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REVIEW

Glycosylation of Collagen Provokes Diabetic Wound Ulcers

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Abstract
The objective of this manuscript is to provide a comprehensive understanding of the general etiology of diabetic ulcers. While it is commonly perceived that "peripheral neuropathy" is the sole cause of diabetic ulcers due to reduced arterial blood supply and impaired venous circulation to the wound, there is a significant oversight at the nano-molecular level regarding the impact of high blood glucose/glycans in diabetic patients. A significant number of research literature talk about the influence of high blood glucose, the impact of glycosylation, the role of lysyl oxidase in collagen maturation along with the impact on peripheral nerve cells causing neuropathy. Such peripheral neuropathy could also be playing a major role in the reduction of arterial blood supply. Through this review article, the author aims to shed light on the unexplored mechanisms involving the glycosylation of lysine residues caused by excessive blood glucose/glycans/polysialic acids, and other related processes. These alterations disrupt the normal pathway of oxidative deamination of lysine residues, which are supposed to serve as substrates for lysyl oxidase. Consequently, the conversion of amino groups to aldehyde groups is impeded, leading to a disruption in the aldol-condensation reaction necessary for the regular maturation of wound bed collagen and proper healing of the wound.

Keywords Diabetic ulcer · Hyperglycemia · Collagen · Glycosylation · Lysyl oxidase · Delayed wound healing and treatments

Introduction

Any medical professional would readily acknowledge that the cause of diabetic ulcers is peripheral neuropathy, coupled with poor arterial blood supply to the wound. However, the biochemical pathway underlying the etiology of diabetic ulcers has not been thoroughly analyzed to date. This review article attempts to elucidate the potential chemical interventions resulting from excessive blood glucose in diabetic patients, which adversely affect the normal wound healing process and lead to ulcer formation.

Among the two factors, peripheral neuropathy and poor circulation or peripheral artery disease (PAD), the former pathological symptom could also be attributed to hyperglycemia, whereas PAD may be caused by the accumulation of fatty material inside the arteries, which subsequently hardens into plaque.

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The primary focus of this article is on the impact of protein glycosylation and its contribution to delayed wound healing, ultimately leading to ulcer formation (See Fig. 1).

Current General Perception of Diabetic Ulcer Etiology

The onset of diabetic ulcers is widely perceived to be caused by peripheral neuropathy and poor blood circulation.

Peripheral Neuropathy

First and foremost, it is crucial to understand peripheral neuropathy caused by hyperglycemia. High blood sugar can result in a condition known as diabetic neuropathy, which involves nerve damage. Prolonged periods of elevated blood sugar levels can lead to nerve damage, where

the affected nerves may cease to transmit messages to various parts of the body [1, 2] (See Fig. 2).

The nerves responsible for carrying sensation can also be damaged over time due to high blood sugar levels, resulting in a condition called "diabetic neuropathy" [3, 4].

The duration of diabetes and levels of glycated hemoglobin have been strongly associated with a higher incidence of neuropathy [5, 6].

Reduced Blood Circulation

Poor blood supply to the wound, also known as peripheral artery disease (PAD), is caused by the accumulation of fatty material inside the arteries, which hardens and forms plaque. This process restricts the flow of blood throughout the body [7–9] (See Fig. 3).

Prolonged high blood sugar levels can lead to damage in the blood vessels, resulting in reduced blood flow to the feet. Insufficient circulation can weaken the skin, contribute to the development of foot ulcers, and impair the healing of wounds [10].

Untrodden Causes of Diabetic Ulcer

Hyperglycemia (High Blood Glucose) in Diabetic Patients

Hyperglycemia is the medical term used to describe high blood glucose or blood sugar levels. It occurs when the body either has insufficient insulin or cannot effectively use the available insulin [11–13].

The term "hyperglycemia" is derived from the Greek words hyper (high) + glykys (sweet/sugar) + haima (blood). Medically, hyperglycemia is defined as blood glucose levels greater than 125 mg/dL while fasting and greater than 180 mg/dL 2 h after eating. If left untreated, hyperglycemia can lead to severe and life-threatening complications, including damage to the eyes, kidneys, nerves, heart, and peripheral vascular system [14–16]. Therefore, effective management of hyperglycemia is crucial in order to prevent disease complications and improve patient outcomes [17, 18].

Hyperglycemia resulting in Glycosylation

Protein glycosylation is a fundamental process in nature that regulates essential biological pathways, including protein trafficking, cell adhesion, and host-pathogen interactions. The intricate and diverse structure of glycans on proteins plays a crucial role in directing specific biological processes. When these structures are altered, it can give rise to various diseases [19–23]. Understanding the fundamental principles of protein glycosylation is therefore of great importance in both basic biology and medicine [24, 25].

Glycosylation is the process by which a carbohydrate is covalently attached to a target macromolecule, typically proteins and lipids [26, 27]. As such, glycosylation serves as a form of post-translational modification for proteins and other biological molecules [28, 29].

Impacts of Glycosylation

Glycosylation is frequently utilized by viruses to shield viral proteins from immune recognition. A notable example is the dense glycan shield present on the envelope spike of the human immunodeficiency virus [26, 30, 31]. This utilization of glycosylation by viruses to evade immune recognition suggests that if collagen's epitope is obscured by glycosylation, it will severely impact the interconnected biochemical mechanisms.

Previous in vitro studies have demonstrated that glucose inhibits collagen fibril formation and subsequent cross-linking [32]. Collagen with reduced cross-linking is more susceptible to degradation by collagenolytic enzymes, which may explain the decreased collagen levels observed. It is suggested that the diminished collagen levels in the connective tissues of individuals with diabetes may be attributed to a combination of inhibited collagen fibril formation, impaired cross-linking, and increased collagen degradation [33].

Sialic acids (Sias) are commonly found as terminal branches of N-glycans, O-glycans, and glycosphingolipids (such as gangliosides). They occasionally act as capping side chains of GPI anchors as well [34].

Normal Wound Collagen Maturation Through Lysyl Oxidase

The functions of collagen are diverse. For example, during wound formation, exposed collagen activates the clotting phase and facilitates the migration of inflammatory cells to the wound bed. It possesses natural binding sites for various cytokines, including epidermal growth factor (EGF), fibronectin, fibrinogen, histamine, platelet-derived growth factor (PDGF), serotonin, and von Willebrand factor, among others [35, 36].

In a normal maturation process, lysyl oxidase facilitates the oxidative deamination of lysine residues, ultimately leading to aldehyde-amino group Schiff-base condensation and aldol condensation, resulting in the formation of cross-links [37–40] (shown on the left side of Fig. 4).

Enzymatic crosslinking is a crucial step in the development and repair of collagen connective tissues [41, 42]. Collagen crosslinks play a key role in tissue mechanics, cell

signaling, matrix damage accumulation, and tissue repair [43–45]. The mechanical integrity of individual Type-I collagen fibrils heavily relies on the enzyme lysyl oxidase, which regulates the robust formation of stable intermolecular collagen crosslinks during maturation. The absence of these head-to-tail chemical bonds significantly reduces collagen fibril strength and overall tissue function. Lysyl oxidase specifically acts on lysine or hydroxylysine residues in the telopeptide region of the collagen molecule, resulting in the formation of immature divalent crosslinks with opposing amino acids in the triple-helical region [46–49]. These immature crosslinks later spontaneously convert into more stable trivalent crosslinks, increasing collagen interconnectivity, fibril stability, and mechanical integrity of the entire tendon [50].

Lysine modifications of collagen involve complex sequential processes catalyzed by several groups of enzymes, ultimately leading to covalent intermolecular cross-linking [51, 52]. Within the cell, specific lysine residues are hydroxylated to form hydroxylysine. Then, hydroxylysine residues in the helical domain of the collagen molecule undergo glycosylation by the addition of galactose or glucose-galactose. Outside the cell, lysine and hydroxylysine residues in the *N*- and C-telopeptides can undergo oxidative deamination, producing reactive aldehydes that undergo a series of non-enzymatic condensation reactions, resulting in the formation of covalent intra- and intermolecular cross-links [53].

Direct Impact of Glycosylation on Maturation of Collagen in the Healing Wound Bed

The excessive amount of glucose in diabetic conditions glycosylates the same lysine residues that serve as substrates for lysyl oxidase [54–56] (shown on the right side of Fig. 4), which, in turn, inhibits the normal maturation of collagen. This biochemical phenomenon, called glycosylation, hinders the normal enzymatic maturation mediated by lysyl oxidase, leading to non-healing ulcers [57]. Furthermore, this glucose also affects the extracellular matrix that supports the nerves and their endings, resulting in significant matrix structural alterations that render it unfit to support synapses [58].

In conclusion, protein glycosylation is differentially regulated in a tissue- and disease-specific manner and is associated with the inflammatory response during wound healing. This altered glycosylation likely contributes to the observed decreased healing potential [59, 60] in the skin compared to the oral mucosa and in diabetic skin compared to non-diabetic skin, respectively. However, further validation is required.

Overall, this study demonstrates that three glycosylation-related genes related to mucins and glycogenolysis, respectively, are downregulated, while 18 genes associated with neutrophil degranulation, sulfation, polysialylation, and others are upregulated in tissues with impaired healing. Additionally, time-dependent increases in protein sialic acids and polysialic acids were observed in the skin compared to the oral mucosa, while diabetic skin exhibited increases in *N*-linked glycan sialic acids and fucosylated, sialosyl-poly-*N*-acetyllactosamines compared to non-diabetic skin. Interestingly, increased sialic acid carbohydrates have been observed in other models of acute inflammation, and both polysialic acid and fucosylated, sialosyl-poly-*N*-acetyllactosamine carbohydrate determinants are involved in selectin-selectin ligand-mediated inflammatory responses [61].

Polysialic acid (PSA) has been adsorbed and/or linked to other natural or synthetic polymers, such as hyaluronic acid (a natural polysaccharide), polylysine and polyornithine (synthetic polypeptides), or LM and gelatin (proteins) [62].

This study demonstrates a significant blood glucose concentration-dependent increase in glycosylation in newly synthesized collagen in hyperglycemic animals, which is associated with increased collagenase activity and decreased wound collagen content [63].

It is worth noting, when compiling wound-healing histories, that individuals with lower HbA_1c levels had faster healing. For example, the clinical course of two individuals who presented to the Johns Hopkins Wound Clinic with foot wounds. The individual with an HbA_1c level of 5.6% had a wound-healing rate of 0.35 cm^2 per day, and the wound was completely resolved 64 days after the initial presentation. The individual with an HbA_1c level of 11.1% had a more variable clinical course, where the wound area increased and decreased over time, and 727 days after the initial presentation, the wound was not resolved. During the time when the wound was decreasing in size, the wound-healing rate was 0.001 cm^2 per day. This suggests that a relationship might exist between a faster wound-healing rate and low HbA_1c levels [64–67].

Current Treatment Options for Hyperglycemic Patients

Regarding the treatment of hyperglycemic patients, in addition to the usage of insulin as a supplement, there are various oral antihyperglycemic drugs [68, 69] currently available. These agents include Sulfonylureas, Meglitinides, Biguanides, Thiazolidinediones, α-Glucosidase inhibitors, DPP-4 inhibitors, SGLT2 inhibitors, Cycloset, and others. A summary of the mechanisms of action [70] for different classes of oral antihyperglycemic agents is provided in Table 1 above.

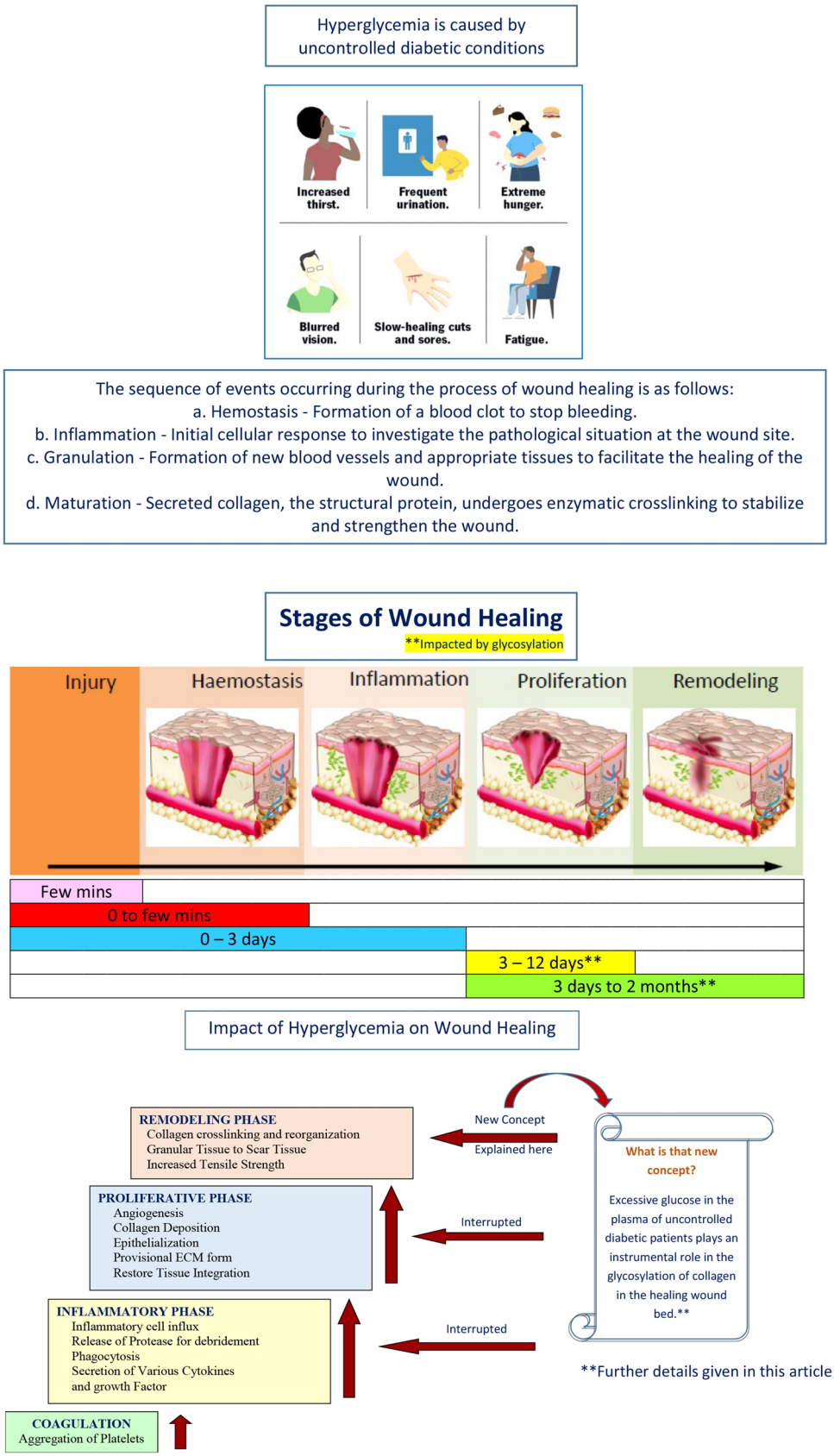

Fig. 1 Collagen glycosylation—unrevealed concept in diabetic wound etiology

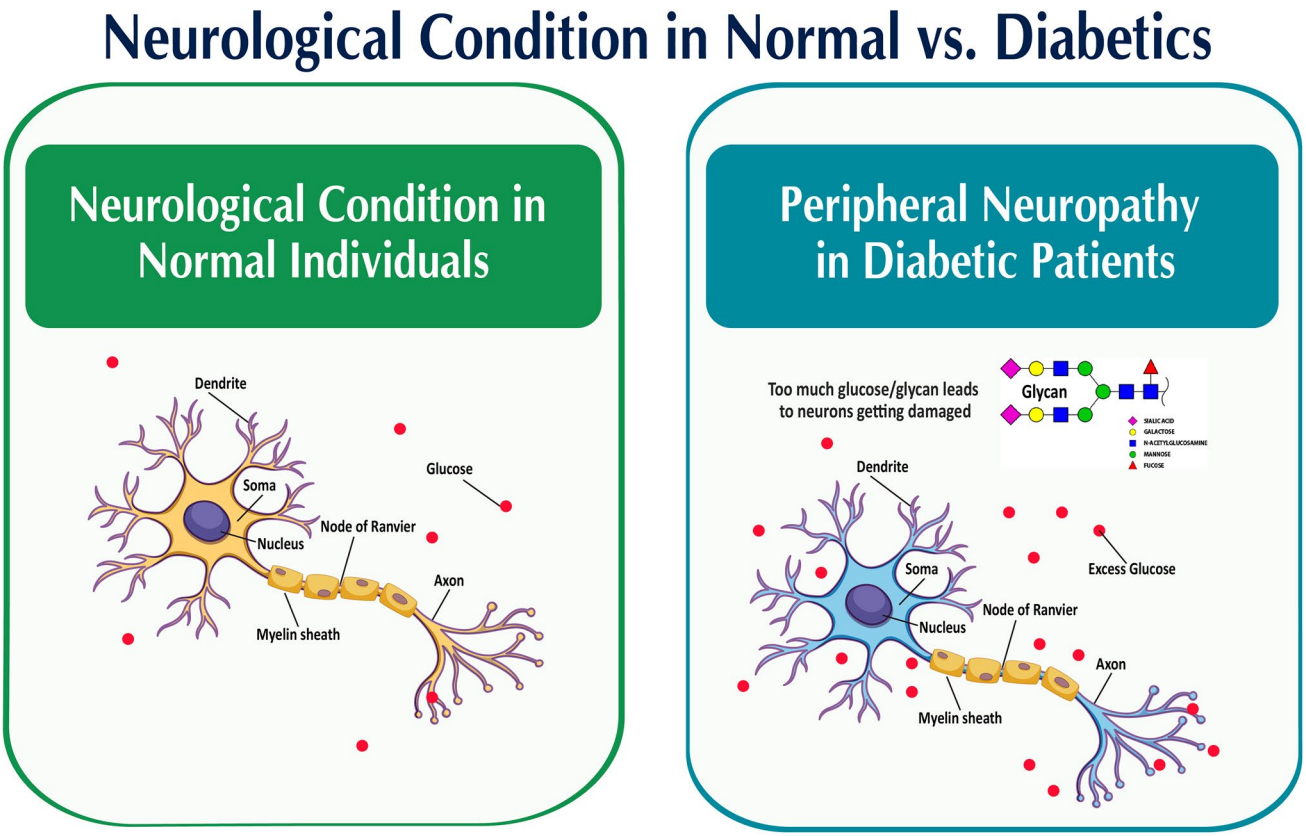

Fig. 2 Excessive glucose in diabetic patients cause neuronal damage leading to peripheral neuropathy

Discussion & Conclusion

The author of this article attempts to explain the etiology of diabetic ulcers with an emphasis on "what is generally perceived" versus "what needs to be enlightened". Such a detailed understanding is also essential for developing better control mechanisms for the treatment of diabetic ulcers.

Ongoing efforts are being made to develop better methods for the treatment of diabetic patients and control ulcerous wounds. The above-explained eye-opening unexplored causes of diabetic ulcers may pave new paths for treating them through the local administration of non-immunogenic, bioactive, and un-crosslinked Type-I collagen at the wound site. This collagen type would absorb excess glucose by serving as a substrate for free-floating glucose/glycans,

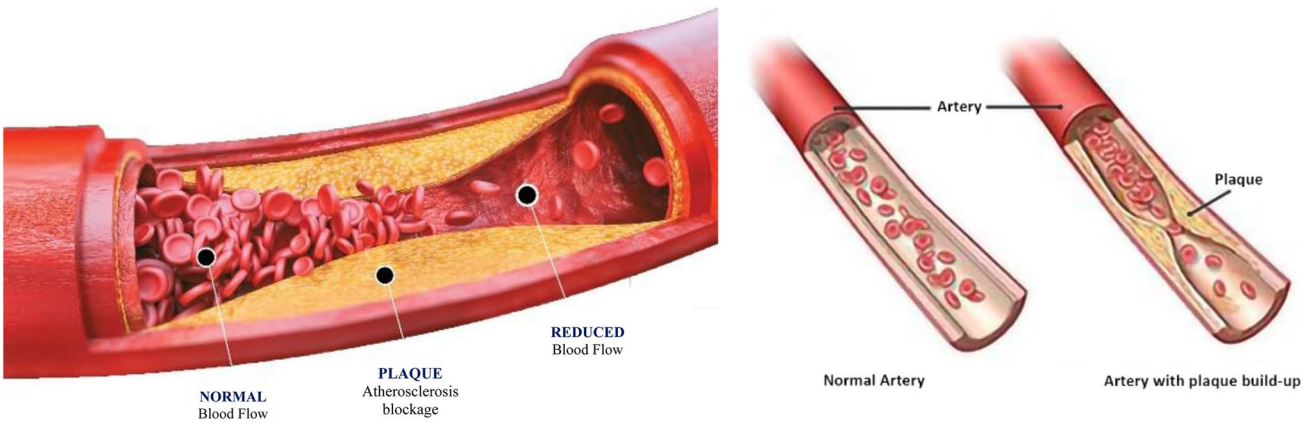

Fig. 3 Peripheral arterial disease development in diabetic patients

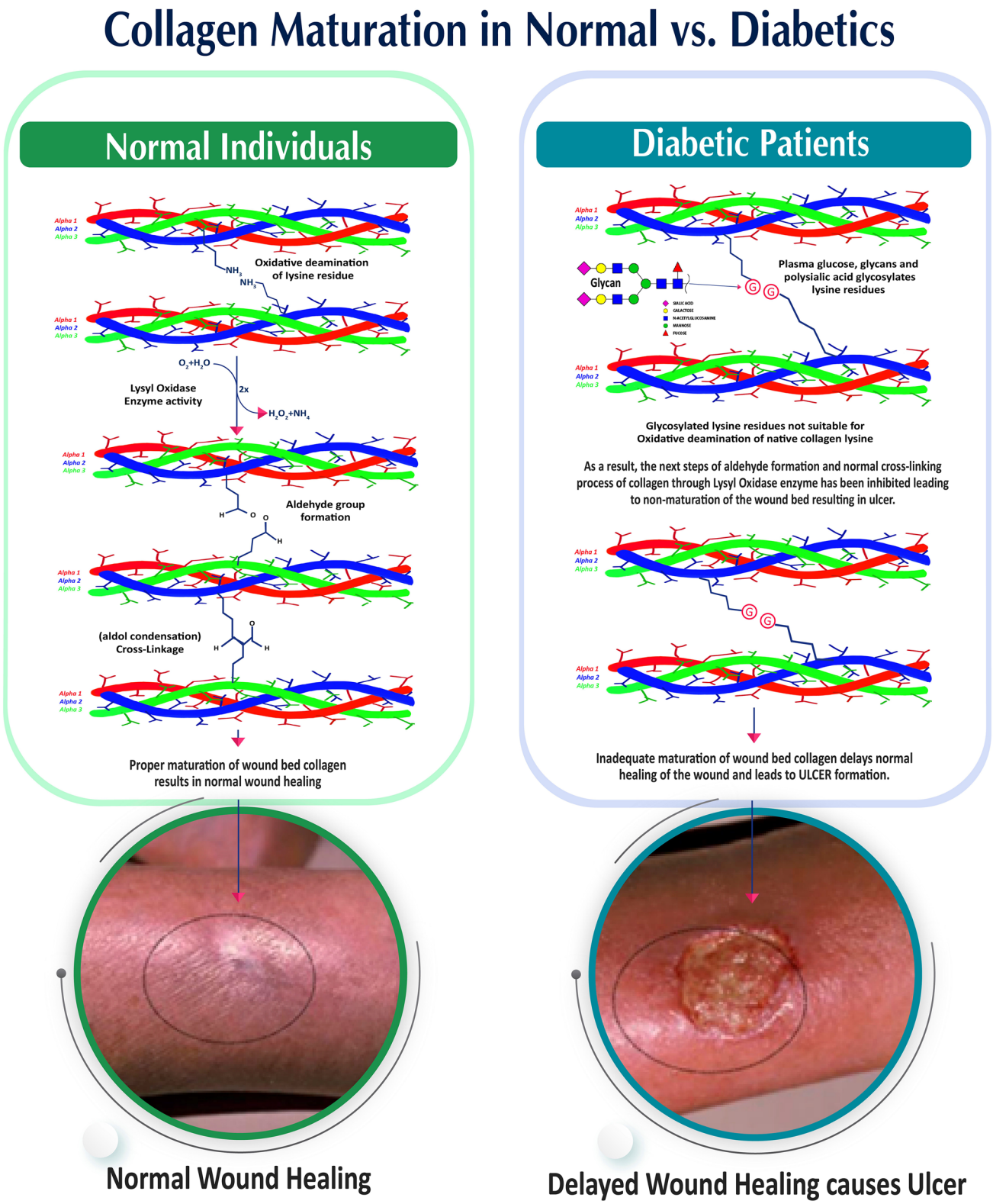

Fig. 4 Wound collagen maturation by lysyl oxidase mediated cross-linking is inhibited by glycosylation in diabetic patients—resulting to ulcer wound

Table 1 Biological actions of diabetic medications

Generic name	Mechanism of action
Sulfonylureas & Meglitinides	This binds to ATP-sensitive potassium channels in the beta cells of the pancreas that alters the resting membrane potential of the cell causing an influx of calcium to stimulate insulin secretion
Biguanides	This decreases hepatic glucose production and intestinal absorption of glucose
Thiazolidinediones	This increases the number of insulin-sensitive adipocytes
Alpha-glucosidase inhibitors	This inhibits polysaccharide reabsorption and the metabolism of sucrose to glucose and fructose
DPP-4 inhibitors	This decreases glucagon release and increases glucose-dependent insulin release
SGLT2 inhibitors	This causes inhibition of 90% glucose reabsorption
Cycloset	This reverses insulin resistance and decreases glucose production

thereby reducing the unwanted impact of glucose on the wound-bed collagen. Most other collagens may contain non-biocompatible molecules as contaminants, which are mostly cross-linked (knowingly or unknowingly) to avoid any potential rejection of the matrix material in the host tissue.

Consequently, the synthesized collagen can avoid potential glycosylation damage and undergo maturation for proper wound healing.

Data Availability All data generated or analyzed during this study are included in this published article.

Declarations

Conflict of interest The author states that there is no conflict of interest and it's a general review article for better understanding of science of diabetic ulcer etiology.

References

1. CDC (2020). Diabetes and nerve damage. Centers for Disease Control and Prevention. https://www.cdc.gov/diabetes/library/features/diabetes-nerve-damage.html. Accessed 4 Apr 2023
2. S.F. Spampinato, G.I. Caruso, R. De Pasquale, M.A. Sortino, S. Merlo, The treatment of impaired wound healing in diabetes: looking among old drugs. Pharmaceuticals **13**(4), 60 (2020)
3. Foot care for people with diabetes beyond the basics. www.uptodate.com. (n.d.). UpToDate. [online] https://www.uptodate.com/contents/foot-care-for-people-with-diabetes-beyond-the-basics/print#:~:text=Poor%20circulation%20can%20weaken%20the,skin%20and%20make%20ulcers%20worse. Accessed 4 Apr 2023
4. E.L. Feldman, B.C. Callaghan, R. Pop-Busui, D.W. Zochodne, D.E. Wright, D.L. Bennett, V. Bril, J.W. Russell, V. Viswanathan, Diabetic neuropathy. Nat. Rev. Dis. Prim. **5**(1), 41 (2019)
5. S. Yagihashi, H. Mizukami, K. Sugimoto, Mechanism of diabetic neuropathy: where are we now and where to go? J. Diabetes Investig. **2**(1), 18–32 (2011)
6. G. Casadei, M. Filippini, L. Brognara, Glycated hemoglobin (HbA1c) as a biomarker for diabetic foot peripheral neuropathy. Diseases **9**(1), 16 (2021)
7. Elko Daily Free Press. (n.d.). Neuropathy or poor circulation: Diagnosing the difference. [online] https://elkodaily.com/lifestyles/neuropathy-or-poor-circulation-diagnosing-the-difference/article_e03b7960-287f-11ed-9216-3bf32967e86e.html Accessed 27 April 2023
8. M.R. Zemaitis, J.M. Boll, M.A. Dreyer, *Peripheral arterial disease* (StatPearls [Internet], 2017)
9. N.M. Hamburg, M.A. Creager, Pathophysiology of intermittent claudication in peripheral artery disease. Circ. J. **81**(3), 281–289 (2017)
10. J. Deborah, Patient education: foot care for people with diabetes (beyond the basics). www.uptodate.com. (n.d.). UpToDate. [online] https://www.uptodate.com/contents/foot-care-for-people-with-diabetes-beyond-the-basics. Accessed 27 Apr 2023
11. American Diabetes Association (n.d.). Hyperglycemia (High Blood Glucose) | ADA. [online] diabetes.org. https://diabetes.org/healthy-living/medication-treatments/blood-glucose-testing-and-control/hyperglycemia#:~:text=Hyperglycemia%20is%20the%20technical%20term. Accessed 27 Apr 2023
12. Medlineplus.gov. (2019). Hyperglycemia. https://medlineplus.gov/hyperglycemia.html. Accessed 27 Apr 2023
13. Mayo Clinic (2022). Hyperglycemia in diabetes—symptoms and causes. [online] Mayo Clinic. https://www.mayoclinic.org/diseases-conditions/hyperglycemia/symptoms-causes/syc-20373631. Accessed 27 Apr 2023
14. American Diabetes Association, Diagnosis and classification of diabetes mellitus. Diabetes care **37**(Supplement_1), S81–S90 (2014)
15. H.R. Karrar, Diabetic ketoacidosis: a review article. World Fam. Med. **20**(6), 66–71 (2022)
16. Wikipedia Contributors (2019). Hyperglycemia. https://en.wikipedia.org/wiki/Hyperglycemia. Accessed 27 Apr 2023
17. M. Mouri, M. Badireddy, *Hyperglycemia* (StatPearls Publishing, Tampa, 2022)

18. L. Corsino, K. Dhatariya and G. Umpierrez, Management of diabetes and hyperglycemia in hospitalized patients. Endotext. (2000). Available at www.endotext.org
19. R. Sackstein, K.M. Hoffmeister, S.R. Stowell, T. Kinoshita, A. Varki and H.H. Freeze, Glycans in acquired human diseases. Essentials of glycobiology. (2022)
20. E. Maverakis, K. Kim, M. Shimoda, M.E. Gershwin, F. Patel, R. Wilken, S. Raychaudhuri, L.R. Ruhaak, C.B. Lebrilla, Glycans in the immune system and the altered glycan theory of autoimmunity: a critical review. J. Autoimmun. **57**, 1–13 (2015)
21. M.L. Bermingham, M. Colombo, S.J. McGurnaghan, L.A. Blackbourn, F. Vučković, M. Pučić Baković, I. Trbojević-Akmačić, G. Lauc, F. Agakov, A.S. Agakova, C. Hayward, N-glycan profile and kidney disease in type 1 diabetes. Diabetes Care **41**(1), 79–87 (2018)
22. I. Trbojević Akmačić, N.T. Ventham, E. Theodoratou, F. Vučković, N.A. Kennedy, J. Krištić, E.R. Nimmo, R. Kalla, H. Drummond, J. Štambuk, M.G. Dunlop, Inflammatory bowel disease associates with proinflammatory potential of the immunoglobulin G glycome. Inflamm. Bowel Dis. **21**(6), 1237–1247 (2015)
23. M.C. Patterson, Metabolic mimics: the disorders of N-linked glycosylation. Semin. Pediatr. Neurol. **12**(3), 144–151 (2005)
24. H.C. Hang, and M.R. Pratt, in *Chemistry, Molecular Sciences and Chemical Engineering*. Molecular Probes for Protein Glycosylation (Elsevier Publishing, 2013)
25. R. Zhu, l. Zacharias, K.M. Wooding, W. Peng, and Y. Mechref, Glycoprotein enrichment analytical techniques: advantages and disadvantages. In Methods in enzymology Vol. 585, pp. 397–429. (Academic Press, Cambridge 2017)
26. Wikipedia. (2021). Glycosylation. https://en.wikipedia.org/wiki/Glycosylation. Accessed 27 Apr 2023
27. C. Walsh, *Posttranslational modification of proteins: expanding nature's inventory* (Roberts and Company Publishers, Boston, 2006)
28. A. Varki, R.D. Cummings, J.D. Esko, P. Stanley, G.W. Hart, M. Aebi, D. Mohnen, T. Kinoshita, N.H. Packer, J.H. Prestegard, R.L. Schnaar, *Essentials of glycobiology* (Cold Spring Harbor Laboratory Press, Cold Spring Harbor, 2022)
29. M.E. Taylor, K. Drickamer, *Introduction to glycobiology* (Oxford University Press, Oxford, 2011)
30. M. Crispin, D.J. Harvey, D. Bitto, C. Bonomelli, M. Edgeworth, J.H. Scrivens, J.T. Huiskonen, T.A. Bowden, Structural plasticity of the Semliki forest virus glycome upon interspecies transmission. J. Proteome Res. **13**(3), 1702–1712 (2014)
31. M. Crispin, K.J. Doores, Targeting host-derived glycans on enveloped viruses for antibody-based vaccine design. Curr. Opin. Virol. **11**, 63–69 (2015)
32. S. Bansode, U. Bashtanova, R. Li, J. Clark, K.H. Müller, A. Puszkarska, I. Goldberga, H.H. Chetwood, D.G. Reid, L.J. Colwell, J.N. Skepper, Glycation changes molecular organization and charge distribution in type I collagen fibrils. Sci. Rep. **10**(1), 1–13 (2020)
33. Y.H. Lien, M.M. Tseng, R. Stern, Glucose and glucose analogs modulate collagen metabolism. Exp. Mol. Pathol. **57**(3), 215–221 (1992)
34. A. Varki, R. Schauer, *Chapter 14. Sialic acids. Essentials of glycobiology*, 2nd edn. (Cold Spring Harbor Laboratory Press, Cold Spring Harbor, 2009)
35. S.H. Park, T. Uzawa, F. Hattori, S. Ogino, N. Morimoto, S. Tsuneda, Y. Ito, "All-in-one" in vitro selection of collagen-binding vascular endothelial growth factor. Biomaterials **161**, 270–278 (2018)
36. S. Tada, T. Kitajima, Y. Ito, Design and synthesis of binding growth factors. Int. J. Mol. Sci. **13**(5), 6053–6072 (2012)
37. Wikimedia.org. (2010). File: Tropocollagen cross-linkage lysyl oxidase (EN).svg - Wikimedia Commons. [online] https://commons.wikimedia.org/wiki/File:Tropocollagen_cross-linkage_lysyl_oxidase_%28EN%29.svg#filehistory. Accessed 27 Apr 2023
38. S. Zaffryar-Eilot, P. Hasson, Lysyl oxidases: orchestrators of cellular behavior and ECM remodeling and homeostasis. Int. J. Mol. Sci. **23**(19), 11378 (2022)
39. K. Yamaguchi, M. Itakura, R. Kitazawa, S.Y. Lim, K. Nagata, T. Shibata, M. Akagawa, K. Uchida, Oxidative deamination of lysine residues by polyphenols generates an equilibrium of aldehyde and 2-piperidinol products. J. Biol. Chem. **297**(3), 101035 (2021)
40. R.B. Rucker, T. Kosonen, M.S. Clegg, A.E. Mitchell, B.R. Rucker, J.Y. Uriu-Hare, C.L. Keen, Copper, lysyl oxidase, and extracellular matrix protein cross-linking. Am. J. Clin. Nutr. **67**(5), 996S-1002S (1998)
41. M.R. Aronoff, P. Hiebert, N.B. Hentzen, S. Werner, H. Wennemers, Imaging and targeting LOX-mediated tissue remodeling with a reactive collagen peptide. Nat. Chem. Biol. **17**(8), 865–871 (2021)
42. R.C. Siegel, G.R. Martin, Collagen cross-linking: enzymatic synthesis of lysine-derived aldehydes and the production of cross-linked components. J. Biol. Chem. **245**(7), 1653–1658 (1970)
43. M.D. Shoulders, R.T. Raines, Collagen structure and stability. Ann. Rev. Biochem. **78**, 929–958 (2009)
44. S.S. Mathew-Steiner, S. Roy, C.K. Sen, Collagen in wound healing. Bioengineering **8**(5), 63 (2021)
45. T.B. McKay, S. Priyadarsini, D. Karamichos, Mechanisms of collagen crosslinking in diabetes and keratoconus. Cells **8**(10), 1239 (2019)
46. S.N. Gacheru, P.C. Trackman, M.A. Shah, C.Y. O'Gara, P. Spacciapoli, F.T. Greenaway, H.M. Kagan, Structural and catalytic properties of copper in lysyl oxidase. J. Biol. Chem. **265**(31), 19022–19027 (1990)
47. J.A. Chirinos (ed.), *Textbook of arterial stiffness and pulsatile hemodynamics in health and disease* (Academic Press, Cambridge, 2022)
48. S.D. Vallet, M. Guéroult, N. Belloy, M. Dauchez, S. Ricard-Blum, A three-dimensional model of human lysyl oxidase, a cross-linking enzyme. ACS Omega **4**(5), 8495–8505 (2019)
49. H. Schilter, A.D. Findlay, L. Perryman, T.T. Yow, J. Moses, A. Zahoor, C.I. Turner, M. Deodhar, J.S. Foot, W. Zhou, A. Greco, The lysyl oxidase like 2/3 enzymatic inhibitor, PXS-5153A, reduces crosslinks and ameliorates fibrosis. J. Cell Mol. Med. **23**(3), 1759–1770 (2019)
50. J.G. Snedeker, A. Gautieri, The role of collagen crosslinks in ageing and diabetes-the good, the bad, and the ugly. Muscles Ligaments Tendons J. **4**(3), 303 (2014)
51. J. Myllyharju, Intracellular post-translational modifications of collagens. Collagen: primer in structure, processing and assembly, pp.115–147, 2005
52. M. Terajima, Y. Taga, T. Nakamura, H.F. Guo, Y. Kayashima, N. Maeda-Smithies, K. Parag-Sharma, J.S. Kim, A.L. Amelio, K. Mizuno, J.M. Kurie, Lysyl hydroxylase 2 mediated collagen post-translational modifications and functional outcomes. Sci. Rep. **12**(1), 14256 (2022)
53. M. Yamauchi, M. Sricholpech, Lysine post-translational modifications of collagen. Essays Biochem. **52**, 113–133 (2012)
54. W. Li, S. Shen, G.A. Robertson, M. Khatami, J.H. Rockey, Increased solubility of newly synthesized collagen in retinal capillary pericyte cultures by nonenzymatic glycosylation. Ophthalmic Res. **16**(6), 315–321 (1984)
55. B. Buckingham, K.M. Reiser, Relationship between the content of lysyl oxidase-dependent cross-links in skin collagen,

nonenzymatic glycosylation, and long-term complications in type I diabetes mellitus. J. Clin. Investig. **86**(4), 1046–1054 (1990)
56. A. Shin, Y. Vazmitsel, S. Connolly, K. Kabytaev, Comprehensive profiling and kinetic studies of glycated lysine residues in human serum albumin. Anal. Bioanal. Chem. **414**(17), 4861–4875 (2022)
57. J.L. Burgess, W.A. Wyant, B. Abdo Abujamra, R.S. Kirsner, I. Jozic, Diabetic wound-healing science. Medicina **57**(10), 1072 (2021)
58. Y. Huang, T.R. Kyriakides, The role of extracellular matrix in the pathophysiology of diabetic wounds. Matrix Biol. Plus **6**, 100037 (2020)
59. S. Patel, S. Srivastava, M.R. Singh, D. Singh, Mechanistic insight into diabetic wounds: pathogenesis, molecular targets and treatment strategies to pace wound healing. Biomed. Pharmacother. **112**, 108615 (2019)
60. Diabetic wound and care: Reasons for delayed wound healing family medicine austin learning diabetes care and factors affecting diabetic wound healing comments. https://familymedicineaustin.com/factors-affecting-diabetic-wound-healing/ Accessed 16 May 2023
61. V.A. Haywood, Glycosylation and sialylation during wound healing, Doctoral dissertation, University of Illinois at Chicago, 2019
62. J. Nicolas, S. Magli, L. Rabbachin, S. Sampaolesi, F. Nicotra, L. Russo, 3D extracellular matrix mimics: fundamental concepts and role of materials chemistry to influence stem cell fate. Biomacromol **21**(6), 1968–1994 (2020)
63. P.J. Hennessey, E.G. Ford, C.T. Black, R.J. Andrassy, Wound collagenase activity correlates directly with collagen glycosylation in diabetic rats. J. Pediatr. Surg. **25**(1), 75–78 (1990)
64. A.L.C Schneider, E. Selvin, D.J. Margolis, G.S. Lazarus and L.A. Garza, Hemoglobin A1c is a predictor of healing rate in diabetic wounds. J Invest Dermatol. **131**(10), 2121–2127 (2012)
65. J. Xiang, S. Wang, Y. He, L. Xu, S. Zhang, Z. Tang, Reasonable glycemic control would help wound healing during the treatment of diabetic foot ulcers. Diabetes Ther. **10**, 95–105 (2019)
66. A.B. Mathew, M. Isac, Association of hemoglobin-A1c with healing in diabetic cutaneous wound–a prospective study. Int. J. Sci. Study **8**(10), 83–91 (2021)
67. R. Appil, E.L. Sjattar, S. Yusuf, K. Kadir, Effect of family empowerment on HbA_1c levels and healing of diabetic foot ulcers. Int. J. Low. Extrem. Wounds **21**(2), 154–160 (2022)
68. B. Lorenzati, C. Zucco, S. Miglietta, F. Lamberti, G. Bruno, Oral hypoglycemic drugs: pathophysiological basis of their mechanism of actionoral hypoglycemic drugs: pathophysiological basis of their mechanism of action. Pharmaceuticals **3**(9), 3005–3020 (2010)
69. M. Baretić, V. Bralić Lang, Hypoglycemia in patients with type 2 diabetes treated with oral antihyperglycemic agents detected by continuous glucose monitoring: a multi-center prospective observational study in Croatia. BMC Endocr. Disord. **20**(1), 1–8 (2020)
70. K. Ganesan, M.B.M. Rana, S. Sultan, in *StatPearls*. Oral Hypoglycemic Medications. (StatPerals Publishing, Treasure Island, FL, USA, 2023)