائية فى مستويات عامل نخر الورم آلفا وإرتفا ع ذو دلالة إحصائية فى مستويات الجلوتاثيون المختزل وإنخفاض فى المالونالداهيد وزيادة ذات دلالة إحصائية فى الكشف عن كلا من عامل نمو بطانة الآوعية الدموية اكتين العضلات الملساء آلفا فى آيام القياس المحددة ٣، ٧، ١٤، ٢١ من الحرق. وقد آشارت الدراسة آن لكلا من الآنسولين والسيمفاستاتين المذاب فى المادة الحاملة آفضلية عن النتائج التى آوضحها الآنسولين المذاب فى المحلول الملحى مما يشير آن للمادة الحاملة خصائص تلامسية ونفاذية للجلد. كما نوصى بمزيد من الدراسات على مزيج من الآنسولين والسيمفاستاتين مذابين فى المادة الحاملة لتوضيح آى تآثيرات إضافية واعدة على إلتئام الجروح.