WOULGAN® GEL
Bioactive Beta-Glucan

# Can the activation of the body's own key cells in wound healing, WOUND MACROPHAGES, make a positive contribution in the treatment of chronic wounds?

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A moist wound healing environment has for long been recognized as the principle for optimal healing in the treatment of wounds. Hence there are many products in the market that cater to this principle, both in terms of pure hydrogels and dressings containing moisturizing agents. Despite a huge range of products to choose from in the field of wound treatment, there is still a need for new and better products to treat complex, chronic wounds that do not heal or heal very slowly. This has resulted in the research and development of active products that not only safeguard the principles of moist wound healing, but which can also directly expedite the actual wound healing process. Products that have incorporated recombinant growth factors, enzymes or artificial skin tissue are designed to contribute to, and accelerate, the wound healing process. Common to the majority of the active and advanced products are very high price tags. These demand specialized usage, and thus remain essentially niche products.

A new active product is on the way to the market that expedites wound healing, both as a classic moisture carrier and through a macrophage activating substance. The product will have a cost effective price and therefore have a potential for wider usage than is the case for other active products. Woulgan® Biogel safeguards the important principles for an optimal moist wound healing environment, promotes natural autolyse, and will remain as a protective gel on the surface of the wound. The gel contains the medicinal substance soluble beta-glucan (SBG®- Soluble Beta-Glucan), that beyond the gel properties also holds macrophage activating properties that contribute to speeding up wound healing. Since the positive properties of hydrogels are well known, this article will focus on the macrophage activating properties of the beta-glucan.

## Beta-glucan is recognized by our innate immune system

Beta-glucans, or compounds that are primarily beta- glucans, have been used for medical purposes in the far East for more than 2000 years. These compounds have been recognized in Western medicine in the last century as a result of their ability to modulate the innate immune system, particularly through the action on white blood cells (monocytes and macrophages) *(2-4)*. Beta-glucan has a so-called pathogen associated molecular structure (referred to as the PAMPs in immunological context). Beta-glucan can be found in different micro-organisms like certain types of bacteria, but mainly in yeast and fungi. The innate immune system has developed recognition mechanisms (cell receptors) for these structural motifs as a signal for microbiological attack. Several different receptors on white blood cells are able to bind to the beta- glucan *(5-6)*. Binding to receptors signals that an attack is in progress, and the white blood cells mount suitable counterattack mechanisms. In this context this means in the first place increased ability to kill microbial causing agents in the wound, but also faster closing of the wound both in terms of new formation of blood vessels, increased re-epitelasition and not least increased wound contraction.

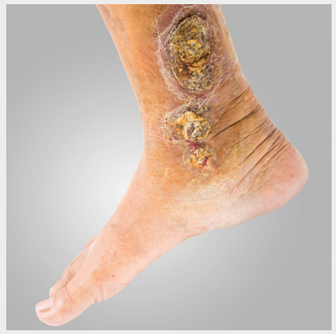
Stimulation of macrophages with SBG in the wound will cause more phagocytic cells to be attracted to the wound, and thereby helps with the actual clean-up as these cells are key in combating microbial organisms, as well as in removing the necrotic tissue. SBG stimulation of wound macrophages also results in the release of several different signal molecules that modulate the acute inflammation *(7)*. Macrophages contribute in all the different phases of wound healing by producing the signal molecules and growth factors that both contribute directly to wound healing, but also coordinate the various stages in the healing process *(8-9)*. It is acknowledged that chronic wounds seem to stagnate in the early stages of wound healing (inflammation phase) for various reasons. Characteristic of these wounds is not lack of cells or reactions necessary for healing, but the imbalance between these. Products that can contribute to driving the chronic wound on to the next stage in the normal healing process will thus be desirable *(Figure 1)*.

Fibroblast cells from chronic wounds, and in diabetics in general, are proven to have a premature aging process (so called senescence cells). Such cells respond poorly to signal molecules and have far lower cell-proliferation rate than normal cells *(10-11)*. In addition, it is known that macrophages from diabetics are dysfunctional in terms of the production of neurotransmitters and growth factors *(12-13)*, which are believed to be contributing factors to the impaired wound repair in this patient group. It is known that macrophages from diabetic animals and humans are receptive to stimulation with beta-glucans and can thus "restore" this function *(14)*. The main role of the macrophages in wound healing makes targeted treatment for this type of cell especially attractive for chronic and complex wounds.

# Practical use of beta-glucans in wound treatment

A recently published article *(15)* where soluble beta-glucan (SBG®) was used in the treatment of diabetic foot ulcers showed complete wound healing in about 45% of the group treated with SBG during 8 weeks of treatment, compared to just under 20% for the control group *(Figure 2)*. The differences in treatment efficacy were statistically significant at this early time point. In comparison, the normal treatment period needed for demonstrating differences in complete wound healing between treatment groups is typically 12 weeks *(16-19)* between different treatments. One assumes that the positive effect observed for the glucan group is due to its effect on the macrophages. In addition, it appears that beta-glucans are able to induce collagen production by fibroblasts in vitro *(20)*, which suggests that SBG has the potential to be working through the different cell types and processes of the wound bed.

These promising results from the clinical study were the background for the further development of this gel product for use in the treatment of chronic and difficult wounds. The action of the beta-glucan was studied closer on wounds in diabetic mice, an acknowledged model for chronic wounds. The wound reduction, contraction, the formation of new blood vessels and cell division/proliferation were studied *(Figure 3)*. It was demonstrated that the SBG component in the gel was central to all parameters measured and had a positive effect on the closure of the wound. Both increased cell proliferation and angiogenesis can be explained by the activities of macrophages stimulated by SBG. It is also known that wounds heal best in an acidic environment. The product is slightly acidic with a pH around 6 to further facilitate healing. A low pH will also be beneficial in reducing increased protease activity that breaks down new and fragile tissue, a well-known factor in chronic wounds *(21)*.



Practical wound treatment has typically been characterized by handcraft workmanship where the individual health professional's own assessment of product selection and their experience has formed the basis for a treatment regime. In recent years, there has been an increased focus on evidence-based wound management, where blinded, randomized, controlled trials are the "gold standard". Not all products on the market may refer to such studies, but through experience they have become acknowledged as effective. As the level of detail in the knowledge of basal wound healing and chronic wound issues increases, the new products that leverage this new knowledge and affecting key factors identified in wound healing, could set new standards in practical wound care.

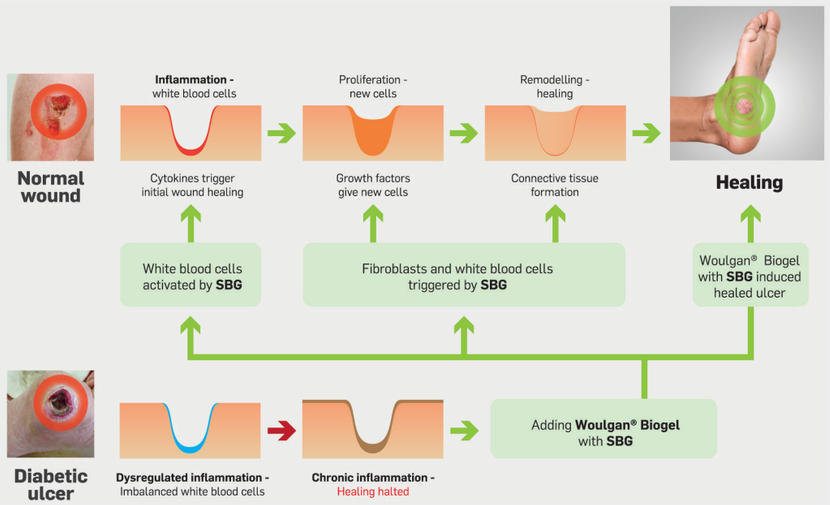



***Figure 1:*** *Beta-glucans have a documented effect on multiple cell types, especially macrophages that help during all phases of the wound healing process. Thus, treatment with SBG has a beneficial effect through the whole course from the open wound to complete healing.*

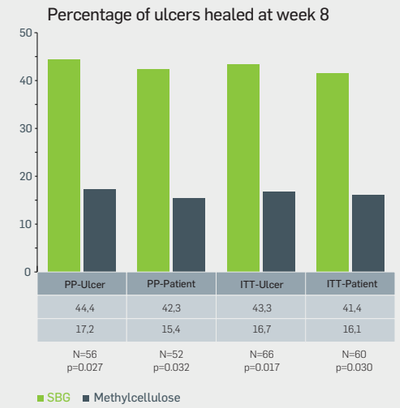
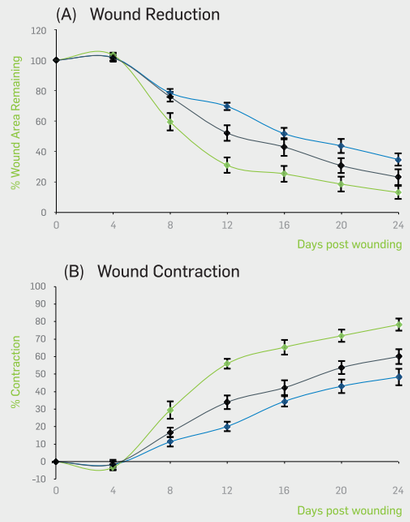



***Figure 2*** *(above)****:*** *In a phase II clinical trial, diabetic foot ulcers were treated with Soluble Beta-Glucan (SBG) and compared with another gel preparation (Methylcellulose). At week 8, there were already statistically significant differences in complete wound healing in favour of the SBG treatment. The figure shows the graphical representation of the results from the 8 week time (retrieved from 15).*

***Figure 3*** *(right)****:*** *A diabetic mouse model was used to study the beta-glucan action in wound healing in detail. The mouse model used is a recognized model for studying chronic wounds. Beta-glucan has a positive effect on the reduction of the wound size (A) and the main mechanism behind this effect is contraction of the wound (B). Beta-glucan also has a positive effect on the proliferation of the cells and the formation of new blood vessels (C and D, respectively). These parameters were studied in different regions of the wound: the outer edges of the wound (marginal zone) responded less on treatment compared to the centre of the wound (centre) and the intermediate areas. In this area the beta-glucan induced significantly increased proliferation of cells and increased angiogenesis. The SBG gel product was compared to the corresponding gel composition without SBG to allow the study of the specific impact of the beta-glucan on the various measured parameters. Water was used as a negative control.*

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