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Diabetes Medications: Impact on Inflammation and Wound Healing

Jay J. Salazar¹, William J Ennis^{2,3}, and Timothy J Koh^{1,3,*}

¹Department of Kinesiology and Nutrition, University of Illinois at Chicago, Chicago, IL, USA

²Department of Surgery, University of Illinois at Chicago, Chicago, IL, USA

³Center for Tissue Repair and Regeneration, University of Illinois at Chicago, Chicago, IL, USA

Abstract

Chronic wounds are a common complication in patients with diabetes that often lead to amputation. These non-healing wounds are described as being stuck in a persistent inflammatory state characterized by accumulation of pro-inflammatory macrophages, cytokines and proteases. Some medications approved for management of type 2 diabetes have demonstrated anti-inflammatory properties independent of their marketed insulinotropic effects and thus have underappreciated potential to promote wound healing. In this review, the potential for insulin, metformin, specific sulfonylureas, thiazolidinediones, and dipeptidyl peptidase-4 inhibitors to promote healing is evaluated by reviewing human and animal studies on inflammation and wound healing. The available evidence indicates that diabetic medications have potential to prevent wounds from becoming arrested in the inflammatory stage of healing and to promote wound healing by downregulating pro-inflammatory cytokines, upregulating growth factors, lowering matrix metalloproteinases, stimulating angiogenesis, and increasing epithelization. However, no clinical recommendations currently exist on the potential for specific diabetic medications to impact healing of chronic wounds. Thus, we encourage further research that may guide physicians on providing personalized diabetes treatments that achieve glycemic goals while promoting healing in patients with chronic wounds.

Keywords

wound healing; insulin; metformin; sulfonylurea; thiazolidinedione; DPP-4 inhibitor

1. INTRODUCTION

Diabetes is an increasing healthcare problem in the United States, affecting 6.5 million patients in 1990 to over 29 million in 2014 and incurring yearly costs that exceed \$245

*Correspondence to: TJ Koh, Department of Kinesiology and Nutrition, University of Illinois at Chicago, 1919 West Taylor Street (m/c 994, Room 650), Chicago, IL 60612, USA. tjkoh@uic.edu.

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billion (American Diabetes Association 2013, Centers for Disease Control and Prevention 2014, Gregg, Li et al. 2014). Diabetes is associated with impaired wound healing, making patients susceptible to chronic non-healing wounds (Eming, Martin et al. 2014). Such wounds precede 84% of all diabetic lower extremity amputations (Reiber, Vileikyte et al. 1999) and once amputation occurs, patients have a 5-year mortality rate of 50% (Faglia, Favales et al. 2001, Eming, Martin et al. 2014, Gregg, Li et al. 2014).

Chronic diabetic wounds are trapped in a persistent inflammatory state with elevated levels of pro-inflammatory cytokines and proteases together with impaired expression of growth factors (Eming, Martin et al. 2014, Mirza, Fang et al. 2014). At the same time, the CDC reported that out of 20.9 million respondents with diabetes in the National Health Interview Survey, 2.9 million take insulin only, 11.9 million take oral diabetic medications only, 3.1 million take both, and 3 million take none (Centers for Disease Control and Prevention 2014). Thus, while over 70% of patients with diabetes take diabetic medications regularly at an annual cost of over \$50 billion (American Diabetes Association 2013), little is known about whether these medications influence wound healing outcomes, either directly through effects on cells involved in wound healing or indirectly through effects on systemic processes that can affect healing. As a result, no clinical recommendations exist regarding the impact of diabetic medications on healing of chronic wounds.

Wound healing involves a complex sequence of cellular and molecular processes including inflammation, cell proliferation, angiogenesis, collagen deposition, and re-epithelialization (Falanga 2005, Reiber and Rauig 2005). Among the early events of a wound-healing response is infiltration of inflammatory cells at the wound site (Martin and Leibovich 2005). This inflammatory response includes accumulation of macrophages which are an important contributor to healing, since monocyte/macrophage depletion results in delayed re-epithelialization, reduced collagen deposition, impaired angiogenesis, and decreased cell proliferation (Leibovich and Ross 1975, Mirza, DiPietro et al. 2009, Lucas, Waisman et al. 2010). However, prolonged inflammatory responses in wounds are associated with impaired healing (Loots, Lamme et al. 1998, Eming, Martin et al. 2014). Our laboratory has demonstrated that macrophages exhibit a persistent pro-inflammatory phenotype expressing high levels of pro-inflammatory molecules like interleukin-1 beta (IL-1 β), tumor necrosis factor alpha (TNF- α), and the protease matrix metalloprotease-9 (MMP-9) during impaired healing associated with diabetes (Mirza, Fang et al. 2013, Mirza, Fang et al. 2014, Mirza, Fang et al. 2015). This pro-inflammatory phenotype may be induced by hyperglycemia, which has been reported to increase oxidative and inflammatory stress via production of reactive oxygen species (ROS) and TNF- α (Mohanty, Hamouda et al. 2000, Aljada, Friedman et al. 2006).

Since macrophages are the primary producers of pro-inflammatory cytokines in wounds (Mirza, Fang et al. 2015), recent wound healing studies have focused on studying macrophage dysfunction in chronic wounds of diabetic humans and mice. Classically activated or M1-like macrophages are known for killing microorganisms and producing pro-inflammatory cytokines, such as IL-1 β , TNF- α and interleukin 6 (IL-6) (Novak and Koh 2013). In contrast, the alternatively activated or M2-like macrophages produce anti-inflammatory factors like IL-10, pro-healing factors such as insulin-like growth factor-1

(IGF-1) and transforming growth factor β (TGF- β), and promote wound regenerative actions (Novak and Koh 2013). Thus, the transition of macrophages from a pro-inflammatory M1-like phenotype to an alternative M2-like phenotype has been suggested as a pre-requisite for the switch from inflammation to proliferation in the healing wound (Koh and DiPietro 2011).

Initial studies have compared anti-inflammatory properties between diabetic medications by measuring their effects on the systemic inflammation marker C-reactive protein (CRP) or high-sensitive CRP (hs-CRP) (Kahn, Haffner et al. 2010). Both measure CRP but at different ranges (CRP: 0–10 mg/dL and hs-CRP: < 3 mg/L). CRP is an acute-phase reactant primarily synthesized in the liver by macrophages and fat cells under the stimulation of pro-inflammatory cytokines, such as TNF- α and IL-6. Furthermore, CRP has been shown in large clinical trials to provide prognostic information regarding the state of diabetogenesis and metabolic syndrome (Pradhan, Manson et al. 2001). In the case of the multinational clinical study “A Diabetes Outcome Progression Trial” (ADOPT) where 904 drug-naïve patients with type 2 diabetes were treated for a median of 4.0 years with rosiglitazone (a thiazolidinedione), glyburide (a sulfonylurea), or metformin, a subset analysis of patients with CRP measurements concluded that CRP reduction was greatest in the rosiglitazone group by 47.6% relative to glyburide and by 30.5% relative to metformin (Kahn, Haffner et al. 2010).

Many diabetic medications have demonstrated anti-inflammatory properties independent of their known marketed insulinotropic effects. Since an increased inflammatory state is linked with impaired healing and diabetic medications may have anti-inflammatory properties, it seems reasonable to speculate that diabetic medications could have an influence on wound healing. The aim of this article is to critically review the available literature on the influence of commonly prescribed medications for the treatment of type 2 diabetes on inflammation and wound healing. For each medication section, we focus on mechanisms of action, human clinical trial data, animal study results, study limitations and safety concerns. To identify relevant studies, we performed a literature search on PUBMED and clinicaltrials.gov using the generic name of the medications on this study and “wound healing”, “inflammation”, or “diabetes”. We illustrate that investigating the effects of diabetes medications on wound healing may allow clinicians the opportunity to offer personalized diabetic patients treatments that both treat the systemic diabetic condition that target the persistent inflammatory conditions associated with chronic wounds.

2. INSULIN

Decreased insulin action is a hallmark of diabetes. Systemic insulin treatment is used for glycemic control and according to the CDC, over 6 million Americans use insulin as daily diabetes treatment (Centers for Disease Control and Prevention 2014). Insulin serves an important role in glucose metabolism, protein synthesis, and proliferation and differentiation of different cell types suggesting that the hormone is capable of affecting different processes involved in wound healing (Apikoglu-Rabus, Izzettin et al. 2010). Additionally, insulin has been shown to induce an anti-inflammatory effect in monocytes from obese patients via reduction of NF κ B signaling and ROS generation (Dandona, Aljada et al. 2001).

Despite the millions of patients taking insulin, no large prospective or retrospective clinical trials have been performed on the effects of systemic insulin treatment on the incidence or healing of diabetic chronic wounds. However, several studies including small clinical trials have shown that application of topical insulin improves wound healing in diabetic humans and animals (Rezvani, Shabbak et al. 2009, Apikoglu-Rabus, Izzettin et al. 2010, Lima, Caricilli et al. 2012). In a recent study, topical use of a 0.5 units (U)/100 gram insulin cream on chronic wounds of patients with type 2 diabetes as part of a prospective, double-blind randomized clinical trial showed complete wound closure in 4 out of 10 patients by 8 weeks vs. none in the placebo group of 12 patients (Lima, Caricilli et al. 2012). In addition, a pilot trial tested the angiogenic potential of insulin treatment on 8 diabetic patients presenting with full-thickness wounds by treating half of their wounds topically with 10 U of insulin while leaving the other half untreated for 14 days. Their results indicated that biopsies from the insulin treated half showed a higher number of new vessels (96 ± 47) vs. the non-insulin side (32.88 ± 45) (Martinez-Jimenez, Aguilar-Garcia et al. 2013). Furthermore, in the outpatient clinical setting, topical application of 10 U of insulin on non-diabetic patients with acute (crush wounds, burns) and chronic wounds (pressure ulcers) resulted in a faster daily rate of wound closure ($46.09 \text{ mm}^2/\text{day}$) when compared to saline treated patients ($32.24 \text{ mm}^2/\text{day}$). However, while time to heal ($45 \text{ days} \pm 2 \text{ days}$) was not different between the two groups, the wound sizes in the insulin treatment group were larger at treatment initiation (Rezvani, Shabbak et al. 2009).

In animal studies, several investigators have used streptozotocin (STZ)-injected diabetic rats (a model of type 1 diabetes) to examine the effects of topical insulin on wound healing. One of those studies showed that application of topical insulin on wounds of STZ-injected diabetic rats shortened the median time needed for complete epithelialization from 13 to 11 days (Apikoglu-Rabus, Izzettin et al. 2010). A larger study showed that that topical application of 0.5 U/100 g insulin cream to wounds of STZ-injected diabetic rats induced faster wound healing which was associated with increased activation of the AKT and ERK pathways and increased vascular endothelial growth factor (VEGF) and stromal cell-derived factor 1 α (SDF1 α) expression on wounds (Lima, Caricilli et al. 2012). Furthermore, they showed a dose-dependent response where 0.5 U of insulin led to wound closure around 9 days compared to the 11 days for the group treated with 0.25 U insulin and 16 days for the 0.1 U and non-insulin cream control groups.

Mechanistically, insulin has been shown to increase VEGF expression in keratinocytes in excisional wounds of C57BL6 and ob/ob mice via increased AKT signaling (Goren, Muller et al. 2009). Previous studies using cultured keratinocytes from insulin receptor knock out mice showed that absence of insulin signaling induces abnormal differentiation despite increased IGF-1 signaling (Wertheimer, Spravchikov et al. 2001). In addition, recent studies using transgenic mice with an inducible Cre-LoxP deletion of both the insulin and IGF-1 receptors on vascular endothelial cells showed that deletion of insulin and IGF-1 receptors in endothelial cells had little effect on days to superficial wound closure but that the loss of insulin signaling resulted in a large reduction of wound vascularization and granulation tissue formation underscoring the need for insulin signaling in this aspect of wound healing (Aghdam, Eming et al. 2012).

Using non-diabetic mouse models, insulin was also shown to affect early accumulation of inflammatory cells in wounds of mice. Topical treatment with 0.03U insulin/20 µl saline was reported to increase macrophage infiltration in the first 2 days of full-thickness skin wounds of non-diabetic C57BL/6J mice by increasing expression of monocyte chemoattractant protein-1 (MCP-1), a potent chemotactic factor for macrophages. Blockage of MCP-1 resulted in reduced macrophage infiltration and impaired wound healing despite the presence of insulin (Chen, Liu et al. 2012).

One limitation of topical insulin studies is the use of zinc to crystallize insulin. Zinc is an essential mineral with anti-inflammatory properties that has been publicized to promote wound healing. One recent randomized pilot study used 90 non-diabetic patients with various community-acquired wounds to compare topical insulin (containing zinc), aqueous zinc chloride solution, and saline controls on healing of open uncomplicated wounds. Their results showed that the insulin and zinc solution induced faster wound healing than saline treated groups. However, the insulin treated groups appeared to provide a superior effect compared with the zinc group, but this effect was not significant due to the heterogeneity of the wounds types and sizes (Attia, Belal et al. 2014).

It is important to mention that endogenous production of human insulin by pancreatic beta cells includes proinsulin C-peptide which is secreted into circulation in equimolar concentrations to regular insulin. Despite previous reports of no effect in diabetic wounds of STZ-injected SKH-1 mice using 10 nM of C-peptide (Langer, Born et al. 2002), a recent study using STZ-injected C57BL6 mice showed that administration of a 35 pmol/kg per minute dose of C-peptide delivered by mini-osmotic pumps in saline for 2 weeks was able to induce 95% wound closure 30% faster (10 vs. 14 days) than untreated diabetic control mice with sham pump surgeries (Lim, Bhatt et al. 2015). If future studies validate these findings, insulin secretagogue diabetic medications might mediate a synergistic wound healing effect by increased c-peptide secretion that exogenous insulin injections cannot offer.

Considering that most patients with diabetes will eventually be placed on insulin treatment, further investigations should be pursued on the effects of insulin on wound healing. In addition, while the literature contains some evidence that topical insulin may promote wound healing, a large multi-center clinical trial is still needed to demonstrate whether such treatment is effective on a large numbers of patients.

3. METFORMIN

Metformin, a biguanide, is currently the first line medication for initial treatment of type 2 diabetes and works by suppressing glucose production by the liver via activation of AMP-activated protein kinase (AMPK) (Hundal, Krssak et al. 2000). Despite being one of oldest medications prescribed to patients with type 2 diabetes, few studies have investigated its influence on wound healing.

Unfortunately, a review of the literature revealed no studies on the effects of metformin on wound healing in diabetic patients. However, some clinical studies indicate that oral metformin may induce modest amelioration of systemic inflammation. An outpatient clinic

follow-up study of 110 patients with type 2 diabetes taking only metformin or the sulfonylurea glyburide for 4 years indicated that metformin users had lower levels of the inflammatory marker CRP (5.56 ± 1.5 mg/L) than patients taking the glyburide (8.3 ± 1.4 mg/L) (Akbar 2003). Metformin has also been shown to decrease the pro-inflammatory cytokine macrophage migration inhibitor factor (MIF) in the plasma and monocytes from obese patients when compared to untreated patients (Dandona, Aljada et al. 2004). Furthermore, a meta-analysis of 33 human studies looking at the effects of metformin on CRP levels of patients with type 2 diabetes indicated decreases on serum levels of CRP (Shi, Tan et al. 2014).

In laboratory experiments, metformin treatment of isolated human monocytes stimulated with lipopolysaccharide (LPS) showed that the drug inhibits production of TNF- α via inhibition of the extracellular signal-regulated protein kinase (ERK) pathway (Arai, Uchiba et al. 2010). Another study indicated that RAW276.4 macrophages stimulated with LPS and treated with various concentrations of metformin (1–10 mM) exhibited decreased production of TNF- α , IL-6, and IFN- γ in a dose dependent manner (Nath, Khan et al. 2009). In addition, diabetic nephropathy related studies demonstrated that metformin decreased reactive oxygen species (ROS) generation via suppressing RAGE expression on human renal proximal tubular cells in vitro (Ishibashi, Matsui et al. 2012). Lastly, AMPK activation (a known metformin effect) has been shown to induce anti-inflammatory properties via suppression of NF- κ B signaling (Salminen, Hyttinen et al. 2011).

Despite the potential for metformin to ameliorate inflammation, there is little information available on the potential for metformin to influence wound healing. However, a bioengineering group recently demonstrated that biodegradable nanofibrous drug-eluting membranes designed to sustainably release metformin, accelerated epithelization in wounds of STZ-injected diabetic rats. Specifically, the metformin-eluting membrane induced an 85% vs. 67% wound closure by day 7 and 97% vs. 85% closure by day 14 compared to non-eluting membrane treated wounds (Lee, Hsieh et al. 2014). In addition, there is a large on-going Phase II clinical trial studying whether oral metformin (1000 mg three times a day) can help wound healing on burned children with expected results in 2017. The clinicians hypothesize that compared to a sugar pill placebo, metformin will provide greater anabolic activity that will translate into improved wound healing of burned tissues in children (Herndon 2015).

4. SULFONYLUREAS

Sulfonylureas such as glyburide (glibenclamide) and glimepiride are some of the most commonly used medications for the treatment of type 2 diabetes. Sulfonylureas work by binding to a receptor on the ATP-dependent potassium channel in the pancreatic beta cells. The binding inhibits the potassium channels which changes the resting potential of the beta cells allowing higher sensitivity to glucose which induces greater insulin secretion (Bressler and Johnson 1997).

Again, although no studies were found on the effects of sulfonylureas on wound healing in diabetic patients, a few studies have investigated effects on inflammation. To investigate the

potential influence of different sulfonylurea drugs on inflammation, a small number of type 2 diabetes patients were switched from glyburide to glimepiride for 28 weeks and titrated up to 6 mg/day. The switch was associated with increased adiponectin and decreased plasma TNF- α , IL-6, and hs-CRP levels compared to patients maintained on glyburide or insulin treated patients (Koshihara, Nomura et al. 2006). Another study on treatment naive type 2 diabetes patients comparing glyburide vs. metformin monotherapy titrated for glycemic control to dosages up to 20 mg/day for glyburide or 2,550 mg/day for metformin indicated that only glyburide was able to induce a reduction in CRP levels within a 3 month time-frame (Putz, Goldner et al. 2004). Together, these studies point to the systemic anti-inflammatory potential of sulfonylureas in patients with diabetes.

One sulfonylurea, glyburide, has been shown to downregulate inflammation and promote wound healing through its ability to inhibit the nod-like receptor protein (NLRP)-3 inflammasome. Previous studies had found that the sulfonyl and benzamido groups on glyburide chemical structure allow for its specific (NLRP)-3 inflammasome inhibitory activity, which is not shared by other sulfonylureas (Lamkanfi, Mueller et al. 2009). Targeting the (NLRP)-3 inflammasome may be particularly useful for reducing inflammation in diabetes since its activation under chronic hyperglycemic states has been shown to initiate an intracellular inflammatory cascade that promotes a persistent pro-inflammatory state (Zhou, Tardivel et al. 2010). In addition, diabetes-mediated metabolic syndrome induces accumulation of lipid activators that facilitate assembly of the (NLRP)-3 inflammasome leading to activation of caspase-1 and increased secretion of IL-1 β and IL-18, both pro-inflammatory factors, which exacerbate systemic inflammation and insulin resistance (Bitto, Altavilla et al. 2013).

Since IL-1 β is predominantly produced by monocytes and macrophages (Mirza, Fang et al. 2015), use of an inflammasome inhibitor to lower IL-1 β expression may be an appealing anti-inflammatory strategy since these inflammatory cells are key regulators of the wound healing process (Koh and DiPietro 2011). Notably, treatment of excisional wounds on db/db diabetic mice with topical glyburide was shown to accelerate epithelialization and increase granulation tissue formation. In addition, glyburide treatment decreased levels of pro-inflammatory IL-1 β and IL-18 in wound homogenates and reduced mRNA expression in macrophages isolated from wounds. Glyburide treatment also induced concurrent increased expression of pro-healing IGF-1, TGF- β , and IL-10 growth factors (Mirza, Fang et al. 2014). Separate confirmatory studies using local wound treatment of incisional wounds in diabetic db/db mice with the I- κ B kinase- β inhibitor, BAY 11-7082, which also inhibits the (NLRP)-3 inflammasome, showed improved wound healing and increased angiogenesis with upregulation of VEGF and SDF-1 α (Bitto, Altavilla et al. 2013).

Together, these studies show promise for the use of glyburide as a topical treatment to inhibit the inflammasome and promote healing of chronic wounds on diabetic patients. By restricting the use of glyburide to the wound area, there is also a decreased risk of side effects like hypoglycemia that is commonly reported when used systemically (Shorr, Ray et al. 1996). Future studies testing its effectiveness for ameliorating inflammation and accelerating wound closure in a clinical trial appears to be warranted. In addition, wound

healing studies comparing glyburide to newer generation sulfonylureas may identify other candidates for therapeutic use.

5. THIAZOLIDINEDIONES

Thiazolidinedione (TZD) medications improve insulin resistance in patients with type 2 diabetes mellitus by targeting the peroxisome proliferator-activated gamma receptor (PPAR- γ), which is thought to increase insulin sensitivity by retention of fatty acids in adipose tissue and regulation of adipocyte secreted hormones that impact glucose homeostasis (Rangwala and Lazar 2004). Early studies evaluating anti-inflammatory properties by rosiglitazone showed its ability to lower MCP-1 and CRP in plasma and NF κ B-binding activity in mononuclear cell extract from a group of non-diabetic and diabetic obese patients treated for 6 weeks (Mohanty, Aljada et al. 2004).

A single-centre, randomized, open-label study in type 2 diabetes patients showed that 12 weeks of rosiglitazone treatment leads to greater reductions in inflammatory biomarkers compared to metformin/glyburide treatment including greater decreases in hs-CRP (58% vs. 26% non-significant reduction in metformin/glyburide group) (Gupta, Teoh et al. 2012). When studies were performed on human macrophages isolated from blood, TZD mediated PPAR- γ activation was shown to inhibit the expression of the pro-inflammatory genes TNF- α , IL-6, and IL-1 β suggesting its role as a negative regulator of macrophage activation (Jiang, Ting et al. 1998). However, in vitro studies that blocked all PPAR activity demonstrated that TZD medications can induce anti-inflammatory and pro-angiogenic effects independent of PPAR (Schiefelbein, Seitz et al. 2008).

Another commonly prescribed TZD, pioglitazone, was shown in a prospective clinical trial of 50 patients with type 2 diabetes to decrease inflammatory cytokines and increase pro-angiogenic factors in plasma (Vijay, Mishra et al. 2009). Specifically, 20 patients on 45mg pioglitazone daily for 16 weeks showed decreased TNF- α , CRP, and lipid profile proteins (due to its partial PPAR- α activity) with increases in VEGF, IL-8 and angiogenin when compared to 10 control patients on sulfonylureas or other insulin secretagogues. An additional 20 patients taking 4mg rosiglitazone showed similar but less robust effects than patients on pioglitazone except for no changes in TNF- α or lipid profile. Overall, a recent meta-analysis of 27 randomized controlled trials evaluating pioglitazone and rosiglitazone therapy on circulating levels of inflammatory markers in patients with type 2 diabetes showed that both medications decreased levels of hs-CRP and MCP-1 with limited effects on IL-6 and MMP-9 (Chen, Yan et al. 2015).

Recent studies have reported that topical treatment of wounds on db/db diabetic mice with rosiglitazone reported improved wound healing by inducing a switch of pro-inflammatory macrophages towards a pro-healing phenotype (Mirza, Fang et al. 2015). They also found that diabetic wounds from mouse and human patients showed impaired PPAR- γ activity due to sustained expression of IL-1 β , which maintained wounds in a persistent inflammatory state. Mechanistically, PPAR- γ has been reported to control the inflammatory response by inhibition AP-1, NF- κ B, or STAT-3 signaling pathways in macrophages (Chinetti, Fruchart et al. 2003) and likely other cells. Additionally, a recent study showed that macrophages

deficient in PPAR γ from PPAR γ knock out mice exhibited impaired skin wound healing with high expression of TNF- α and reduced collagen deposition, angiogenesis and granulation formation (Chen, Shi et al. 2015). They also found that treatment with rosiglitazone on wounds of wild type mice resulted in accelerated wound healing and decreased TNF- α levels compared to wounds of vehicle treated controls, but that rosiglitazone did not elicit these changes in PPAR γ -knock out mice. In the case of pioglitazone, a study showed its ability to inhibit matrix metalloproteinase-9 (MMP-9) which is a potent protease shown to be associated with impaired healing in diabetes. Using an in-vitro model of HaCaT cells, treatment with advanced glycation end product (AGE) induced high levels of MMP-9 protease, which was inhibited with pioglitazone in a dose dependent manner (Zhang, Huang et al. 2014).

Today, pioglitazone and rosiglitazone are the only TZDs that remain on the market after safety concerns caused the withdrawal of the other TZD medications. However, both medications have been associated with increased incidence of heart failure, weight gain, peripheral edema, and more recently, bone fractures (Dormandy, Charbonnel et al. 2005, Colhoun, Livingstone et al. 2012). In summary, TZD medications may represent an option to dampen inflammation and have potential to promote healing of chronic wounds. In addition, their recent availability as generic medications lowers their costs significantly. Importantly, topical TZD treatment may benefit chronic wounds while avoiding the risks associated with systemic administration.

6. DIPEPTIDYL PEPTIDASE 4 INHIBITORS

The incretin hormones glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP) are reported to account for 50% to 70% of postprandial insulin secretion from pancreatic beta cells (Baggio and Drucker 2007). The hormones are secreted after a meal from the small intestine but have a circulating half-life of less than 2 minutes from its rapid degradation by dipeptidyl peptidase 4 (DPP-4) (Lovshin and Drucker 2009). Dipeptidyl peptidase 4 inhibitors (DPP-4i) are diabetes medications that work by blocking DPP-4 inactivation of the incretin hormones to allow extended stimulation of pancreatic insulin secretion and inhibition of glucagon release in a glucose-dependent manner (Koliaki and Doupis 2011, Shah, Kampfrath et al. 2011). Since DPP-4 and GLP-1 receptors are widely expressed throughout the human body including monocyte/macrophages; it has been proposed that incretin based therapies may exert pleiotropic effects that extend beyond pancreatic islet stimulation (Koliaki and Doupis 2011). Studies on diabetic humans and mice have indicated that DPP-4i improve postprandial lipemia, reduce inflammatory markers, improve endothelial function, reduce platelet aggregation, and are weight neutral (Scheen 2015).

In human studies, a prospective randomized study with 22 type 2 diabetes patients treated with sitagliptin or placebo for 12 weeks resulted in decreases on plasma levels of CRP, IL-6, free fatty acids, and mononuclear cell expression of TNF- α , JNK-1, TLR-2, and TLR-4 indicating an anti-inflammatory response (Makdissi, Ghanim et al. 2012). Another prospective randomized study comparing two DPP-4i medications, sitagliptin and vildagliptin, in patients with type 2 diabetes inadequately controlled by metformin showed

that, as an add on therapy, the medications lowered plasma pro-inflammatory cytokines IL-6, IL-18, and TNF- α (Rizzo, Barbieri et al. 2012).

A review of the literature revealed only two studies on the effects of DPP-4i on wound healing, one in humans and one in mice. In the first study, an open label study showed that diabetic patients for whom vildagliptin was added to their diabetes treatment plan (+/- insulin, metformin, and/or a sulfonylurea) had improved healing of foot ulcers after 12 weeks compared to foot ulcers from patients without vildagliptin. Biopsies from patients treated with vildagliptin showed increased staining of HIF-1 α and VEGF that suggested pro-angiogenic involvement (Marfella, Sasso et al. 2012). Since they also detected decreases on nitrotyrosine levels and proteasome 20S activity on tissues from treated patients, investigators proposed that vildagliptin may work by reducing oxidative stress and preventing increased ubiquitin proteasome system degradation of HIF-1 α leading to increased VEGF expression.

In the second study, linagliptin improved wound healing in diabetic ob/ob mice by increasing re-epithelialization and myofibroblast differentiation compared with untreated mice. Linagliptin treatment also induced increases in SDF-1 α and MIP-2 protein expression (Schurmann, Linke et al. 2012). Unexpectedly, their studies using cultured HaCaT keratinocytes indicated that DPP-4 does not directly influence keratinocyte proliferation, since linagliptin was unable to induce increased proliferation at any concentration. Furthermore, addition of active GLP-1 to keratinocytes induced a reduction of EGF-induced phosphorylation of p42/44 MAPK arguing against an effect by GLP-1 on the regulation of keratinocyte proliferation.

It is important to note that while vildagliptin is not available in the US since it has not received FDA approval, there are six other DPP-4i medications that are currently offered. As for adverse effects, DPP-4i and GLP-1 receptor agonists have been associated with pancreatitis and pancreatic cancer although several studies have indicated no increased risk including a recent meta-analysis (Li, Shen et al. 2014). Also, vildagliptin has been recently associated with skin reactions although the reported instances are very rare (7 cases in total) and most patients were on metformin as well (Bene, Jacobsoone et al. 2015) making a clear inference difficult. In summary, as the most recent diabetes medication class to show anti-inflammatory potential, further research is needed to determine whether DPP-4i can be used to promote wound healing.

7. CONCLUSION

In 2012, 30% of the \$176 billion in direct medical costs of treating diabetes in the United States was used to purchase medications to treat diabetes and its complications (American Diabetes Association 2013). At the same time, introducing new diabetic medications costs billions of dollars and years of research. Thus, millions of patients could benefit from identification of favorable pleiotropic effects of available diabetes medications that may ameliorate diabetes related complications including poor wound healing. While several factors contribute to impaired wound healing in patients with diabetes, amelioration of the persistent inflammation involved in chronic wounds may be a goal that can be achieved with

existing medications. Such therapies could provide an anti-inflammatory effect to prevent wounds from becoming arrested in the inflammatory stage and promote non-healing wounds to progress to epithelization.

Recent investigations of insulin, metformin, specific sulfonylureas, thiazolidinediones, and DPP-4 inhibitors indicate that they possess anti-inflammatory properties. Many of these medications are now known to downregulate the pro-inflammatory phenotype of macrophages and to increase the anti-inflammatory and healing-associated macrophage phenotypes, decrease levels of matrix metalloproteinases, increase keratinocyte and fibroblast proliferation, induce new vessel formation from endothelial cells, and accelerate wound closure. In addition, many of the reviewed medications appear to exhibit potential to stimulate angiogenesis and granulation tissue formation that is necessary for effective wound healing.

Our review of clinical data suggests that the thiazolidinedione rosiglitazone results in the lowest levels of the inflammation marker CRP followed by the sulfonylurea glyburide when compared to metformin. However, it remains to be seen whether the reported anti-inflammatory results translate to improved healing of chronic wounds. Thus, further research is needed to determine the potential of the different diabetes medications currently available in the market on improving the healing of chronic wounds. Considering the millions of patients taking these medications, future wound healing research efforts should involve both clinical studies (e.g. retrospective studies, prospective cohort studies, as well as clinical trials) and basic science studies using animal models of diabetes. The focus should be on elucidating which drugs are most beneficial for type 2 diabetes patients suffering from chronic wounds. Also, since in clinical practice most patients with type 2 diabetes take multiple diabetic medications at the same time and there is a lack of studies on the effects of concomitant diabetic medications on wound healing, it seems necessary to perform studies on the impact of combining multiple diabetic medications on healing. A future aim should be the creation of recommendations in collaboration with wound healing clinicians and primary care diabetes physicians to provide personalized diabetes treatments that achieve glycemic goals while promoting wound healing conditions in patients with chronic wounds.

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Highlights

- Chronic wounds in diabetic patients exhibit persistent inflammation.
- Diabetes medications exhibit anti-inflammatory properties
- These medications have underappreciated potential to promote wound healing
- Further research needed to guide diabetes treatment in patients with chronic wounds

Figure 1. Diabetes Medications Associated Mechanisms of Action Involved in Wound Healing

The figure shows signaling pathway that may be targeted by diabetic medications on epithelial cells (keratinocytes), vascular endothelial cells, “classically activated” M1-like macrophages, and “alternative activated” M2-like macrophages present in chronic wounds. Classically activated M1-like macrophages produce pro-inflammatory gene products that maintain wounds on a persistent inflammatory state. Alternative activated M2-like macrophages produce more pro-healing gene products that allow wound to resolve the inflammatory state and proceed to healing. All receptors (Insulin R, PPAR γ R and GLP-1 R) and cell targets are present in both types of macrophages.

Table 1

Summary of Reported Changes on Molecular Pathways and Cytokine Levels by Diabetes Medications in Wound Healing.

Medications	Reported Molecular Pathways Affected	Reported Effects on Growth Factors and Cytokines Involved in Wound Healing		FDA Reported Clinical Side Effects
		Pro-Inflammatory	Pro-Healing	
Insulin	AKT ERK	↑ MCP-1 ↓ ROS	↑ VEGF ↑ SDF1 α	
Metformin	AMP-Activated Protein Kinase (AMPK) ERK NF κ B	↓ TNF α ↓ IL-6 ↓ INF- γ ↓ ROS ↓ MIF		Lactic Acidosis (Black Label Warning)
Sulfonylureas (Glyburide)	Inhibit Nod-Like Receptor NLRP-3 Inflammasome	↓ IL-1 β ↓ IL-18	↑ IGF-1 ↑ TGF- β ↑ IL-10	Hypoglycemia
TZD	PPAR γ Activation NF κ B P38 MAPK	↓ TNF α ↓ IL-6 ↓ Resistin ↓ IL-1 β ↓ MCP-1 ↓ MMP-9	↑ VEGF ↑ IL-8 ↑ Adiponectin	Congestive Heart Failure (Black Label Warning)
DPP-4 Inhibitors	Inhibition of DPP-4 proteases Extend GLP-1 bioavailability	↓ TNF α ↓ IL-6 ↓ IL-18 ↑ MIP-2	↑ VEGF ↑ SDF1 α	Heart Failure (Saxagliptin)