

## Diabetes, wound healing in the eye, and cholesterol crystals in the retina

This issue of Primary Eye Care brings news about two new developments in the understanding of diabetes-related connections.

### Disease-Related Changes to the Cornea and Potential Therapeutic Approaches to Correct Diabetic Wound Healing

Investigators from Cedars-Sinai have provided new understanding of how diabetes delays wound healing in the eye, identifying for the first time two related disease-associated changes to the cornea. The study also identified three therapeutic pathways that reversed these changes and partially restored wound-healing function to the cornea.

The major discovery entails specific epigenetic alterations which modify DNA gene expression. The study also identified for the first time an important role of Wnt-5a, a secreted signaling protein, found responsible for corneal wound healing and the function of stem cells.

More than 300,000 New Zealanders are living with diabetes and most diabetes drugs do not address molecular and cellular changes or their associated complications. The researchers are hopeful that better understanding of the newly discovered, epigenetically-regulated wound-healing mechanism could lead to treatments that help people with diabetes avoid long-term ocular health issues.

The research team compared cells from the corneas from six diabetic patients with those of five healthy donors.

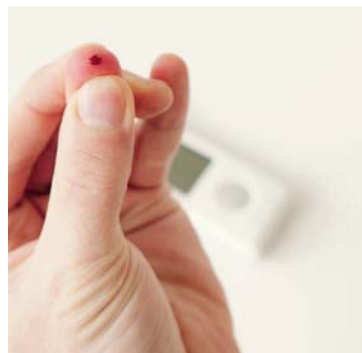


Photo Credit: pexels Artem Podrez

They found that in diabetic corneas, the protein product of the WNT5A gene was repressed. Additionally, in diabetic samples, they found an increase in the microRNA that inhibits WNT5A.

After inducing wounds to corneal cells in culture and corneal organ cultures, the team tested three interventions designed to normalize Wnt-5a protein expression.

1. They added the Wnt-5a protein directly;
2. They introduced a DNA methylation inhibitor, originally approved to treat cancer; and
3. They targeted microRNA levels with a novel gene therapy approach using a nanoscale compound. - developed by the researchers, which uses synthetic molecules to block the microRNA.

In the diabetic samples, all three therapeutic methods stimulated stem cell marker production, improved tissue regeneration and accelerating wound healing.

The long term goal of the researchers is to develop topical, sustained-release drugs for corneal wound healing. Ultimately, drugs that are FDA [Food and Drug Administration] approved and easily applied may be one of the most promising approaches for effective future therapies.”

Shah et al., 2023. Full citation as endnote

## Researchers discover new link between cholesterol and diabetic retinopathy

Advancements that could lead to earlier diagnosis and treatment for diabetic retinopathy have been identified by a multi-department research team from Michigan State and other universities. The researchers found that diabetes, age-related health conditions, and other metabolic disorders can lead to a buildup of cholesterol in the retina. This tends to crystalize and contribute to the development of diabetic retinopathy.

The retina is a very isolated organ with a blood barrier that separates the retina from the rest of the body. This makes the retina hard to study and extremely complex.

The cholesterol crystals found in the retina are like the crystals found in atherosclerotic plaque, a finding discovered in the lab of George Abela, chief of the MSU Division of Cardiology who helped the research team identify ways to scan retinas using modified tissue preparation for scanning electron microscopy. This process helps researchers analyze the composition of the crystals, which typically result when there is too much cholesterol in one place.

The crystalized deposits are very reflective and can be seen in images of the retina. This is important because noninvasive retina evaluations can be done by most optometrists, creating an opportunity for earlier diagnosis for more people.



Photo Credit: pexels Ksenia Chernaya

As retinopathy is the leading cause of preventable blindness and one of the most feared complications of Type 1 and Type 2 diabetes, treatments that directly lower cholesterol in the retina would offer the potential for earlier management than is

currently the case. At present, treatment approaches are very invasive and are only directed at the late stages of retinopathy.

While there is also hope that new treatments to address crystals formed by cholesterol could be less invasive than current options for diabetic retinopathy, there may be other areas of the body where these crystals could be treated to prevent other diseases.

### Citations:

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2. Hammer S S, Dorweiler T F, McFarland D, Adu-Agyeiwaah Y, Mast N, El-Darzi N, Fortmann SD, Nooti S, Agrawal D K, Pikuleva I A, Abela G S, Grant M B, Busik J V. Cholesterol crystal formation is a unifying pathogenic mechanism in the development of diabetic retinopathy. *Diabetologia*. 2023 Sep;66:1705-1718. doi.org: 10.1007/s00125-023-05949-w. Epub 2023 Jun 14. PMID: 37311879; PMCID: PMC10390399.



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