Inflammation and chronic wounds – better than its reputation?

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The knowledge of factors affecting wound healing has increased significantly in recent years, ranging from holistic factors such as nutrition, mobility, circulation and weight, to molecular factors in the wound. It is well recognized that the majority of chronic wounds stalls during the inflammatory phase [1]. This is mainly due to either a poor inflammatory response as in diabetic patients [2], or an abnormally long-term inflammatory response that ends up being destructive to the tissues [3]. The result of this has been that inflammation often is perceived as the problem in wound healing.

During normal wound healing, the inflammatory phase is characterized by a large number of pro-inflammatory cells entering the wound. These secrete pro-inflammatory signal molecules (cytokines) and other molecules that help fight any incoming pathogenic microbes. They also start phagocytosis of necrotic tissue, debris and microbes. The majority of these cells are the neutrophilic cells that are specialists in phagocytosis and secrete antimicrobial compounds, including proteases and reactive oxygen compounds (ROS). These are also harmful to surrounding tissues and molecules and cause problems when the wounds stagnate in the inflammatory phase. These factors have had an increased focus in chronic wound treatment the recent years and have contributed to the bad reputation of inflammation as a whole in chronic wounds.

Neutrophil cells are short lived and during the inflammation phase, dead cell residues mainly consisting of this cell type builds up in the tissue and needs to be removed. This is taking care of by another cell type, namely the macrophages. Macrophages are a key player in wound healing and are responsible for coordinating the overall healing process. The macrophages are the cell type responsible for terminating the inflammatory phase [4]. Also macrophages have phagocytic properties and they cleanse the wound of dead neutrophil cells and other debris. Phagocytosis of neutrophilic cells is a major trigger for macrophages to resolve the inflammatory phase and causes macrophages to go from a pro-inflammatory type (M1) to an anti-inflammatory type (M2) [4]. During this process anti-inflammatory signal molecule are secreted that signals to the other cells in the wound that the inflammation is over and it is time to start the next step in the healing process. The inflammatory phase is followed by the proliferation phase characterized by cell division (due to secreted growth factors from M2 macrophages), granular tissue promotion and angiogenesis, all coordinated by M2 macrophages.

It is established that macrophages in elderly patients and diabetics do not function optimally, they age prematurely (so-called senescence) – often before they complete their tasks. In addition, they are less responsive to the environment and respond poorly to surrounding signal molecules [3]. This contributes to the fact that wounds in these patient groups are at greater risk of stalling and develop into a chronic progression. Macrophages play a key role in coordinating the healing process, and when they function properly, they have the potential to correct the majority of the molecular imbalances in stalled and chronic wounds. This makes them attractive targets for wound treatment [5].

The good news is that the dysfunctional macrophages of, for example, diabetics and elderly patients are susceptible to activation with beta-glucan, causing them to gain some of their original capacity and function [6]. By activating macrophages in stagnated wounds with beta-glucan, you can restart the healing process, including the inflammation phase. As the macrophages after glucan activation are more capable of finish their jobs and resolve the inflammation to progress to the proliferation phase, the potential outcome for these wounds are significantly improved (Figure 1).

The potential for using beta-glucan in wound treatment is described in a randomized, blinded clinical study [7] on diabetic foot ulcers. The study concluded that beta-glucan was superior to placebo - a comparative product in the treatment and healing of diabetic foot ulcers already at week 8, the results were statistically significant at this time. A beta-glucan containing commercial product* is also described to be effective in treating various types of stalled wounds where standard treatment did not give the desired results [8]. Here the product was tested in 26 patients with wounds that were not expected to heal, ranging from at least 4 weeks to 8 years old. In this study 10 of the wounds healed, 7 within the evaluation period of 12 weeks, and 3 shortly after the evaluation period was over. In addition, 5 of the wounds showed more than 50% reduction in size, 5 showed moderate healing and 6 wounds did not respond to treatment. Altogether, this represented a 77% response rate on treatment, among the 7 wounds that healed within 12 weeks was a 6 year old diabetic foot ulcer.

The product has started to enter the markets in the Nordic countries where it is being evaluated at a large number of clinics. The following case study was performed at a Norwegian wound care clinic where Woulgan has been tested. An 80-year-old man with venous insufficiency and a 14-week-old foot ulcer located on the dorsum was treated with bioactive beta-glucan gel. The wound was caused by trauma. The wound was 3.5 months old before treatment with bioactive beta glucan gel was started. Previous standard treatment included: Prontosan, zinc paste around the wound edges and a foam bandage, along with compression treatment. The standard care did not improve or heal this wound. The exudate levels were low with some oedema present. At the startup with the beta-glucan treatment the wound edges were white. It is somewhat unclear whether this was due to maceration from previous treatment.

*Commercial product is a tradename
The clinic - specializing in wound treatment - considered that this was a wound where the standard treatment had not been effective in the healing. It was therefore decided to choose a new approach and switch to an active treatment program with bioactive beta-glucan that activates cells (macrophages) in the wound. The purpose of the treatment were to restore the balance of a stalled wound by restarting the healing process, including the inflammation phase. The treatment was started on 17th of September 2015. The wound was then approximately 1 cm² (Figure 2).

The wound was assessed and treated by the wound clinic twice a week. Dressing changes were performed according to local practice and new beta-glucan gel was applied in a thin layer. This is enough for the active gel to come into contact with the cells in the wound. Too much gel can cause maceration of surrounding tissues. In this case, maceration was not reported due to gel treatment. As a secondary dressing, a standard foam bandage was used. The same compression regime used during standard care was continued. The patient did not use painkillers or antibiotics throughout the course of treatment and the wound showed good progression during treatment (Figure 3). After 4 weeks of treatment - 8 dressing changes- the wound was completely healed on 20th October 2015 (Figure 4).

The patient experienced no discomfort when using the product. The healthcare professionals who followed up the treatment found that the product was easy and safe in use.

There is continued progress made in the knowledge of and possible treatment options for chronic and stalled wounds. Several advanced treatment options have entered the market in recent years, at the same time there are several reports of wrong treatment in the form of unsuitable bandages used(e high absorbent bandages on dry wounds), poor compression techniques and the like. Thus, active treatment options that are effective, but at the same time easy to use where no specialist procedures or training are required, help wound care nurses to provide proper treatment to their patients. Active and advanced treatment options can be as simple as a gel in a tube.

*Bioactive beta-glucan gel is marketed as Woulgan Gel in Europe

References: