

Review Article

Healing the chronic wounds in diabetes using old drugs

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Received: 26 August 2020

Revised: 01 September 2020

Accepted: 04 September 2020

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ABSTRACT

People with uncontrolled diabetes may develop poor circulation. As circulation slows down, blood moves more slowly, which makes it more difficult for the body to deliver nutrients to wounds. As a result, the injuries heal slowly, or may not heal at all. Due to the effects of diabetes on the nerves and blood vessels, diabetic patients might also experience other complications. These include heart disease, kidney disease, and eye problems. Hence, the need for therapeutic drugs is a must. In this review we analyze some drugs that have been used in diabetes wound healing including antiglycemic agents like dipeptidylpeptidase-4 (DPP4) inhibitors and metformin, statins and phenytoin. These drugs showed satisfying results giving the diabetes patients a glimmer of hope regarding their wound healing.

Keywords: Chronic wounds, Wound closure, Diabetic foot ulcer, Dipeptidylpeptidase-4 inhibitor, Metformin, Phenytoin, Statins, Drug repurposing

INTRODUCTION

Diabetes mellitus, also called diabetes, is a term for several conditions involving how your body turns food into energy. Diabetes is a chronic disease associated with abnormally high levels of the sugar glucose in the blood.

Insulin is a hormone that allows the body to efficiently use glucose as fuel. After carbohydrates are broken down into sugars in the stomach, glucose enters the blood circulation and stimulates the pancreas to release insulin in the proper amount. Insulin allows body cells to uptake glucose as energy. Diabetes is due to one of two mechanisms viz. inadequate production of insulin (which

is made by the pancreas and lowers blood glucose), or inadequate sensitivity of cells to the action of insulin.¹

TYPE 1 DIABETES MELLITUS

Type 1 diabetes mellitus is much rarer than type 2. Approximately 15% of people with diabetes mellitus have type 1. Type 1 diabetes mellitus usually appears at a young age, but can occur at any time. People with type 1 diabetes mellitus have to have daily insulin injections to manage their condition.²

TYPE 2 DIABETES MELLITUS

Type 2 diabetes mellitus affects around 85-90% of people with diabetes, and is usually diagnosed at a later age than type 1 diabetes mellitus. Type 2 diabetes is often, but not always, associated with excess body weight and lack of exercise. Type 2 diabetes mellitus affects people of different ethnicities to a different degree.³

High levels of blood glucose caused by diabetes can, over time, affect the nerves (neuropathy) and lead to poor blood circulation, making it hard for blood – needed for skin repair – to reach areas of the body affected by sores or wounds. Wound healing is usually slowed when the patient is diabetic. An important point to remember about a diabetic patient wound is that it heals slowly and can worsen rapidly, so requires close monitoring. This can cause them to remain open and unhealed for months, increasing the risk of: Fungal infections, Bacterial infections, and Gangrene. Diabetes and high blood sugar can cause nerve damage called diabetic neuropathy. Neuropathy causes tingling and numbness, which makes it harder to feel if you're injured. Significantly, about 15–25% of diabetic patients have a lifetime risk of developing diabetic foot ulcers.⁴

WOUND REPAIR IN DIABETES

In diabetic patient, aberrant vascular architectures in diabetic wounds occurred. That is to say, wounds in diabetes mellitus (DM) patients have disrupted angiogenic process, chronicization of the inflammatory conditions, reduction of endothelial progenitor cells, and an imbalance in extracellular matrix regulation. Moreover, neutrophils and macrophages are elevated, hence infiltrate the area of the lesion. As a result, infiltrating cells release both inflammatory cytokines such as interleukin 1 β (IL-1 β) and tumor necrosis factor α (TNF α) to high concentrations in the wounded area for longer time leading to prolonged inflammatory response.⁵

THE AVAILABLE TREATMENTS

The treatment of chronic wounds has a main aim. This aim is to prevent the occurrence of infection and to clean the area from non-viable tissue material. The removal of debrides gives the cells in the healthy tissue beside the

wound the opportunity to migrate and proliferate to be healed.⁶

Dressings

Different kinds of dressings have been manufactured. They all accelerate wound healing by providing the moist environment required for proper healing which ease the production of granulation tissue and epithelialization.⁷

Antidiabetic drugs

Many Drugs have been using in the therapy of diabetes such as insulin, metformin, some sulfonylureas, thiazolidinedione, and DPP-4 inhibitors. According to many studies, these drugs have shown not only anti-inflammatory properties, but also a broad range of different effects that may facilitate the treatment of chronic wounds.⁸

Growth factor

Using exogenous growth factors in the treatment of chronic wounds has many issues. They can in fact stimulate the formation of granulation tissue, modulate the inflammatory response, promote angiogenesis, and stimulate extracellular matrix (ECM) formation, remodeling, and also re-epithelization. Some of them including platelet-derived growth factor (PDGF), vascular endothelial growth factor (VEGF), epidermal growth factor (EGF), fibroblast growth factor (FGF), and transforming growth factor beta 1 (TGF β 1) all of them have also been tested in clinical trials, more specifically for the treatment of diabetic foot ulcers.⁹ Moreover, results of these studies revealed a high risk of bias and safety issues were not well addressed. It has been shown that degradable biomaterials carrying the growth factors or, alternatively, a gene-mediated therapeutic delivery to yield high concentration of the growth factor(s) selectively in the wounded area.¹⁰

Stem cells

Applying stem cell therapy in the treatment of impaired wound healing in DM patients appears outstanding. In particular, transplanted stem cells in the wound lesion release each of cytokines and growth factors able to promote cell recruitment, angiogenesis and ECM remodeling and exert an immunomodulatory action. Stem cell shows efficacy in several clinical trials carried out in animal models. Stem cells are considered as a promising treatment that gives the opportunity to translate pluripotent stem cells (iPSC) into a new therapeutic tool for wound healing also in humans in the near future.¹¹

REPURPOSING TO DRUGS

Repurposing to drugs means use the same drug but in new different purposes. Different therapeutic approaches are available but with a lot of limitations that do no

guarantee a successful, conclusive, non-recurrent healing. Hence, the need to find new treatment alternatives is a must.¹² In fact, several molecules have shown beneficial effects in promoting wound healing but with different therapeutic indications. It has been shown that the female hormone, estrogen, have many benefits in the treatment of chronic wounds. Accordingly, estrogens accelerate wound healing, by facilitate the formation of capillary-like structures in endothelial cells, stimulate the release of PDGF by macrophages and TGFβ1 by fibroblasts and promote wound contraction, formation of granulation tissue and collagen deposition.¹³

Besides those mentioned above, there are several used drugs that have shown some activities in the wound repair process. However, we will here selectively focus on few classes of drugs (including some antidiabetic medications) whose potential to be effective in the treatment of wound healing finds support in preclinical and clinical observation and is also substantiated by detailed molecular evidence.¹⁴

Statins

Statins, also known as β-Hydroxy β-methylglutaryl-CoA (HMG-CoA) reductase inhibitors, are a class of drugs that lower cholesterol in blood. They are the most common cholesterol-lowering drugs. Statins are effective in lowering low-density lipoprotein (LDL) cholesterol and so are widely used for in people at high risk of cardiovascular disease, as well as in secondary prevention for those who have developed cardiovascular disease. Inhibition of cholesterol production by statins implies also inhibition of the synthesis of the wound-healing inhibitors farnesyl pyrophosphate (FPP) and cortisol.¹⁵ It also exerts anti-inflammatory and antibacterial activity in a variety of wound conditions including impaired diabetic healing in animal models. Interestingly, different statins including mevastatin, atorvastatin and pravastatin share the same ameliorating effect on wound healing. In fact, it has been shown that application of a lovastatin-loaded tissue engineering scaffold, which offers the advantage of mimicking ECM with integrated drug delivery capacity, was able to increase wound healing rate by enhancing endothelial NO synthase (eNOS) and skin blood flow within and around the wounded skin.¹⁶

Phenytoin

Phenytoin is used to control certain type of seizures, and to treat and prevent seizures that may begin during or after surgery to the brain or nervous system. Phenytoin is in a class of medications called anticonvulsants. It works by decreasing abnormal electrical activity in the brain. A crystalline anticonvulsant compound C₁₅H₁₂N₂O₂ used in the form of its sodium salt in the treatment of epilepsy. Phenytoin stimulates the formation of granulation tissue, reduces collagenase activity, and promotes collagen production and deposition thus causing enhanced strength of the wounded area. Phenytoin has also shown the ability

to increase VEGF and FGF at the wound site with a consequent stimulation of new vessel formation. Accordingly, biopsies of wound tissue treated with phenytoin exhibit signs of increased collagenization, neovascularization, and reduced infiltration of circulating inflammatory cells. It has been shown that there are a lot of positive effects of topical phenytoin in wound healing in a large range of concentrations used, without significant systemic side effects.¹⁷

Metformin

It is the first-line medication for the treatment of type 2 diabetes, particularly in people who are overweight. In other words, it is a drug used in the form of its hydrochloride C₄H₁₁N₅HCl especially to treat type 2 diabetes. It is also used in the treatment of polycystic ovary syndrome and it is taken by mouth. Metformin has been shown to also modulate specific pathways of inflammation such as nuclear factor kappa B (NF-κB) and mitogen-activated protein kinase (MAPK)/c-Jun NH2-terminal kinase (JNK).¹⁸ All this demonstrated that immunomodulatory and anti-inflammatory properties may support the potential of metformin for the treatment of wound healing. Notably, metformin was effective in accelerating wound healing by improving epidermis, hair follicles, and collagen deposition also when applied topically in young rats undergoing an excision wound and confirmed its efficacy also in patients carrying non-healing lower limb traumatic wounds or ulcer. Interestingly, systemic administration of metformin and photobio-modulation showed a synergistic impact on skin repair by increasing fibroblasts, with improved formation of granulation tissue, by inducing new blood vessels and by modulating the inflammation and proliferation steps of wound healing.^{17,18}

DISCUSSION

Many drugs have shown outstanding results when were used in the treatment of wounds in diabetic patients. For example, statins may play a role in the prevention and treatment of diabetic foot ulcers, and possibly other non-healing. Moreover, Statins have been shown to reduce cardiovascular disease in patients with diabetes, which is thought to be due to their pleiotropic effects on the vasculature. The pathogenesis of diabetic foot ulcers is complex, involving mechanical, vascular, inflammatory, oxidative, endothelial and nutritive factors. The micro- and macro-vascular complications associated with DM have led many scientists to research the effects of statins in the treatment of impaired diabetic wound healing.¹⁸

On the other hand, Phenytoin is cheap, easy to use, and readily available. Clinical studies using topical phenytoin therapy suggest that it may be useful for the treatment of both acute and chronic wounds of various etiologies. Although these results are encouraging, the efficacy of topical phenytoin therapy has yet to be confirmed by double-blind placebo-controlled studies. Large, controlled

studies are needed to confirm the benefits of topical phenytoin in wounds of varied etiologies, as well as to determine the optimal dose and method of delivery.

In addition, Metformin is widely viewed as the best initial pharmacological option to lower glucose concentrations in patients with type 2 DM. However, the drug is contraindicated in many individuals with impaired kidney function because of concerns of lactic acidosis.

Currently, much attention and faith are being placed on the development of expensive topical molecular factors for wound healing. The efficacy of such agents still needs to be proven in clinical trials and the cost factor should be kept in mind.¹⁸

CONCLUSION

Drug repurposing is a concept that has grown in recent years for two main reasons. Firstly, exploit the knowledge we have on drugs. Secondly, try to use them to different purposes. Recent studies on several drugs have shown the ability of some drugs to improve skin reparative processes. In this study, we have here briefly focused our research on a few molecules (or classes of drugs) that appear particularly promising in the therapy of impaired wound healing.

Funding: No funding sources

Conflict of interest: None declared

Ethical approval: Not required

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Cite this article as: Hassan KM, Hamdi AA, Alhamad SA, Alanzi RQ, Aleid YA, Aldarwish AS, et al. Healing the chronic wounds in diabetes using old drugs. *Int J Community Med Public Health* 2020;7:4185-8.