

Side Effects of Frequently Used Oral Antidiabetics and Antihypertensive Drugs on Wound Healing *in vitro*

Stuermer EK*

Institute for Health Services Research in Dermatology and Nursing (IVDP), University Medical Center Hamburg-Eppendorf, Germany

Introduction

Worldwide, the number of people with wound healing disorders, which often turn into chronic wounds, is increasing. The underlying diseases are diabetes mellitus, obesity or hypertension, but also vascular diseases [1]. While a negative effect on wound healing is postulated for drugs such as cortison, cytostatics or NSAIDs, the (secondary) effects of antihypertensive drugs and antidiabetics on wound healing are largely unknown. These drugs are taken regularly by the affected patients, so interference with wound healing - should it exist - would be clinically relevant.

Methods

Based on the drug report 2016 of a very large German health insurance, the five most prescribed antihypertensive drugs and four antidiabetics were identified. A systematic review was carried out on each of these active ingredients, focusing on wound healing, skin and vascular cells. The results of the research provided the background for the following systematic and comparative *in vitro* analysis of antihypertensive drugs and antidiabetics in serum equivalent doses: Cell metabolism, cell activity and migration potential were analyzed on the basis of human fibroblast and keratinocyte cultures. In order to get closer to the physiology of the wound, further analyses were performed to affect healing in the 3D wound model modified according to Timpon [2]. Epidermal thickness (μm) and fibroblast density ($\text{n}/\mu\text{m}$) at the wound margin and wound bed were determined histologically and immunohistochemically. Cell proliferation, cell migration and apoptosis were investigated after twelve days of application of the antihypertensive drugs and antidiabetics.

Results

Systematic literature research revealed that only a few scientific studies exist on the effect of antihypertensive drug and antidiabetics on wound healing, and additionally their findings are partially contradictory. According to *in vitro* studies, ACE inhibitors have a negative effect on cell growth and cell migration [3,4]. This was confirmed in our analyses in the 3D wound model. ACE inhibitors have an inhibitory effect on collagen biosynthesis [5] as well, which can lead to a delay in wound healing. Studies on calcium channel blockers show that they improve the tensile strength, but not

the epithelialization of the skin [6-8], accordingly their effect on wound healing cannot be evaluated exactly. β -blockers have a systemic and locally accelerating effect on wound healing [9,10]. In a clinical study, they activate keratinocytes, which may have positive effects on wound closure, but negative effects on existing psoriasis [9,11]. In our own *in vitro* studies, positive effects have been confirmed.

Of the antidiabetic agents, the biguanide metformin causes a qualitative and quantitative deterioration of wound healing *in vivo* and *in vitro* [8,12]. The negative influence on cell metabolism is particularly noteworthy here. In contrast, the relatively new dipeptidyl peptidase inhibitors have a positive effect on wounds and their blood circulation [13,14]. Sulfonylureas do not appear to have a positive or negative effect on wound healing [15]. Own results in the *in vitro* 3D wound model support the above-mentioned effects as far as possible, whereby keratinocytes react much more sensitively to antidiabetic agents than fibroblasts. The negative influence of hydrochlorothiazide and metformin in monocultures as well as in the 3D wound model has to be emphasized.

Discussion

Most patients with chronic wounds also suffer from hypertension and/or diabetes. It is therefore even more astonishing that the medical and scientific focus in wound healing does not address possible "side effects" of the necessary drug therapy of these underlying diseases. Almost all antidiabetics and antihypertensive drugs have a measurable *in vitro* effect on wound healing. This varies significantly between the substance classes: Differently than with systemic application, the application of metformin - despite serum-equivalent concentration in the *in vitro* analyses - led to negative effects on the cells of the wound healing process. Glinides also tended to have a negative influence on the metabolism of skin cells. In contrast, dipeptidyl peptidase inhibitors [13,14] and sulfonylureas had a (low) positive effect. Interestingly, antidiabetics in direct in-vitro application led to an increased rate of apoptosis of the cells of the wound bed (fibroblasts).

In the case of antihypertensive drugs, β -blockers improve wound healing in both in-vivo and in-vitro tests. The results after local Timolol application are particularly to be emphasized [7]. Calcium channel blockers showed a positive effect on the wound healing. The opposite seems to be the case for ACE inhibitors and thiazide diuretics (e.g. HCT): Wound healing in ex vivo and *in vitro* 3D skin model is already delayed by HCT in serum equivalent doses. In

addition, a possible connection between thiazide diuretics and skin cancer should not be neglected.

Conclusion

The results shown should be considered due to their possible relevance in patients with chronic wounds who do not respond to adequate (local) wound therapies. In particular, metformin, the first-choice drug for type 2 diabetes with very positive systemic effects, should continue to be investigated translationally and clinically.

References

1. Sen CK, Gordillo GM, Roy S, et al. (2009) Human skin wounds: A major and snowballing threat to public health and the economy. Wound Repair Regen 17(6): 763-771.
2. Timpson P, McGhee EJ, Erami Z, et al. (2011) Organotypic collagen I assay: A malleable platform to assess cell behaviour in a 3-dimensional context. J Vis Exp 13: e3089.
3. Baroni A, Buommino E, Ruocco E, et al. (2011) Captopril modulates acetylcholinesterase in human keratinocytes. Arch Dermatol Res 303(7): 491-497.
4. Karna E, Szoka L, Palka JA (2010) Captopril-dependent inhibition of collagen biosynthesis in cultured fibroblasts. Pharmazie 65(8): 614-617.
5. Zeeli T, Langberg M, Rotem C, et al. (2011) Vitamin D inhibits captopril-induced cell detachment and apoptosis in keratinocytes. Br J Dermatol 164(1): 62-67.
6. Bodiga VL, Eda SR, Chavali S et al. (2014) *In vitro* biological evaluation of glyburide as potential inhibitor of collagenases. Int J Biol Macromol 70: 187-192.
7. Braun LR, Lamel SA, Richmond NA, et al. (2013) Topical timolol for recalcitrant wounds. JAMA Dermatol 149(12): 1400-1402.
8. Ochoa-Gonzalez F, Cervantes-Villagrana AR, Fernandez-Ruiz JC, et al. (2016) Metformin induces cell cycle arrest, reduced proliferation, wound healing impairment *in vivo* and is associated to clinical outcomes in diabetic foot ulcer patients. PLoS One 11(3): e0150900.
9. Kim GK, Del Rosso JQ (2010) Drug-provoked psoriasis: Is it drug induced or drug aggravated? Understanding pathophysiology and clinical relevance. J Clin Aesthet Dermatol 3(1): 32-38.
10. Uchino Y, Matsumoto J, Watanabe T, et al. (2015) Nifedipine prevents sodium caprate-induced barrier dysfunction in human epidermal keratinocyte cultures. Biol Pharm Bull 38(6): 926-929.

11. Armstrong AW (2014) Psoriasis provoked or exacerbated by medications: Identifying culprit drugs. JAMA Dermatol 150(9): 963.
12. Li W, Ma W, Zhong H et al. (2014) Metformin inhibits proliferation of human keratinocytes through a mechanism associated with activation of the MAPK signaling pathway. Exp Ther Med 7(2): 389-392.
13. Saboo A, Rathnayake A, Vangaveti VN, et al. (2016) Wound healing effects of dipeptidyl peptidase-4 inhibitors: An emerging concept in management of diabetic foot ulcer-A review. Diabetes Metab Syndr 10(2): 113-119.
14. Schürmann C, Linke A, Engelmann-Pilger K, et al. (2012) The dipeptidyl peptidase-4 inhibitor linagliptin attenuates inflammation and accelerates epithelialization in wounds of diabetic ob/ob mice. J Pharmacol Exp Ther 342(1): 71-80.
15. Sato N, Matsumoto H, Akimoto Y, et al. (2005) The effect of IL-1alpha and nifedipine on cell proliferation and DNA synthesis in cultured human gingival fibroblasts. J Oral Sci 47(2): 105-110.

***Corresponding author:** Prof. Dr. med. Ewa K. Stuermer, Institute for Health Services Research in Dermatology and Nursing (IVDP), University Medical Center Hamburg-Eppendorf, Martinistr. 52, 20246 Hamburg, Germany; Email: e.stuermer@uke.de

Received date: November 19, 2019; **Accepted date:** December 10, 2019; **Published date:** December 17, 2019

Citation: Stuermer EK (2019) Side Effects of Frequently Used Oral Antidiabetics and Antihypertensive Drugs on Wound Healing *in vitro*. Ann Biomed Res 2(2): 118.

Copyright: Stuermer EK (2019) Side Effects of Frequently Used Oral Antidiabetics and Antihypertensive Drugs on Wound Healing *in vitro*. Ann Biomed Res 2(2): 118.