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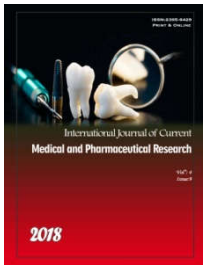

Research Article

WOUND HEALING POTENTIAL OF INSULIN SENSITIZERS-THIAZOLIDINEDIONE PIOGLITAZONE AND BIGUANIDE METFORMIN

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ABSTRACT

Diabetes mellitus is a noninfectious disease having high morbidity and mortality due to the complications arising as a result of uncontrolled hyperglycemia, excessive advanced glycation end products and vasculopathy affecting various vital organs. Frequently encountered complication of diabetes mellitus is a chronic wound, the treatment of which is still unsatisfactory. The choice of antidiabetic drugs can modify the course of wound healing favorably. Various studies have proved that Insulin sensitizers like thiazolidinediones and biguanides accelerate the wound healing. They are not hypoglycemic drugs hence they are quite safe. If they are selected after ruling out the contraindications and keeping a watch on their adverse drug reactions they prove to be a best choice. Thiazolidinedione drug pioglitazone promotes wound healing due to its anti-inflammatory, antioxidant mechanisms and by controlling the production of advanced glycation end products and the inhibition of expression of matrix metalloproteinase-9.Metformin, a biguanide drug activates AMPK, controls hyperglycemia, inhibits the generation of advanced glycation end products, promotes angiogenesis, possesses strong antiinflammatory and antioxidant properties and thereby accelerate the process of wound healing. These drugs need to be studied by various clinical trials to encourage their use regularly for wound healing. The local use of pioglitazone needs to be studied for wound healing as metformin has already been proved to heal the wounds after local application. Metformin forms a superior drug choice than pioglitazone as it has additional antimicrobial property and affects the hemostasis favorably to maintain the blood flow.

INTRODUCTION

Diabetes mellitus [DM] is a non communicable disease growing worldwide at the alarming rate every year. It has high grade morbidity and mortality due to its complications. Prevalence of diabetes mellitus is likely to exceed 591.9 million by 2035, leading to serious international health crisis.[1,2]

Complications of DM are due to uncontrolled hyperglycemia resulting in to angiopathy, nephropathy, neuropathy, ischemic heart disease, cerebrovascular accidents, retinopathy, fatty liver progressing to cirrhosis and the development of chronic wounds. Chronic wounds are the common complications in patients of DM which often lead to amputations, as the treatment of these wounds is still unsatisfactory.[3,4]The choiceof theantidiabetic drugs do modify the healing and the prognosis of these wounds. Thiazolidindione like pioglitazone andbiguanide like metformin affect the wound healing favorably.

Wound healing could be divided in to three major overlapping phases-inflammation, proliferation and remodeling. During these phases, various types of cells like immune cells, epithelial cells, endothelial cells and fibroblasts migrate and proliferate in coordination, which help in the process of wound healing through neo-vascularization, extracellular matrix production, granulation formation and re-epithelization.[5]

Role of advanced glycation end products in wound healing-
Advanced glycation endproducts (AGEs) are derived from the non-enzymatic reaction of reducing sugars with proteins, lipids or nucleic acids.[6] They contribute to the development of vascular complications in diabetics through the increased production of reactive oxygen species (ROS), thickening of basement membrane and increased extracelluar matrix formation. They affect various cellular signaling pathways through the receptors for AGEs (RAGEs).[7] The binding of AGEs to RAGEs triggers oxidative stress and activates the transcription factor Nf-κB, thus promoting the expression of pro-inflammatory mediators and local cellular responses. This all results in to the impairment of wound healing.[8,9]

Thiazolidinediones [TZDs] and biguanides are a class of antidiabetic insulin sensitizers. Rosiglitazone and pioglitazone

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are the TZDs. Rosiglitazone is not preferred due to its observed adverse effect on cardiovascular mortality. Biguanides are phenformin and metformin. Phenformin is discontinued long back due to the incidence of lactic acidosis. Metformin forms a first choice of anti diabetic drug in the treatment of type 2 diabetes mellitus [T2DM].

Thiazolidinediones

Peroxisome proliferator-activated receptors (PPARs), mainly PPAR-γ, play an important role in insulin resistance,T2DM and atherosclerosis.[10] TZD slike Rosiglitazone and pioglitazone, are selective agonists of nuclear transcription factor PPAR-γ which is expressed predominantly in adipose tissue and is shown to reduce inflammatory markers in visceral adipose tissue, fatty liver, circulating plasma and atherosclerotic plaques.[11] Data in animal and human studies have proved that TZDs along with their metabolic effects possess anti-inflammatory properties also.10

Anti inflammatory potential of TZDs

In patients of T2DM treatment with pioglitazone reduced adipose tissue macrophage infiltration, their number and activity.It also decreased inflammatory markers in macrophage, neutrophils, and dendritic cells.[12] It decreased pro inflammatory M1 macrophages and increased anti inflammatory M2 macrophages in adipose tissue.[13] In obese patients pioglitazone was found to decrease insulin resistance and some inflammatory markers like IL-6, IL-1β, and inducible nitric oxide synthase [iNOS] in adipose tissue.[14] Itsignificantly improved ballooning degeneration, lobular inflammation, and steatosis in patients with nonalcoholic steatohepatitis as compared to the placebo.[15,16] Pioglitazone decreased atherosclerotic plaque inflammation, significantly increased high density lipoprotein cholesterol level and decreased hsCRP.[17,18]Rosiglitazone reduced inflammatory markers, ubiquitin, proteasome 20S activity, nitrotyrosine, and superoxide anion production and increased collagen content in carotid plaques compared to placebo. The stabilization of the plaque was possibly due to the down regulation of Nf-κB-mediated inflammatory pathways.[19]

In patients with T2DM and coronary artery disease, treatment with pioglitazone reduced the rate of progression of coronary atherosclerosis and improved cardiovascular outcome which was associated with decrease in hsCRP levels, increase in high-density lipoprotein level, and reduction in triglyceride levels.[20] Therapy with TZD in patients of T2DM showed the significant reductions in the plasma cytokines, hsCRP, MCP-1, fibrinogen, and E-selectin.[21] Decrease in serum CRP levels were found in both DM and non-DM patients when treated with rosiglitazone and pioglitazone.[22]Reduction in CRP levels in patients correlated with decreased vascular inflammation and improved cardiovascular outcome.[23] This effect of pioglitazone on coronary vascular inflammation was irrespective of blood glucose control. Pioglitazone also reduced the risk of allcause mortality, myocardial infarction, stroke, acute coronary syndrome and leg amputation.[24,25]

Role of matrix metalloproteinase in wound repair

Increased expression of the potent protease, matrix metalloproteinase -9 [MMP-9] is associated with impaired wound healing in diabetic wounds.[26,27] AGEs induce high levels of MMP-9.Pioglitazone has shown the ability to inhibit the expression of MMP-9 via a transcriptional mechanism and enhanced the functional recovery and reduced the size of wounds after injury.[28]

The role of PPAR-γ in inflammatory responses and gastric ulcer were reported and pioglitazone was found to accelerate the gastric ulcer wound healing and reduced the inflammation.[29] Pioglitazone inhibited the TGF induced myofibroblast differentiation. It was also found to reduce TGF-beta induced type 1 collagen and fibronectin mRNA and protein production which were involved in the healing of burn wounds.[30,31]

Both PPAR-γ dependent and PPAR-γ independent mechanisms were responsible for the actions of pioglitazone.[32] Antioxidant defense mechanism of PPAR-γ agonist pioglitazone-

It has been reported that pioglitazoneis able to reduce oxidative stress.[33-37] PPAR-γ agonist like roziglitazone and pioglitazone were found to have antioxidant potential in various studies. In diabetic rabbit testis, pioglitazone normalized the activity of enzyme catalase and ascorbic acid and significantly inhibited lipid and protein oxidation irrespective of the control of blood sugar.[33] In cerebral ischemia/reperfusion injury rat model rosiglitazone and pioglitazone reduced oxidative stress,COX-2 expression, activation of mitogen activated protein kinases [MAPKs] and Nf-kB resulting in to reduction in the oxidative stress and inflammatory responses.[34]PPAR -γ activation can regulate oxidative stress responses and the expression of various antioxidant molecules including manganese SOD [MnSOD], antioxidant enzyme glutathione peroxidase-3 [GPx3],the scavenger receptor CD-36, hemeoxygenase-1 [HO-1],e ndothelial nitric oxide synthase [eNOS]and mitochondrial uncoupling protein-2 [UCP-2] along with the down regulation of COX-2 and inducible nitric oxide synthase [iNOS].[35] Pioglitazone exerted protective effect in the lung of diabetic rabbit by inhibiting nitrosative stress and normalizing the nitrite and nitrotyrosine levels.[36]PPAR-γ agonists promoted oligodendrocyte progenitor cell differentiation and enhanced their antioxidant defenses by increasing the levels of catalase and copper-zinc superoxide dismutase and maintained the homeostasis of glutathione system. [37]

Thus through anti inflammatory, antioxidant mechanisms and by the inhibition of generation of AGEs and the expression of MMP-9, TDZ like pioglitazone helps in wound repair in patients of DM.

Biguanide-metformin

Met form in is derived from French lilac [Galega officinalis]. It is the first choice of oral antidiabetic drug in the treatment of T2DM and preferred in overweight patient. Glucose lowering effect of met form in is through the activation of adenosine monophosphate activated protein kinase (AMPK), a cellular energy sensor.[38,39]

Antiinflammatory action of metformin

Met form in not only control hyperglycemia and insulin resistance but also possesses anti-inflammatory, anticancer, and antiaging effects. It also reduces cardiovascular risk, decreases body weight, corrects dyslipidemia and the procoagulant state.[40]Metformin activates AMPK, inhibits Nf-κB via PI3K-Akt pathway in human vascular smooth muscle cells which contributes for its anti inflammatory action.[41]Metformin through the inhibition of Nf-kB activation

in macrophages may also reduce the production of NO, prostaglandin E2, and proinflammatory cytokines like IL-1β, IL-6, and TNF-α.[41] AMPK interacts with tumor suppressor gene PTEN, antagonize PI3K, and affect cell survival, growth and proliferation.[42] It can also regulate inflammation through SIRT1/LKB1/AMPK pathway, suppresses reactive oxygen species/Poly ADP-ribose polymerase (PARP) signaling.[43] In addition, metformin exhibit antiinflammatory action through inhibition of AGEs which promote inflammation and oxidative stress.[44]With the good control of hyperglycemia, weight gain, and lipid profile metformin produces favorable effects on chronic inflammation and atherosclerosis.[40]

Met form in decreased CRP levels in patients of T2DM with long standing impaired glucose tolerance.[45]Krysiak and Okopien showed that treatment with metformin in T2DM patients reduced the release of various proinflammatory cytokines from monocyte and lymphocytes.[46,47] Met form in treatment in patients of T2DM and coronary artery disease showed antiinflammatory effects, reduced plasma insulin, plasminogen activator inhibitor type-1 antigen, CRP, and fibrinogen levels. The anti-inflammatory effect of met form in maybe an indirect effect of the improved insulin sensitivity and glycemic control.[24]

Role of AMPK in wound healing

Cutaneous wounds are the most common soft tissue injuries in aging individuals and in patients of DM which hinders the process of healing. Local application of met form in was found to accelerate the wound healing with improvement in epidermis, hair follicles and deposition of collagen in rhodents. As a result of stimulation of AMPK it enhanced the neo-vascularization in wound beds as AMPK is the important mediator for wound healing. AMPK was found inhibited in aged skin resulting in to reduced blood supply, angiogenic inhibition and reduced healing. Metformin reversed this process, enhanced wound healing and showed anti-aging effect.[48]

Effect on angiogenesis

Impaired wound healing is considered to be a consequence of hyperglycemia induced dysfunction of endothelial precursorcells [EPCs] in DM. EPCs are mobilized from bone marrow in to the circulation. They are the precursors of endothelial cells and play an important role in the angiogenesis and neo-vascularisation after tissue injury.[49-51] In DM patients marked reduction in number as well as dysfunction of circulating EPCs was observed.[52-56]Dysfunction of EPCs contribute to the diabetic vasculopathy and correlates with impaired healing of diabetic wounds.[57]It was observed that metformin was able to increase the number and improve the function of circulating EPCs in T2DM.[57,58] Angiogenesis promotes new vessels formation and enhances the supply of oxygen and nutrients to regenerating tissue.[59,60] Thrombospondin-1 [TSP-1] is a novel antiangiogenicadipokine expressed in animal models of DM, obesity and insulin resistance.[61] TSP-1 was demonstrated to be responsible for vascular complications of DM.[62]In animal studies it was observed that met form in accelerated wound healing, increased circulating EPCs, improved angiogenesis, increased NO production, and decreased the production of O2- and TSP-1.[63]

Antioxidant potential of metformin

Hyperglycemia induced oxidative stress is mediated through NADPH oxidase, xanthine oxidase and electron transport chain.[64]Oxidative stress contributes to the process of inflammation and inflammation itself can enhance oxidative stress.[65]Antioxidant action of metformin is exerted through the inhibition of mitochondrial respiration and by reduction in the generation of reactive oxygen species [ROS]. It also can increase levels of reduced glutathione.66 Metformin controls hyperglycemia in DM, reduces AGSs which are responsible for the oxidative stress and inflammation.[67]Upregulation of uncoupled protein-2 [UCP-2] in adipose tissue by metformin also contributes for antioxidant action. The main function of UCP-2 is the control of mitochondria derived reactive oxygen species.[68]

Effect of metformin on hemostasis

Metformin was found to reduce the circulating levels of coagulation factors like plasminogen activator inhibitor-1,von Willebrand factor, fibrinogen and factor VII.[69,70]It also affects the fibrin structure and function through decreasing factor VIII activity.[71]This all can result in to the prevention of intravascular coagulation which allows the defense machinery of body including the antibiotics and supportive treatment to reach the site of inflammation and wound which helps in wound repair.

Antimicrobial action of metformin

Metformin is one of the non antibiotic antimicrobial agent. It possesses antimicrobial action against various bacteria. Fatima Nasreen found the antimicrobial activity of met form in against Gram positive bacteria like Staphylococcus aureus, Bacillus subtilis, Bacillus magaterium, Bacillus cereus and Sarcinalutea; Gram negative bacteria like Vibrio parahemolyticus, Salmonellatyphi, Escherichia coli, Pseudomonas aeruginosa and fungi like Candida albicans and Aspargillusniger.[72]Animal studies have shown that metformin has antiparasitic action against Trichinella spiralis and Trypanosoma cruziand had antiviral action against hepatitis B and C virus and also against human immunodeficiency virus.[73]The most promising action of metformin was observed against mycobacterium tuberculosis. The possible mechanisms of antitubercular action of metformin are-activation of AMPK and mitochondrial ROS production, acceleration of phagosome lysosome fusion, improved immune response, increased CD 4 and CD 8 cells, rise in mycobacterium specific interferon secretion by CD 8 cells and reduced expression of inflammatory genes.[74]

Thus, it is evident that met form in through various actions like-antiinflammatory, antioxidant, reduction in AGEs, activation of AMPK, favorable effect on angiogenesis, hemostasis and antimicrobial actions promotes wound healing.

CONCLUSION

To conclude insulin sensitizers like pioglitazone and metformin accelerate the wound healing in patients of DM by various mechanisms as highlighted. These drugs are anti diabetics and not hypoglycemic like the insulin secretogogues. They do not produce hypoglycemia and beta cell exhaustion on their own. Hence they should be preferred in the treatment of DM and specially with the coexistent wounds. Local application of met form in has been tried and has been proved

to enhance wound healing. This property needs to be studied by undertaking clinical trials for nondiabetic wounds also.

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