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The Role of PPAR-γ agonist to Improved Wound Healing in Diabetes Mellitus

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Abstract

Aim To provide evidence regarding the role of PPAR-γ agonist to improved wound healing in diabetes mellitus.Methods PubMed, Science Direct, ProQuest, Cochrane and Wiley Online Library were searched for any design study that explore the role of PPAR-γ to improved wound healing in diabetes mellitus. Four studies were identified and analysed from 16 initial ar ticles Data were then extracted from the studies and summarized descriptively Results Sixteen articles were screened, and four studies were identified and eventually selected. All four selected studies were conducted in USA, China and Germany. There were 55 diabetic mice in these studies. Fifty dibetic mice with excisional wound (seven mice with obesity) and fourty diabetic mice with burn wound Conclusion PPAR-γ agonists and highly glucose-stimulated macrophages can accelerate wound healing by tending to enhance granulation tissue formation, angiogenesis and collagen deposition; suppress inflammatory signals from mature adipocytes; and induce VEGF mRNA and protein expression from cultured keratinocytes

Keywords: *Diabetes Mellitus, Obese, Ppar-γ Agonist, Wound Healing*

Introduction

Diabetes-associated severe ulcerations of the skin represent a serious problem of growing clinical importance. Diabetic ulcers still have a poor prognosis with high reulceration rates and a high mortality after limb amputations.1 The disorganized inflammatory response during diabetic wound healing is usually considered as leading factor of diabetic-impaired healing.2 Similarly, the combined diabetes-obesity syndrome can impair acute skin wound regeneration in a mouse model. Obese mice with severely impaired wound formation in skin wounds resulted in impaired processes of keratinocyte proliferation, reepithelialization and granulation tissue formation in conditions of absent or inactive growth factors and exacerbated inflammation integrating into severe wound tissue defects.[3,4]

Over-activation and persistent chronic inflammation are major pathogenic characteristics of impaired diabetic healing, and diabetic wound healing can be promoted by stimulating the transition of the macrophage phenotype from pro-inflammatory (M1) to anti-inflammatory (M2).5-7 Macrophage phenotype transition during wound healing is associated with

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upregulation of peroxisome proliferator-activated receptor (PPAR)-γ and its downstream targets, along with increased mitochondrial content. In a diabetes model, upregulation of PPAR-γ activity is impaired by sustained expression of IL-1 in mice and human wounds. The loss of PPAR-γ in macrophages can prolong wound inflammation and delay healing by reducing collagen deposition, angiogenesis and granulation formation.8,9 In addition, PPARγ has an important role in controlling the clearance of wound macrophages from apoptotic cells to ensure efficient wound healing, and can be a potential new therapeutic target for wound healing.10

This research aimed to review the evidence regarding the role of PPAR-γ agonist to improved wound healing in diabetes mellitus condition with and without obese.

Materials and Methods

Materials and Study Design

A comprehensive search was performed in July 2022 in which we searched the PubMed, ScienceDirect, ProQuest, Cochrane and Wiley Online Library databases, using keywords related to diabetes mellitus, wound healing, and PPAR-γ without language restrictions. The following keywords were used in searches of all the data- bases: "Diabetes Mellitus" and "Wound Healing" and "PPAR-γ".

This study reviewed evidence from any design study published in the period between 2005 and 2022 to explore the role of PPAR-γ to improved wound healing in diabetes mellitus. The sample reviewed were diabetic rat model induction. The criteria for inclusion and exclusion were determined before the search. We included studies with experimental rat models of diabetes with wound. Studies with relevant titles are then collected and filtered. Studies found in more than one database were removed. Full-paper manuscripts were then studied, and manuscripts that were irrelevant to the theme are excluded. Four studies were included in the systematic review.

Methods

This systematic review was written based on the Preferred Reporting Item Guidelines for Systematic Reviews and Meta-Analysis (PRISMA) guidelines for reporting the events evaluated by interventions and health care behaviours.11 The population, intervention, control, and outcome (PICO) questions used in this systematic review were:12 P (population): diabetes mellitus, I (intervention): PPAR-γ agonist, C (comparison/control): with or without placebo and O (outcome): wound healing.

Statistical Analysis

Relevant information was extracted from selected studies. Relevant information included study types, patient characteristics, intervention regimens, comparative regimens (placebo), improved of wound healing, and methods used to analyse the results. The primary outcome assessed was the efficacy of PPAR-γ agonist treatment to improved wound healing

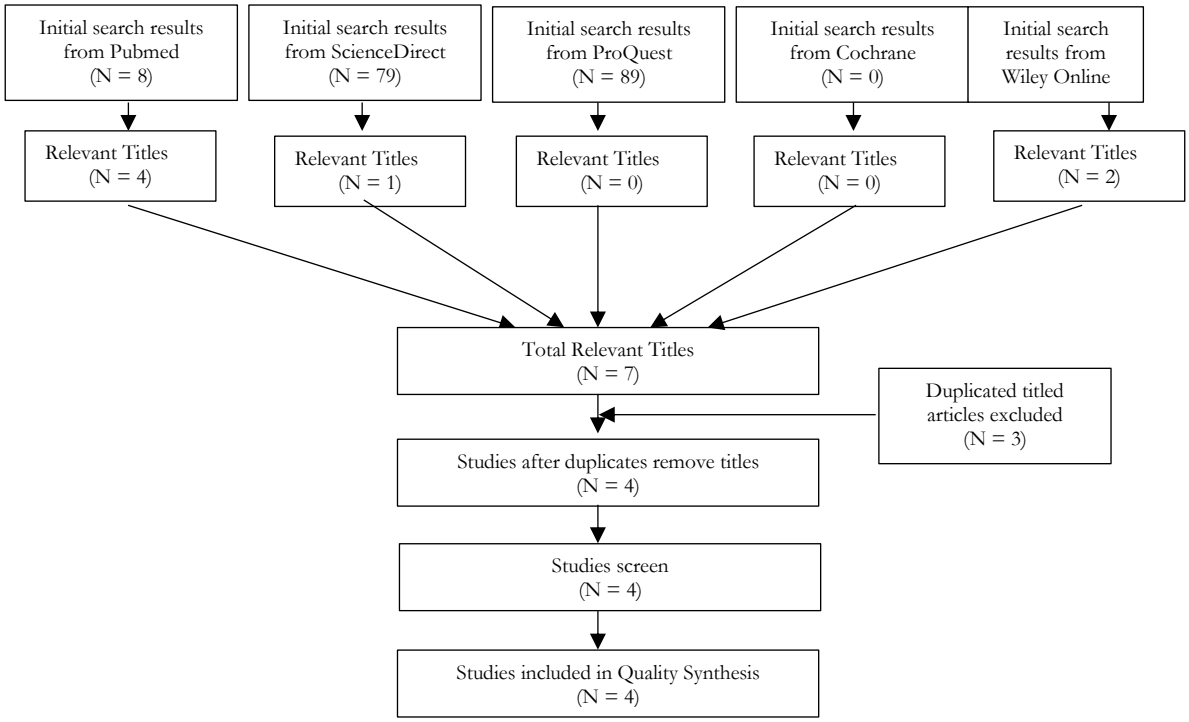

Figure 1: Diagram Flow of the Article's Selection.

Results

The search on the database was resulted in 184 initial articles (8 articles from PubMed, 79 articles from ScienceDirect, 89 articles from ProQuest, 0 articles from Cochrane and 8 articles from Wiley Online Library). Because of the irrelevant titles, 177 articles were excluded, and three articles were removed because of duplicate titles. The title and the abstract of the articles were reviewed, and according to the results, only four fitted the eligibility criteria stated in this systematic review (Figure 1).

All four selected studies were conducted in USA, China and Germany. There were 55 diabetic mice in these studies. Fifty dibetic mice with excisional wound (seven mice with obesity) and fourty diabetic mice with burn wound. In two studies, excision wounds were created with a diameter of 5 mm, 3-4 mm apart on the back of each mouse by excising the skin and the underlying panniculus carnosus. In one other study, excision wound was created with an 8 mm biopsy punch. While burns Was created on the dorsal skin by submerging the dorsal surface of the rats in a 90°C water bath for 20 seconds.

The diabetic model in study Yu et al.,5 was created using procedure with one week adaptive feeding, the rats were fed with a high fat diet (HFD) containing 60% (kcal) fat, 20% (kcal) carbohydrates, and 20% (kcal) protein for two months. The induction of diabetes mellitus was then performed by multiple streptozocin (STZ) injection. STZ (dissolved in citrate buffer, pH 4.5) were given by intraperitoneal injection at a dose of 10 mg/kg body weight (BW) for four consecutive days while in study Siebert et al.,13 diabetic model was created by starved the mice for 16 h and subsequently administered glucose orally (1.5 g/kg body weight) by gastrogavage. The other two studies did not describe the diabetic model procedure in their study sample

Yu et al.,5 found that in immunofluorescence analysis showed that compared with normal skin, diabetic chronic ulcer tissue showed a significant decrease of PPAR-γ distribution. High glucose treatment greatly reduced PPAR-γ expression compared to normal glucose treatment. It was also reported that insulin increased PPAR-γ expression in high glucose-stimulated macrophages.

Siebert et al.,13 found that PPAR-γ agonists induced conditions were paralleled by a significant improvement of wound closure and new tissue formation in obese mice. The inhibitory effect of PPAR-γ activation on CXCL2 release appeared to be a general anti-inflammatory effect in mature adipocytes. Oral administration of PPAR-γ agonists to wounded obese mice significantly changed subcutaneous adipocyte morphology, reduced wound CXCL2 and Cox-2 expression and improved tissue regeneration. Thus, PPAR-γ might provide a target to suppress inflammatory signals from mature adipocytes, which add to the prolonged wound inflammation observed in diabetes-obesity conditions.

Mirza et al.,8 found that expression of PPAR-γ and downstream targets was lower in chronic wound macrophage than in non-stimulated blood-derived macrophage, suggesting that the pro-inflammatory environment of diabetic wounds may downregulate PPAR-γ activity and the diabetic wound environment inhibits macrophage PPAR-γ activity during wound healing. Topical treatment with PPAR-γ agonists accelerated wound closure, as assessed both externally and histologically. The PPAR-γ agonists also tended to increase granulation tissue formation, angiogenesis and collagen deposition, but had no effect on macrophage accumulation or neutrophil accumulation.

Schiefelbein et al.,14 found that PPAR-γ agonists potently induced VEGF mRNA and protein expression from cultured keratinocytes during diabetes-impaired acute skin repair in obese mice so that they can accelerate wound healing in obese diabetic mice. Keratinocytes represent a major source of vascular endothelial growth factor (VEGF) in skin wounds and VEGF expression is induced by cytokines and growth factors in the cells.

Table 1: Summary of Data Description from the Included Studies.

Study	Subject	Outcome
Yu *et al.,* China (2018).[5]	Wistar rats, 6–8 weeks old Diabetic and burn wound n = 40	Increased PPAR-γ expression in high glucose-stimulated macrophages.
Siebert *et al.,* Germany (2016).[13]	Female mice with age of 12 weeks Diabetic, excisional wound and obese mice n = 4	PPAR-γ might provide a target to suppress inflammatory signals from mature adipocytes, which add to the prolonged wound inflammation observed in diabetes-obesity conditions.
Mirza *et al.,* USA (2015).[8]	12–16 week-old male mice Excisional woundn = 8	The PPAR-γ agonists tended to increase granulation tissue formation, angiogenesis and collagen deposition, but had no effect on macrophage accumulation or neutrophil accumulation.
Schiefelbein *et al.,* Germany (2008).[14]	Female mice with 10 weeks of age Diabetic, excisional wound and obese mice n = 3	PPAR-γ agonists potently induced VEGF mRNA and protein expression from cultured keratinocytes during diabetes-impaired acute skin repair in obese mice

Discussion

The source of impaired wound healing in DM is related to several overlapping mechanisms. First, endotheliopathy, which causes micro- and macrovascular changes, can lead to neuropathic changes, which significantly increase the risk of injury and delay wound healing. Then, macroangiopathy lesions which usually occur later than microvascular changes can affect the supply of nutrients to the wound during vascular complications in DM patients which can then slow wound healing. Furthermore, DM microvascular complications, such as diabetic retinopathy, diabetic nephropathy and neuropathy can result in impaired immune response or changes in intracellular pathways.15 Most of the processes responsible for the development of endotheliopathy, including increased activity of the polyol pathway, AGE formation, and the PKC pathway, also simultaneously lead to the development of neuropathy. Other factors such as hyperglycemia, glycemic variability, lipid disorders, smoking and alcohol abuse can also influence the occurrence and severity of neuropathic symptoms. These mechanisms are the main factors in delaying or precluding wound healing in diabetes.16,17,18

In this systematic review, animal models of injury included burns, excision wounds and full-thickness wounds. The experimental animals were also in a state of diabetes mellitus both with and without obesity. This condition is expected to be the cause of delayed wound healing.

In diabetic wound healing, PPAR-γ has been proposed as a central regulator in the macrophage phenotype switch.19 One possible mechanism is the ability of PPARγ to resolve inflammation, where we know that one of the main roles of PPARγ is to mediate anti-inflammatory responses. In addition, PPAR-γ can also activate pro-completion gene expression and/or through the binding of other transcription modulators by binding to specific DNA sequences.13 Loss of PPAR-γ macrophage activity is sufficient to prolong inflammation, reduce growth factor and granulation tissue and induce a slight delay in wound closure, even in the absence of diabetes. This disorder will get worse in diabetic conditions. Under conditions of hyperglycemia, PPAR-γ expression is reduced compared to normal glucose conditions. PPAR-γ expression was also found to be lower in chronic wounds in macrophages. This suggests that the inflammatory environment of chronic diabetic wounds inhibits macrophage PPAR-γ activity during wound healing and then can reduce PPAR-γ activity. In wounds with normal glucose conditions, there is an increase in PPAR-gamma activity, causing mitochondrial biogenesis which is related to healing. However, this pathway is impaired in diabetic mellitus wound macrophages.8

PPAR-γ agonists promote wound healing by altering the production of cytokines and macrophage growth factors. Topical treatment with PPAR-γ agonists can accelerate wound closure, (externally and histologically), increase granulation tissue formation, angiogenesis and collagen deposition.8 In addition, insulin treatment increased PPAR-γ expression in lipopolysaccharide-stimulated macrophages under high glucose conditions. PPAR-γ is considered insulin sensitive; Meanwhile, insulin can synergize with PPAR-γ ligands and activate their receptors which can then increase PPAR-γ expression.5

Conclusion

Based on four studies that have been analysed, can be concluded that in diabetes mellitus with incision wound and burns in both obese and non-obese conditions showed a significant decrease of PPAR-γ distribution. PPAR-γ agonists and highly glucose-stimulated macrophages can accelerate wound healing by tending to enhance granulation

tissue formation, angiogenesis and collagen deposition; suppress inflammatory signals from mature adipocytes; and induce VEGF mRNA and protein expression from cultured keratinocytes.

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