Diabetes technology

https://doi.org/10.1038/s42255-025-01221-0

A future without needles: non-invasive glucose measurements in patients with diabetes

Andreas L. Birkenfeld & Vasilis Ntziachristos

Optical measurements through the skin are challenging because they usually represent averages across the various layers of skin that are illuminated. A study in *Nature Metabolism* uses a depth-selective variant of Raman spectroscopy to probe glucose levels specifically in the skin vasculature, and thereby achieves improved glucose sensing in humans.

Continuous glucose monitoring revolutionized diabetes care from 1999 onwards, and has evolved from large professional systems to patient-friendly, real-time devices that use microneedles for minimally invasive monitoring. Advances in these technologies have focused on enhancing accuracy and reducing the need for frequent calibration using finger-prick tests. Nevertheless, microneedles only measure glucose in the interstitial fluid, and not in the blood. Limitations of this approach include the delayed recording of glucose fluctuations (owing to the time it takes for glucose to diffuse from blood capillaries into the interstitial fluid) and fluctuations in interstitial fluid volume due to water changes, which pose challenges for quantification accuracy[1,2].

The next frontier in continuous glucose monitoring is the use of non-invasive glucose sensing techniques that avoid the use of needles and microneedles. Optical and optoacoustic sensing methods have been broadly considered for non-invasive glucose sensing. In particular, Raman spectroscopy is an analytical technique used to identify and characterize molecules (such as glucose) on the basis of their molecular vibrations after interaction with light at specific wavelengths. In contrast to optoacoustic measurements (which can resolve depth in high resolution using time-gating of a broadband optoacoustic signal)[3], optical methods such as Raman spectroscopy typically average signals from the entire tissue volume into which the illumination light diffuses. This averaging operation has been a limiting factor of optical sensing, because glucose signals from the microvasculature are mixed with contributions from other skin and tissue compartments (such as from the interstitial fluid), which compromises the precision with which glucose levels in the blood can be measured. In this issue of *Nature Metabolism*, Zhang et al.[4] improve the accuracy of Raman spectroscopy by increasing the sensitivity of the technique to cutaneous layers rich in vasculature (Fig. 1).

The authors achieve this depth selectivity by borrowing a technique developed several decades ago for diffuse optical spectroscopy, in which several detectors are spaced out at different distances from the illumination source. Owing to the diffusive propagation patterns of photons in skin tissue, detectors placed further away from the source can probe signals that emerge from deeper skin layers. Zhang et al. use this multidistance approach — which they term multiple μ-spatially offset Raman spectroscopy (mμSORS) — to improve the accuracy of Raman spectroscopy over bulk Raman measurements by probing layers rich in vasculature[4], and thereby reducing the interference of signals that originate from the skin surface[5–7].

The authors conducted a study in which they compared mμSORS signals to plasma glucose values obtained during a 5-h oral glucose tolerance test in 230 participants with and without diabetes. The technique achieved a mean absolute relative difference of 14.6% and 99.4% (ref. 4) of predictions fell within clinically acceptable zones of the consensus error grid[1], which indicates a robust capability for non-invasive blood glucose measurement. Best results were achieved for measurements that corresponded to the dermal–epidermal junction of the skin, where capillary loops are abundant[3,4]. Moreover, the authors show that mμSORS can monitor blood glucose without the need for user-specific calibration or model training, which makes it applicable to a wide range of individuals. The measurement accuracy was consistent across a physiological range of glucose concentrations and independent of the user's sex or the hand from which measurements were taken, which provides a proof of concept for the technology and its clinical use. Advantageously, different skin colours in the studied population did not affect the accuracy of the measurements[4].

Nevertheless, mμSORS also comes with some limitations and challenges that need to be solved before it can be used in a broader community of patients with diabetes. First, prediction accuracy was reduced in patients with very low glucose concentrations (≤4 mmol l^{-1}). Second, mμSORS currently requires an acquisition time of around 8 min per measurement to collect a sufficiently strong signal and to reduce noise. This comparatively long acquisition time potentially limits the ability to capture rapid glucose fluctuations, which is a prerequisite for accurate hypoglycaemia monitoring (a critical clinical requirement)[8–10]. Long acquisition times may also be affected by motion and other physiological variations, which possibly reduces reproducibility. Owing to the comparatively weak intensity of the Raman signal, this challenge may be particularly critical to future mμSORS developments. Moreover, the size of the mμSORS apparatus is currently approximately that of a desktop computer, which makes it impractical for widespread use at home or on the go. Finally, global application of the mμSORS sensor may require validation of its performance with a broader range of skin colours.

Overall, mμSORS is a step in the right direction for non-invasive glucose monitoring, for which layered specific detection appears to offer advantages over bulk measurements. The concept of glucose detection with layer-specific detection of cutaneous layers rich in vasculature was first demonstrated with the depth-gated mid-infrared optoacoustic sensor (DIROS). Compared to DIROS, mμSORS offers considerably less control of which cutaneous layer is selected. There are two major biophysical limitations to optical multidistance measurement. The first is that mμSORS is based on photons that are highly scattered in tissue. Scattering leads to a steep drop in the resolution

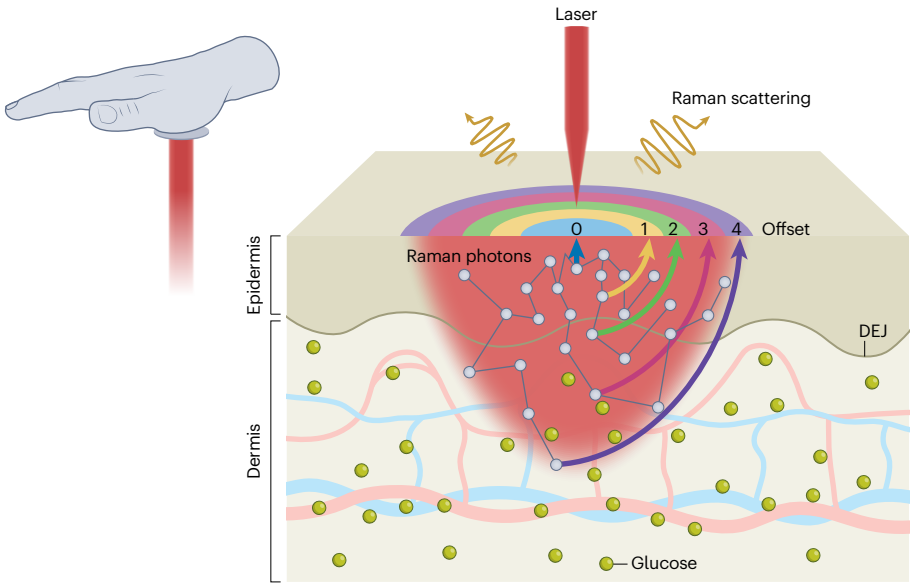

Fig. 1 | mμSORS can determine glucose non-invasively from the thenar of the human hand. Raman technology is used for non-invasive blood glucose monitoring by acquiring Raman signals at various skin depths. Using a 785-nm laser on the human thenar, backscattered photons are collected through a concentrically organized fibre bundle that is designed to capture light at specific offsets (0–4) in the micrometre range. Although signal intensity diminishes with larger offsets, the fibre arrangement compensates for this loss, which enables depth-selective detection of signals. The requirement for the signals to be largely derived from the dermis is due to the fact that this layer contains interstitial fluid and capillaries that correlate with plasma glucose levels. The depth of the dermal layer is assessed via optical coherence tomography. By correlating spectral transitions with dermal–epidermal junction (DEJ) depths, mμSORS assesses signals at the desired depth. This approach shows promise for effective depth-selective detection of glucose concentrations, which potentially facilitates non-invasive glucose monitoring.

of layer discrimination, by at least an order of magnitude or more compared to the time-gating of the broadband optoacoustic signals collected in DIROS. The second is that optical layer discrimination is sensitive to the optical properties of each individual skin, which can vary per individual or as a function of hydration and other parameters. However, the performance shown by the authors points to mμSORS as a method that – despite these biophysical limitations – shows great promise for non-invasive glucose sensing, and moves away from today's minimally invasive continuous glucose monitoring systems.

Taken together, the mμSORS technology appears to be taking non-invasive glucose monitoring to the next level by providing a proof-of-concept for its applicability in people with and without diabetes. Although some aspects (such as accuracy in the hypoglycaemic range, measurement time and the size of the device) need further optimization, the data presented are a compelling step towards a needle-free and non-invasive future for millions of patients to come.

Andreas L. Birkenfeld [1,2,3,4] ✉ **& Vasilis Ntziachristos** [5,6]
[1]German Center for Diabetes Research (DZD), Neuherberg, Germany. [2]Department of Internal Medicine IV, Diabetology, Endocrinology and Nephrology, Eberhard Karls University Tübingen, Tübingen, Germany. [3]Institute for Diabetes Research and Metabolic Diseases of the Helmholtz Center Munich at the University of Tübingen, Tübingen, Germany. [4]Diabetes & obesity theme, School of Cardiovascular and Metabolic Medicine & Sciences, Faculty of Life Sciences & Medicine, Kings College London, London, UK. [5]Chair of Biological Imaging, Central Institute for Translational Cancer Research (TranslaTUM), School of Medicine and Health & School of Computation, Information and Technology, Technical University of Munich, Munich, Germany. [6]Institute of Biological and Medical Imaging, Bioengineering Center, Helmholtz Zentrum München, Neuherberg, Germany.
✉e-mail: andreas.birkenfeld@med.uni-tuebingen.de

Published online: 5 February 2025

References

1. American Diabetes Association Professional Practice Committee. *Diabetes Care* **48**, S146–S166 (2025).
2. Hirsch, I. B. (ed.) *Role of Continuous Glucose Monitoring in Diabetes Treatment ADA Clinical Compendia Series* (ADA, 2018).
3. Uluç, N. et al. *Nat. Metab.* **6**, 678–686 (2024).
4. Zhang, Y. et al. *Nat. Metab.* https://doi.org/10.1038/s42255-025-01217-w (2025).
5. Liu, J., Chu, J., Xu, J., Zhang, Z. & Wang, S. *Spectrochim. Acta A Mol. Biomol. Spectrosc.* **329**, 125584 (2025).
6. Marks, D. L. & Boppart, S. A. *Phys. Rev. Lett.* **92**, 123905 (2004).
7. Åkeson, M., Brackmann, C., Gustafsson, L. & Enejder, A. *J. Raman Spectrosc.* **41**, 1638–1644 (2010).
8. Pistrosch, F. et al. *Acta Diabetol.* **52**, 889–895 (2015).
9. von Loeffelholz, C. & Birkenfeld, A. L. *Lancet Diabetes Endocrinol.* **12**, 277–284 (2024).
10. Capristo, E. et al. *J. Clin. Endocrinol. Metab.* **103**, 2136–2146 (2018).

Competing interests

V.N. is a founder and equity holder in iThera Medical GmbH, Spear UG, sThesis GmbH, I3 Inc. and Maurus OY. A.L.B. declares no competing interests.