Journal of Diabetes and Its Complications 30 (2016) 746–752

Contents lists available at ScienceDirect

Journal of Diabetes and Its Complications

journal homepage: WWW.JDCJOURNAL.COM

Diabetes medications: Impact on inflammation and wound healing

Jay J. Salazar [a], William J. Ennis [b,c], Timothy J. Koh [a,c,*]

[a] Department of Kinesiology and Nutrition, University of Illinois at Chicago, Chicago, IL, USA
[b] Department of Surgery, University of Illinois at Chicago, Chicago, IL, USA
[c] Center for Tissue Repair and Regeneration, University of Illinois at Chicago, Chicago, IL, USA

ARTICLE INFO

Article history:
Received 29 October 2015
Received in revised form 15 December 2015
Accepted 16 December 2015
Available online 19 December 2015

Keywords:
Wound healing
Insulin
Metformin
Sulfonylurea
Thiazolidinedione
DPP-4 inhibitor

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.

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 billion (American Diabetes Association, 2013; Centers for Disease Control and Prevention, 2014; Gregg et al., 2014). Diabetes is associated with impaired wound healing, making patients susceptible to chronic non-healing wounds (Eming, Martin, & Tomic-Canic, 2014). Such wounds precede 84% of all diabetic lower extremity amputations (Reiber et al., 1999) and once amputation occurs, patients have a 5-year mortality rate of 50% (Eming et al., 2014; Faglia, Favales, & Morabito, 2001; Gregg 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 et al., 2014; Mirza, Fang, Weinheimer-Haus, Ennis, & Koh, 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-epithelization (Falanga, 2005; Reiber & Raugi, 2005). Among the early events of a wound-healing response is infiltration of inflammatory cells at the wound site (Martin & 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 & Ross, 1975; Lucas et al., 2010; Mirza, DiPietro, & Koh, 2009). However, prolonged inflammatory responses in wounds are associated with impaired healing (Eming et al., 2014; Loots et al., 1998). Our laboratory has

Conflicts of interest: The authors have no conflict of interest to declare.

Source of funding: Research reported in this publication was supported by the National Institute of Health Award RO1GM092850 (TJK). The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

* Corresponding author at: Department of Kinesiology and Nutrition, University of Illinois at Chicago, 1919 West Taylor Street (m/c 994, Room 650), Chicago, IL 60612, USA.
E-mail address: tjkoh@uic.edu (T.J. Koh).

http://dx.doi.org/10.1016/j.jdiacomp.2015.12.017
1056-8727/

demonstrated that macrophages exhibit a persistent pro-inflammatory phenotype expressing high levels of pro-inflammatory molecules like interleukin-1 beta (IL-1β), tumor necrosis factor alpha (TNF-α), and the protease matrix metalloprotease-9 (MMP-9) during impaired healing associated with diabetes (Mirza, Fang, Ennis, & Koh, 2013; Mirza et al., 2014, 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 (Aljada et al., 2006; Mohanty et al., 2000).

Since macrophages are the primary producers of pro-inflammatory cytokines in wounds (Mirza 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-1β, TNF-α and interleukin 6 (IL-6) (Novak & 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 & 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 & 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 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, Rifai, Buring, & Ridker, 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 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, Turan, & Ercan, 2010). Additionally, insulin has been shown to induce an anti-inflammatory effect in monocytes from obese patients via reduction of NFkβ signaling and ROS generation (Dandona 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 (Apikoglu-Rabus et al., 2010; Lima et al., 2012; Rezvani et al., 2009). 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 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 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 mm2/day) when compared to saline treated patients (32.24 mm2/day). However, while time to heal (45 days +/− 2 days) was not different between the two groups, the wound sizes in the insulin treatment group were larger at treatment initiation (Rezvani 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 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 1α (SDF1α) expression on wounds (Lima 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 et al., 2009) (Fig. 1). 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 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 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