ENCOLL
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Helicoll
White paper for use in Diabetic Foot Ulcers (DFU)

Introduction:

Diabetes affects 30 million children and adults in the US, equivalent to 1 in 11 of the population, and costs the economy $322 billion annually.[1,2]
The overall perception of the delayed diabetic wound healing is neuropathy resulting in poor arterial blood supply and venous circulation.
However, high levels of blood glucose not only affect the nerves but also impedes the natural maturation of the healing/granulation tissue. This is a biochemical phenomenon called glycosylation of structural proteins.

We need to consider all the causes of Diabetic Ulcers at this point as shown below:

Understanding of the causes for Diabetic Foot Ulcers

Commonly recognized concepts of DFU

1. Nerve Damage
Damage to the nerve by increased level of glucose in blood may result in loss of sensation and the inability to feel any pain or pressure.

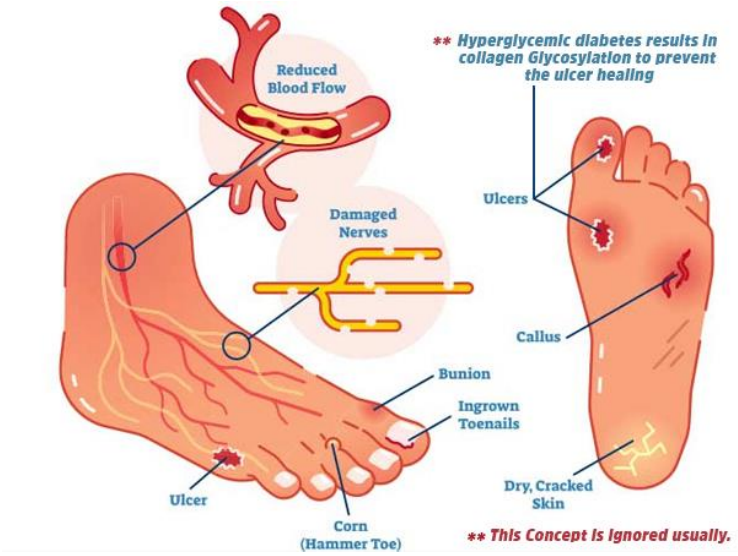
2. Poor Circulation
High blood glucose levels thicken the arteries and narrow its blood vessels, restricting the delivery of the blood and oxygen needed to support the body's natural healing abilities.

3. Infection
Suppressed immune system may facilitate pathogen proliferation eventually leading to an infection like non-healing diabetic ulcer.

4. Immune Suppression
Diabetes may suppress the immune system that could impair the body's ability to fight-off an infection.

Unrecognized concept of DFU

5. Glycosylation of wound bed collagen
In hyperglycemic patients, Glycosylation of the newly formed wound bed collagen hinders the normal enzymatic (lysyl oxidase) maturation leading to non-healing. The hyperglycemic glucose may be absorbed by Helicoll for faster healing of the ulcer wound.



Diagrammatic representation of Hyperglycemic Diabetology

Treatment options for DFU:

Normal materials that are used to cover an ulcer:

1. Non-biological synthetic polymeric sheets and sponges
2. Cotton gauze
3. Vaseline

All such materials are able to protect wound as a wound cover and may absorb the secreted fluid (exudate). Upon usage of such non-biological scaffold materials, cells may not feel comfortable when they come in contact. Accordingly, this would un-necessarily delay the wound healing process because the exudation will continue until the cells are comfortable with the surrounding environment.

On the other hand, **Helicoll** skin substitute may provide a better result. However, all biological materials are not the same. Using an advanced biological skin substitute like **Helicoll** will not disturb the cells on the surface of the wound involved in the tissue granulation process.

All biological skin substitutes may NOT be ideal biocompatible matrices:

Two main categories of Biological matrices:

1. **Reconstituted Collagen membranes:** This includes products made from collagen extracted from animal tissues. Only a few such products are highly biocompatible and bioactive. **Helicoll** happens to be one such unique product.
2. **Intact tissue membrane derived products:** These products are made from intact tissue membranes of amnion, pericardium, intestinal wall, urinary bladder etc. These membranes are contaminated with approximately 15% elastin, type-III collagen, lipids and other proteoglycans which are all highly immunogenic. They have to be cross-linked to minimize their immunogenicity and on the other hand loses the bioactivity and wound healing abilities if the material is not chemically modified or cross-linked, it can effectively be used in tissue regeneration and in the granulation process.

Indications of Helicoll:

1. Diabetic ulcers
2. Pressure ulcers
3. Venous ulcers
4. Draining wounds
5. Partial or full thickness wounds
6. Tunneled, undermined wounds
7. Surgical wounds (i.e., donor sites/grafts, post-Mohs' surgery, post-laser surgery, podiatric, wound dehiscence)
8. Trauma wounds (i.e., abrasions, lacerations, second-degree burns, skin tears)

Description and availability of Helicoll:

Helicoll is an approved FDA product and has been recognized as a high-cost skin substitute by Medicare continuously since 2017.

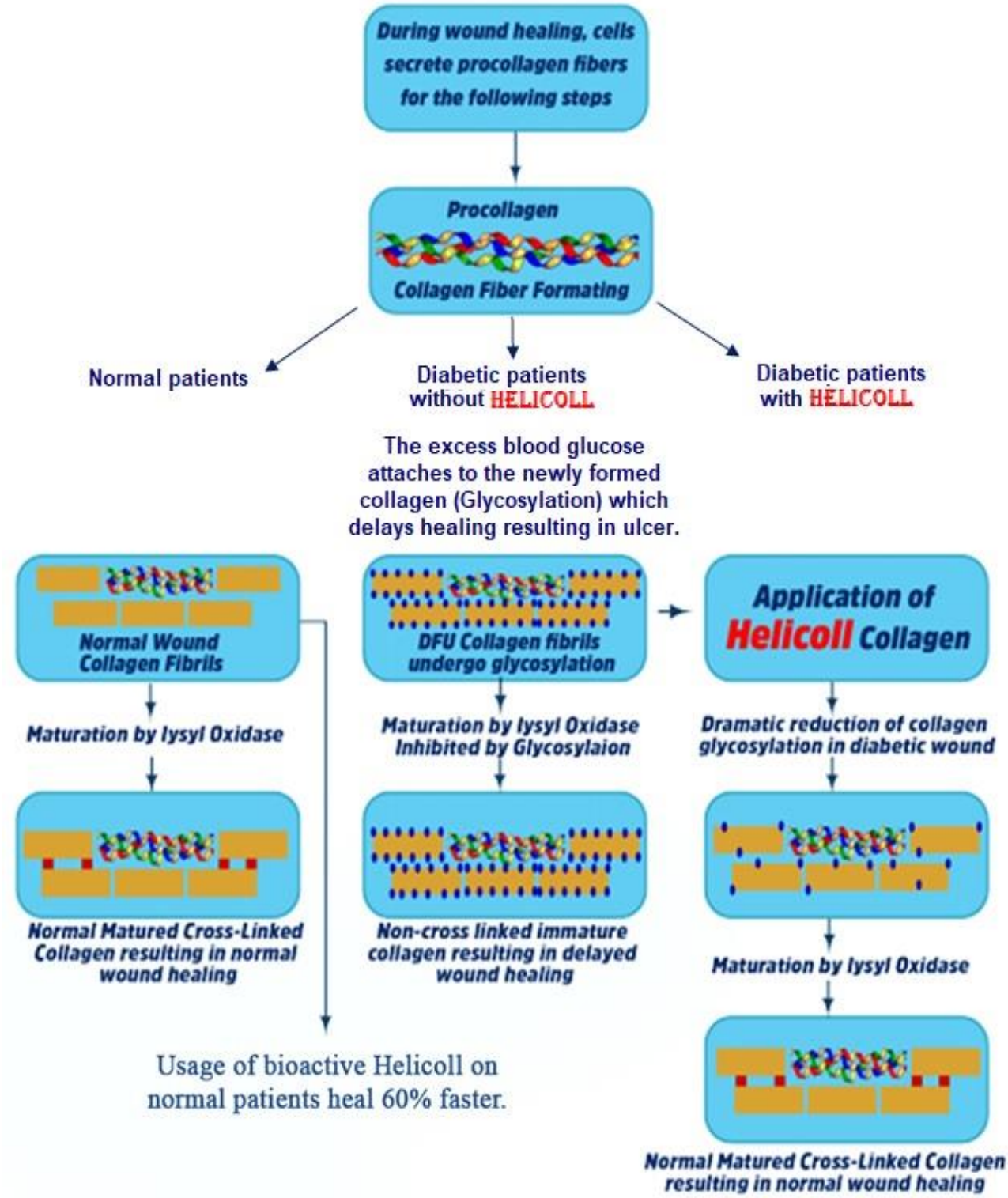
Helicoll may be the ONLY PRODUCT that is relatively highly bio-compatible and bio-active. It is made up of highly purified, non-crosslinked Type-I Collagen (U.S. Patented). Additionally, it is highly bio-active due to its controlled phosphorylation for maximum wound healing benefits.

Helicoll is available in different sizes to accommodate multiple types of wounds. It has the capacity to remain clinically usable for 3 years when stored in room temperature conditions.

Advantage of using Helicoll:

- ✓ **High purity Type-I Collagen:** Helicoll is a patented reconstituted bioactive collagen sheet, free of immunogenic proteins, lipids, and elastin.
- ✓ **Faster Healing:** Collagen phosphorylation attracts cells, regenerates tissue, and stimulates blood capillaries/granulation within 4 to 5 days.
- ✓ **Innovative Technology:** Better than intact tissue-based membranes like amnion, intestinal wall, urinary bladder etc. which contain 15% elastin.
- ✓ **Easy Application:** No washing needed prior to use.
- ✓ **Pain Control:** Effectively reduces pain.
- ✓ **Various Sizes**: Choose from standard or customized dimensions.
- ✓ **Cost**-Effective: Accelerated wound healing and tissue remodeling with minimal
- ✓ **Cost-Effective:** Accelerated wound healing and tissue remodeling with minimal applications.
- ✓ **Long Shelf Life:** Remains clinically usable for 3 years when stored in room temperature conditions.

How Helicoll Nano-technology could heal a Diabetic Ulcer faster than other collagen products.



Etiology of Diabetic Ulcers:

High levels of blood glucose leads to slow healing of DFU

- High levels of blood glucose makes collagen Glycosylated
- Glycosylation is the covalent addition of the excess blood glucose to collagen

Impact of Glycosylation:

- Glycosylation prevents the normal collagen maturation of healing wounds
- Glycosylation inhibits lysyl oxidase that matures collagen to heal the wound (Fig. 2)
- This is the reason why the diabetic patient's foot ulcer doesn't heal easily.
- How an innovative, patented, **HELICOLL** collagen helps

Helicoll's NANOTECHNOLOGY could help heal DFU faster!

- **Helicoll**, as an uncross-linked biocompatible collagen, when tightly applied over the wound, it would osmotically absorb glucose.
- Such glucose pulling of **Helicoll** collagen would reduce the glycosylation of the collagen produced in the wound-bed
- When the collagen in the wound is relieved from glycosylation, it matures and lets the Diabetic wound heal faster.
- This provides a scientific explanation for the successful use of **HELICOLL** to treat the non-healing DIABETIC FOOT ULCERS.

References:

1. American Diabetes Association. 2018. The Staggering Costs of Diabetes. Retrieved from http://main.diabetes.org/dorg/images/infographics/adv-cost-of-diabetes.pdf

2. Dall M et al. The Economic Burden of Elevated Blood Glucose Levels in 2012: Diagnosed and Undiagnosed Diabetes, Gestational Diabetes Mellitus, and Prediabetes. Diabetes Care 37:3172-