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Perspective

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Insulin detection in diabetes mellitus: challenges and new prospects

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Abstract

Tremendous progress has been made towards achieving tight glycaemic control in individuals with diabetes mellitus through the use of frequent or continuous glucose measurements. However, in patients who require insulin, accurate dosing must consider multiple factors that affect insulin sensitivity and modulate insulin bolus needs. Accordingly, an urgent need exists for frequent and real-time insulin measurements to closely track the dynamic blood concentration of insulin during insulin therapy and guide optimal insulin dosing. Nevertheless, traditional centralized insulin testing cannot offer timely measurements, which are essential to achieving this goal. This Perspective discusses the advances and challenges in moving insulin assays from traditional laboratory-based assays to frequent and continuous measurements in decentralized (point-of-care and home) settings. Technologies that hold promise for insulin testing using disposable test strips, mobile systems and wearable real-time insulin-sensing devices are discussed. We also consider future prospects for continuous insulin monitoring and for fully integrated multisensor-guided closed-loop artificial pancreas systems.

Sections

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Introduction

The discovery of insulin is considered a key advance in the progress of modern science. This hormone is secreted by β-cells to regulate plasma levels of glucose, amino acids, keto acids and fatty acids, with glucose being the most potent stimulus of insulin secretion[1–3]. Impaired insulin secretion and action leads to diabetes mellitus, which is characterized by chronic hyperglycaemia. The heterogeneity of the pathophysiology of diabetes mellitus is a major concern for its classification, diagnosis and treatment[4–9]. Typically, type 1 diabetes mellitus is characterized by autoimmune destruction of the insulin-producing β-cells and requires treatment with exogenous insulin, whereas type 2 diabetes mellitus is characterized by β-cell dysfunction, causing decreased insulin secretion, increased hepatic glucose output and insulin resistance. Individuals with type 2 diabetes mellitus are often treated with oral medications (for example, metformin) and not with exogenous insulin. However, many of these individuals experience a decrease in their insulin production over time, which means that insulin administration is required for adequate glycaemic control[10–13]. Patients with diabetes mellitus require tight glycaemic control to prevent long-term cardiovascular complications, including premature atherosclerosis, the principal factor for mortality. Insulin deficiency also causes increased ketone production and alterations in lipid and protein metabolism[14].

Exogenous insulin therapy in diabetes mellitus is intended to mimic the secretion and behaviour of natural endogenous insulin for maintaining blood levels of glucose within a target range[15]. In healthy individuals, pancreatic β-cells secrete insulin at a constant low level (basal insulin secretion) to maintain steady blood levels of glucose over extended periods between meals (fasting plasma levels of glucose). In response to elevated blood concentrations of glucose (such as after a meal, that is, postprandial glucose levels), insulin secretion increases (prandial insulin section). Basal levels of insulin secretion are restored within 2–3 h, once plasma levels of glucose decrease[12–14] (Fig. 1a). Commercial synthetic insulins (insulin analogues) have been designed to mimic the natural endogenous secretion of insulin by offering unique pharmacokinetics and pharmacodynamics in the body[16]. Combinations of bolus and basal insulin analogues have enabled close mimicking of the physiological secretion of insulin, to achieve improved diabetes mellitus management[15]. Historically, a vial and syringe were the only insulin administration options[17]. Even today, subcutaneous insulin injection is the most widely used administration route and is carried out using insulin pens[18] and infusion pumps[19]. Despite the tremendous progress in insulin therapy, exogenous insulin administration still requires accurate dose calculations to closely mimic physiological patterns of insulin secretion. As such, an urgent need exists for technologies that can provide accurate, frequent and real-time measurements of the plasma concentration of insulin, in order to track changes in levels during insulin therapy and guide optimal dosing.

In this Perspective, we discuss the latest efforts and current challenges in moving from traditional laboratory-based insulin assays to frequent and continuous decentralized insulin measurements. In addition, we consider the prospects for addressing the variability of insulin requirements between different individuals (associated with their different metabolic pathways) by continuously monitoring insulin itself along with other chemical, physical and lifestyle inputs.

The importance of monitoring glucose and insulin

Owing to the narrow therapeutic window of insulin replacement therapy, individuals with diabetes mellitus have benefited over the past four decades from frequent and continuous monitoring of blood levels of glucose to tailor their insulin dosing[20,21]. Glucose monitoring has played a critical part in diabetes mellitus management, and tremendous progress has been made towards mobile and wearable devices for frequent and continuous monitoring supported by advanced data processing and communication technologies[20–22]. Glucose-responsive insulin delivery is the latest advance towards optimal insulin dosage based on continuous glucose monitoring (CGM) devices[23]. Closed-loop insulin delivery systems have thus been developed to mimic the natural feedback mechanism of insulin secretion, based on the changes in blood levels of glucose[24,25]. These closed-loop systems rely on CGM readings and advanced algorithms, to provide autonomous adjustments to basal insulin infusion rates and automated bolus corrections[26].

Despite these major advances, less than half of the individuals using insulin therapy achieve optimal glycaemic control (that is, $HbA_{1c} < 7\%$)[27,28]. A major obstacle to this goal is the fear of (or the occurrence of) hypoglycaemia, which is often preceded by an unintentional accumulation of insulin in the bloodstream up to inappropriately high levels due to over-bolusing (referred to as insulin stacking, caused by the fear of not observing the expected blood glucose trend), thereby influencing the patient and the physician to initiate or augment an insulin therapy depending on the case[29]. Additionally, poor reproducibility of meal-induced fluctuations in blood levels of glucose and postprandial hyperglycaemia compensation strategies remain major challenges for automated closed-loop systems[30]. Such limited therapeutic outcomes reflect the fact that closed-loop systems currently rely solely on blood concentrations of glucose and not on the level of insulin itself or the levels of other related markers (such as cortisol, β-hydroxybutyrate, adrenaline, noradrenaline and alcohol)[14].

Currently, diabetes mellitus pharmacological treatment relies on prediction algorithm models of time–action insulin profiles[31] (Fig. 1a). During metabolic modelling studies, simulations of predicted changes in blood levels of glucose following a subcutaneous bolus of insulin are performed. The control algorithm determines the insulin responsiveness to deviations from the target glucose value. Models that have demonstrated a better performance in glucose control use equations for estimating accurate insulin dosing for meals. Parameters such as current blood level of glucose, target concentration of glucose, amount of ingested carbohydrate, insulin-to-carbohydrate ratio, insulin sensitivity factors, predicted pharmacokinetics and pharmacodynamics, insulin on board (the amount of insulin still active in the body from previous bolus doses), insulin feedback (the signalling mechanism that occurs when lowered blood levels of glucose are required) and even the incorporation of glucagon (in the case of bihormonal closed-loop-based control) are taken into consideration[14,30]. Estimation of adequate insulin dosage based on generic insulin action curves is challenging, as these often miss out on interpersonal variations such as age, weight, ethnicity, race, pregnancy, hepatic function and renal function[11,12], as well as contextual factors such as time of day, exercise, medication, sleep[32] and mental health aspects (for example, stress and depressive symptoms)[33] (Fig. 1b).

Another challenge relates to the testing protocols for assessing insulin activity. The glucose clamp method, which is considered the gold standard for evaluating the action of insulin (that is, pharmacokinetics and pharmacodynamics) in vivo[32], monitors glucose metabolism and insulin sensitivity by quantifying insulin secretion capacity (through hyperglycaemic clamping) and insulin resistance (through hyperinsulinaemic–euglycaemic clamping) under clinical settings[16]. Moreover, these assays are often limited to small groups of patients, as they involve numerous blood draws and lengthy insulin detection

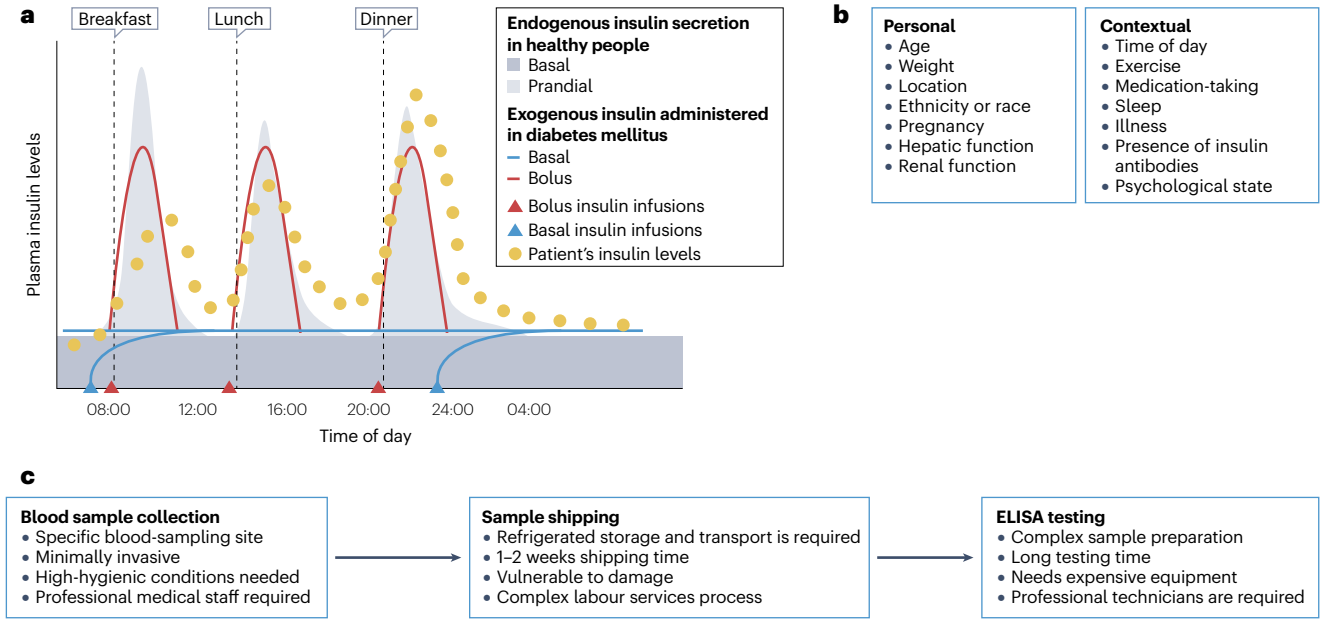

Fig. 1 | Major challenges facing insulin therapy. a, Insulin action curves are shown that correspond to natural endogenous insulin secretion in healthy people, with basal (dark grey) and prandial (light grey) insulin secretion depicted. Also shown are predicted variations in exogenous insulin (blue line, basal levels of insulin; blue triangles, basal insulin infusions; red line, bolus levels of insulin; red triangles, bolus insulin infusions) in a patient with diabetes mellitus, as well as a hypothetical example of real insulin variations (yellow dots) in a patient with diabetes mellitus who experiences insulin stacking and is at risk of hypoglycaemia. **b**, Factors affecting insulin sensitivity, which represent the main contributors to intrapersonal and interpersonal variations in response to insulin therapy. **c**, Current insulin analysis procedure in clinical practice: sample collection in the clinic by a nurse, transportation of the sample to a centralized analytical laboratory and enzyme-linked immunosorbent assay (ELISA)-based insulin analysis by trained personnel, eventually making the whole insulin testing process complex, costly and time-consuming.

protocols. Insulin is typically measured in serum or plasma samples by gold-standard enzyme-linked immunosorbent assay (ELISA) methods[34]. However, these traditional insulin assays cannot support immediate corrections and timely interventions to tackle unforeseen events from glucose imbalance, owing to long shipping and lengthy testing protocols) (Fig. 1c).

With all this in mind, the urgency to advance towards decentralized insulin measurements becomes more evident. This advance will enable clinicians to closely visualize the changing insulin concentration profiles when prescribing insulin therapy for a patient[15]. Such frequent and continuous decentralized insulin measurements would lead to effective treatment regimens, tailored to the degree of hyperglycaemia and the risks associated with hypoglycaemia for each individual[13,15,35]. Continuous measurements will capture in real time the temporal insulin profile, enabling timely interventions within a closed-loop system.

A sensor device enabling frequent decentralized insulin measurements would facilitate reliable characterization of pharmacokinetic and pharmacodynamic parameters of exogenous insulins and enhance comprehensive understanding of the factors affecting insulin action. The derived information would support and improve existing therapies towards optimal personal glycaemic control, leading to the development of new insulin analogues capable of widening the therapeutic window[11,25]. Finally, frequent or continuous point-of-care insulin measurements are critically needed to obtain a timely and accurate diagnosis and design appropriate therapies to minimize the risk to the patient of unfavourable events[34,36]. In this context, such an insulin sensor device would assist the understanding of β-cell dysfunction mechanisms and progression. This understanding will offer an improved assessment of fasting plasma levels of insulin for insulin resistance and hyperinsulinaemia in connection to metabolic syndrome[37]. Such close tracking of dynamic insulin levels will also guide optimal insulin dosing.

Current insulin measurement approaches

Laboratory-based chromatographic and electrophoretic separation methods, coupled to optical, electrochemical and mass spectroscopy detection schemes, have been used routinely over the past few decades for accurate insulin measurements in the pharmaceutical industry or in clinical research[34] (Fig. 2a). Examples of these include high-performance liquid chromatography with optical detection[38], with tandem mass spectrometry[39] or with electrochemical detection[40]; capillary zone electrophoresis coupled to either optical detection or mass spectrometry[41,42]; micellar electrokinetic chromatography[43]; and capillary gel electrophoresis[44]. Among these, mass spectroscopy-based strategies offer high specificity towards insulin and its major degradation products and analogues, along with very low limits of detection. However, such assays rely on bulky and costly equipment and demand precise sample preparation and skilled technicians in specific centralized laboratories. The growing demands for analytical devices that have ultrahigh specificity and separation ability for insulin and insulin analogues in pharmaceutical formulations and in complex biofluids have led to the incorporation of specific insulin receptors in conventional assays to achieve selective insulin enrichment or separation.

Insulin is a small globular protein with numerous active sites, 51 residues, two peptide chains and a unique secondary structure[45].

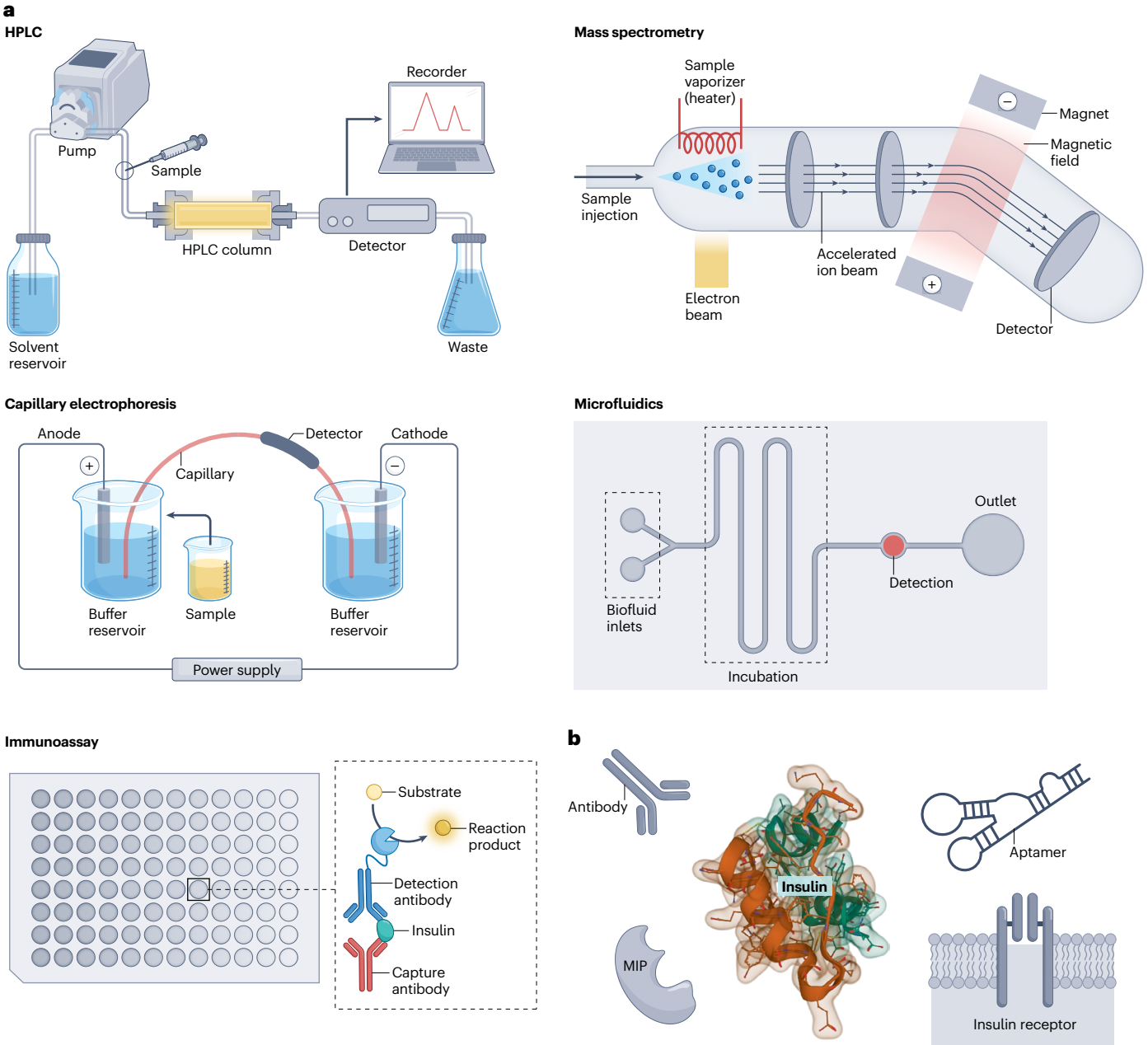

Fig. 2 | Current insulin analysis approaches used in clinical practice and clinical research. a, Conventional analytical methodologies and tools for insulin quantification used in centralized laboratory settings, including high-performance liquid chromatography (HPLC), mass spectrometry, capillary electrophoresis, microfluidics and immunoassays. Equipment for chromatography, electrophoresis and spectrometry is usually bulky and heavy and requires trained professionals for operation, whereas immunoassays and microfluidic-assisted insulin detection rely on compact equipment and facilitate hassle-free insulin monitoring. **b**, Natural and synthetic insulin receptors available for achieving highly selective insulin measurements, including antibodies, aptamers, molecularly imprinted polymers (MIPs) and insulin receptors. Part **b** is adapted from RCSB PDB number 2WFU (https://doi.org/10.2210/pdb2WFU/pdb), CC0 1.0 (https://creativecommons.org/publicdomain/zero/1.0/).

This hormone can specifically interact with distinct affinity receptors to ensure its selective capture from complex biological samples, which include antibodies[35,46], natural cell membrane receptors (such as insulin receptor)[47,48] and synthetic alternatives such as aptamers[49] or molecularly imprinted polymers (MIPs)[50] (Fig. 2b). Antibodies are Y-shaped proteins that are produced by the immune system to recognize and neutralize harmful substances and pathogens. Insulin-binding antibodies have been used in immuno-extraction protocols coupled to liquid chromatography–mass spectroscopy for quantitating insulin and its analogues[51], as affinity probes for capillary zone electrophoresis microfluidic platforms[52,53] and for commonly used insulin immunoassays. Aptamers are three-dimensional nucleic acid sequences capable

of recognizing and binding to a desired target. Aptamers have been utilized for modifying nanoparticles[54], nanocomposites[55] or microarrays[56] for highly selective insulin detection in matrix-assisted laser desorption–ionization-time of flight mass spectroscopy protocols. Aptamers offer strong binding capabilities, and they can be readily synthesized. These characteristics make aptamer-based platforms useful in insulin detection. For example, insulin-binding aptamers can interact with insulin to form insulin–insulin-binding-aptamer complexes, leading to signal changes that can be quantified by different spectroscopic techniques (for example, ultraviolet or visible light absorption, fluorescence and resonance light-scattering spectra)[57]. MIPs are synthetic receptors that possess specific imprinted recognition cavities with shape and functional groups tailored to the target analyte[58–60]. These artificial receptors have been used for fabricating solid-phase extraction cartridges coupled online with liquid chromatography insulin separation[56].

The most commonly used methods for measuring insulin in clinical labs are immunoassays. Such assays rely on confining the insulin-specific antibody onto a transducer surface, which converts the specific insulin recognition event to a measurable physical signal. Typically, these assays employ two antibodies: a primary antibody to capture insulin, followed by the formation of a sandwich-type conjugate with a secondary antibody tagged with an enzyme label that leads to a measurable signal. The most representative example of sandwich immunoassays is the ELISA method, which involves optical measurements of a colorimetric substrate of the enzyme tag[61]. Variations of these insulin immunoassays involve different transduction principles, including chemiluminescent immunoassay[62] and radio-immunoassay[63], which rely on immunoreactions that generate light and radioactivity signals, respectively. However, immunoassays have limitations, such as lengthy protocols that require a washing step and large sample volume, high background signal and lack of scalability.

These conventional methodologies are limited to centralized laboratories and specialized facilities, as they involve complex, slow assays and sample pretreatments and require bulky, costly equipment and highly skilled operators. Accordingly, these methods are not amenable for rapid decentralized insulin measurements outside of controlled lab settings and cannot provide close tracking of dynamically changing blood concentrations of insulin, as required for timely tailored intervention towards optimal insulin dosing. The pursuit of rapid decentralized insulin detection has led to major efforts towards the development of mobile and wearable insulin-sensing devices that feature high speed, simplicity and portability, with the goal of fast and frequent insulin measurements at the point of need, and will eventually lead towards continuous on-body insulin measurements.

Biosensors for decentralized insulin monitoring

Retrospective and our vision for the future

The management of diabetes mellitus could be greatly improved by translating the lessons learned from the monitoring of glucose to decentralized and on-body measurements of insulin. Based on our long experience in developing glucose sensors[21,22], we anticipate an initial introduction of self-testing blood fingerstick insulin-sensing strips for point-of-care settings and eventually for home-based monitoring. Personalized insulin meters would thus enable frequent and easy on-site insulin measurements. However, even the initial introduction of commercial in vitro insulin test strips is expected to be more challenging than common single-use glucose test strips, considering the considerably lower blood concentration of insulin, the sensitive bio-recognition elements required and the complexity of the assay protocol[35,46]. On-spot insulin testing will enable patients to intermittently track their blood levels of insulin and diabetes mellitus status[14,35]. Furthermore, this technology will allow clinicians to periodically check the health condition of the patient to identify gradual deterioration and potentially detect unforeseen events. However, fingerstick testing is invasive and might not be a feasible option for long-term operation. Moreover, if the blood levels of insulin decrease towards developing hyperglycaemia, clinicians would themselves need to deliver insulin, eventually adding manual intervention.

We envision that fingerstick blood insulin testing will be followed by the introduction of needle-based continuous insulin monitoring (CIM) for extended on-body monitoring. Such CIM devices would allow continuous dynamic tracking of subcutaneous interstitial fluid levels of insulin over long time periods. Hence, a CIM would enable clinicians to monitor and advise the patient remotely, leading to rapid alerts to unforeseen emergencies or events. An accurate CIM will enable precise insulin dosing to patients with microneedles, conventional insulin pens or syringes, at the clinic and/or in remote areas, when combined with the feedback received from the corresponding carbohydrate consumption amount and blood glucose corrections[64]. Eventually, reliable CIM operations could be integrated with automated closed-loop systems.

Looking back at decentralized glucose testing, although the CGM vision was presented in the early 1980s, it took nearly two decades for CGM to emerge as a commercial product. Although major efforts are currently being devoted to developing on-body insulin-sensing systems, key fundamental differences make the realization of an effective CIM system substantially more challenging than that of current CGM. First, unlike the millimolar blood levels of glucose, concentrations of insulin are in the picomolar range (that is, 10^9-fold lower). Second, compared to the reversible enzymatic recognition reaction of glucose, the common antibody-based recognition of insulin is not reversible. Such irreversible insulin recognition processes are particularly challenging for realizing continuous wearable sensing applications.

Emerging technologies for insulin biosensors

The desire to address existing knowledge gaps, major challenges for stable and accurate CIM, and major needs for reliable and rapid point-of-need insulin detection devices has led to increasing interest towards developing portable, simple and accurate electrochemical biosensors and microchip devices[65,66]. These miniaturized sensing devices would minimize the sample-to-answer delays and provide timely physiological information.

ELISA insulin measurement methods have been translated to a decentralized simplified electrochemical immunosensing format in which insulin is recognized by a capture antibody confined on a disposable strip-based electrode transducer[35,67–69]. Such compact electrochemical immunosensors translate this specific binding event into an electrical signal for quantitating the concentration of insulin. Similar to ELISA assays, the formation of the antibody–antigen complex is followed by the binding of a secondary enzyme-labelled antibody and electrochemical monitoring of the extent of the enzymatic reaction of the captured label. Adopting a universal slope concept (a constant calibration parameter that has enabled the development of factory-calibrated insulin chips, analogous to commercial blood glucose strips) in the electrochemical immunosensor chip has enabled calibration-free measurements of the serum concentration of insulin, which drastically reduces the assay time and costs[46]. Such strip-based calibration-free measurements could be combined with

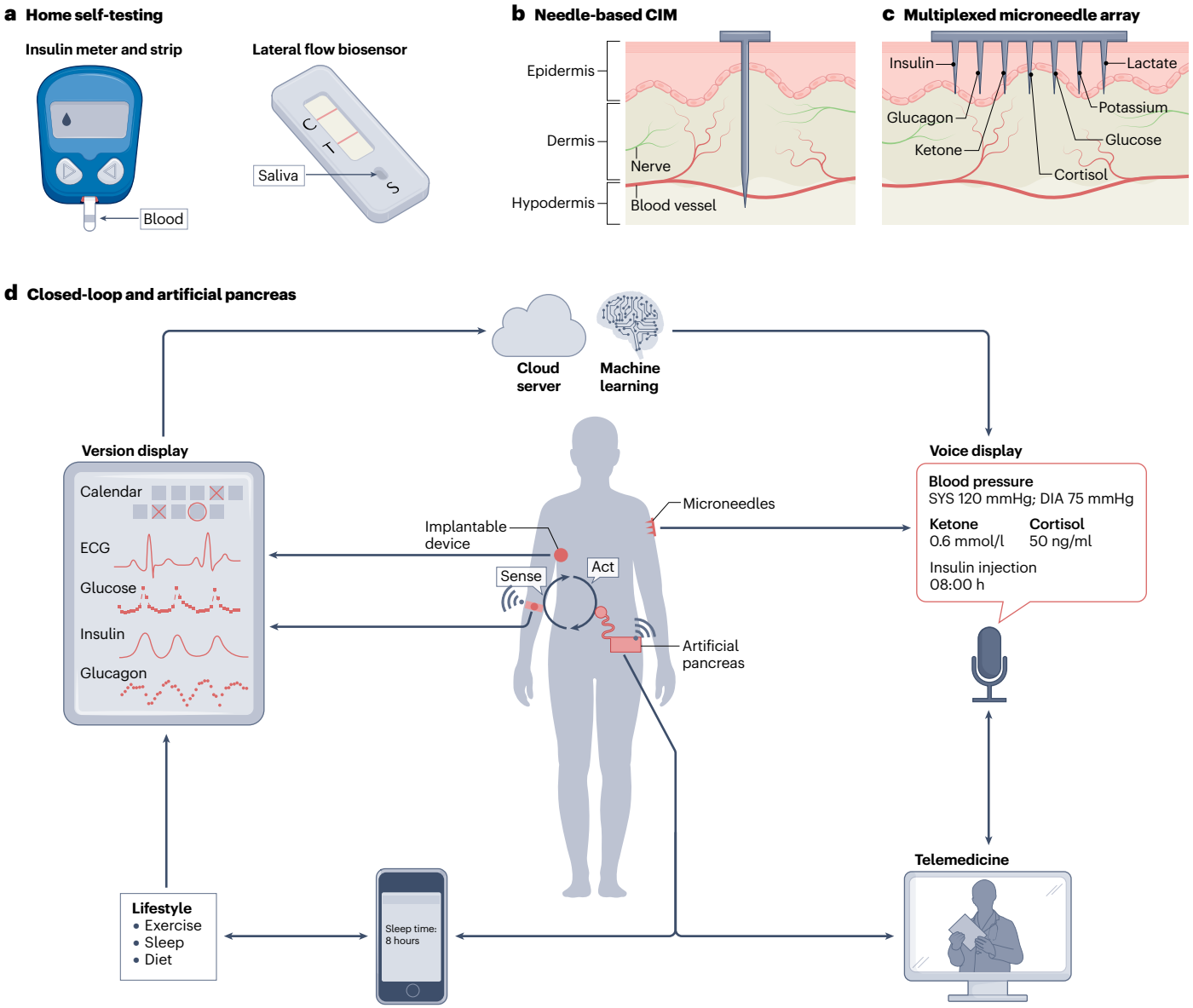

Fig. 3 | Our future vision for decentralized insulin monitoring and diabetes mellitus management. a, Advances in insulin detection technologies could lead to the development of biosensor approaches for home-based self-testing of insulin using capillary blood and saliva, for example, lateral flow tests and strip-based insulin meters. **b**, A theoretical needle-type continuous insulin monitoring (CIM) sensor device for continuous real-time insulin measurements in subcutaneous interstitial fluid. **c**, A theoretical multi-analyte microneedle sensor array for simultaneous monitoring of multiple diabetes mellitus biomarkers in interstitial fluid. **d**, In the future, we envision the development of personalized closed-loop autonomous artificial pancreas 'sense–act' systems that integrate wearable devices for diabetes mellitus care (biosensors and insulin pumps) within an 'Internet of things' (interconnection of devices via the Internet for sharing and managing data) platform. The system relies on multimodal sensory chemical and physical inputs and a multitude of personal variables (regarding meals, exercise and other activities), along with data-driven machine-learning decision-making algorithms towards optimal (timely and accurate) personalized insulin dosing and efficient glucose regulation. C, control line; DIA, diastolic; ECG, electrocardiogram; S, sample well; SYS, systolic; T, test line.

a hand-held insulin meter[46], similar to the existing blood glucose meters (Fig. 3a). However, these enzyme-based immunosensor strips will be initially limited to health clinics or hospital settings because they require trained personnel and involve multiple washing steps. These in vitro insulin immunosensor tests could help clinicians to track both endogenous and exogenous blood levels of insulin in patients more quickly than with currently available assays (a few minutes versus a few weeks) and guide them to evaluate treatment efficacy. Fast and simple home self-testing of insulin could be realized using label-free electrochemical immunosensors (measuring electrical signal changes induced by insulin binding, with no need for enzymatic tags)[70] or with paper-based lateral flow devices[71]. These user-friendly, low-cost lateral flow assays involve a highly sensitive nanoparticle-based colorimetric immunoassay format (such as those used in COVID-19 home tests)

and could permit convenient on-site insulin testing in remote and low-resource areas.

Unlike antibodies, aptamer bioreceptors can be used for reversible and reagentless detection of a target factor, and hence hold considerable promise for continuous on-body insulin detection. In particular, electrochemical aptamer-based sensing platforms offer rapid, label-free detection enabled by the binding-induced folding of an immobilized aptamer receptor with a redox tag in the presence of the target analyte[72]. Specific insulin binding to the immobilized aptamer could thus induce conformational switching and lead to a different rate of electron transfer between the redox reporter and an electrode. The corresponding current change could thus determine the concentration of insulin in complex biofluids. Such aptamer-based electrochemical biosensing holds promise for future CIM in the subcutaneous interstitial fluid (ISF) (Fig. 3b). However, before establishing ISF-based CIM, the correlation between the concentration of insulin in ISF and blood needs to be studied via established clinical detection strategies.

Artificial MIP receptors have also shown promise for highly sensitive, low-cost decentralized insulin measurements[73,74]. Efforts in 2022 towards developing wearable stimuli-responsive reversible MIP sensors for continuous metabolites and nutrients monitoring look encouraging for the future emergence of wearable CIM devices[75,76]. Realizing accurate ultrasensitive continuous aptamer and MIP-based on-body insulin monitoring would require extensive future efforts to tackle major sensitivity and stability challenges. Future in vivo applications of such artificial insulin receptors would require careful assessment of their potential toxicity (even when using a reagentless device and biocompatible receptors) for ensuring stable surface confinement (essential also for high stability). Following the realization of a reliable CIM system, we envision the development of minimally invasive multiplexed microneedle sensor arrays for continuous simultaneous monitoring of multiple diabetes mellitus biomarkers (Fig. 3c). Such a future microneedle array will integrate reagentless aptamer-based insulin, cortisol and glucagon sensors alongside enzymatic sensors for additional analytes (for example, ketone, glucose, lactate and alcohol). Highly integrated minimally invasive microneedle sensor arrays have been introduced recently, demonstrating simultaneous real-time sensing of several metabolites (lactate, glucose and alcohol) during common daily activities, with no crosstalk between the neighbouring microneedle sensors[77].

Conclusions

The new real-time insulin-sensing capabilities discussed in this article will offer useful insights into temporal insulin profiles and trends that are expected to guide optimal insulin dosing towards effective diabetes mellitus management. Creating a personalized fully automated closed-loop system is critical for achieving the goal of normal glycaemia. The development of such a closed-loop system towards effective diabetes mellitus management requires the rational integration of different sensing modalities, along with the insulin pump and a cloud-based control algorithm. Although tremendous progress has been made in glucose-monitoring insulin delivery devices and advanced machine-learning control algorithms towards optimal insulin dosing[78–81], considerable efforts are yet to be made for offering tailored and accurate insulin dosing.

We envision a personalized artificial pancreas system for effective day-and-night individual diabetes mellitus management[82], ideally comprising a personalized sensor network; logged-in information about meals, daily activities (such as exercise) and psychosocial information (such as anxiety, sleep hours and eating habits); an insulin pump; and advanced electronics for wireless data transfer and management[78,83–85] (Fig. 3d). This future artificial pancreas system would benefit from the simultaneous operation of various biophysical sensors that continuously measure blood pressure[86], heart rate[87], step count (via a pedometer), movement (via an accelerometer) or oxygen saturation[88] in parallel to glucose and insulin sensing, along with manual entry of psychosocial information. Such comprehensive analysis will generate useful insights about the correlation of glucose with these other parameters[89], which could help clinicians to gain a better understanding of patients with diabetes mellitus. The inclusion of features such as smart meal detection technology (capable of measuring how fast and how much the individual consumes), swallowing behaviour and image-based interpretation of the nutritional composition of meals, along with details of daily physical activity, will be useful additions for overall decision-making[90–93]. Furthermore, interpretation of results through data processing, via advanced machine-learning algorithms and calibration-free detection strategies, will enable artificial pancreas systems to be deployed under decentralized settings with intelligent decision-making, proving particularly useful for children and older adults[79,83,90].

One should note, however, that we still have a long way to go in terms of achieving clinically manageable and actionable insulin data and connecting it to clinical care. The massive amount of real-time rich biological information and personal lifestyle data obtained with this proposed theoretical device would require critical validation in centralized clinical laboratories before translating the information into practical care[78,83–85]. Also, processing the rich acquired data with cloud-based machine-learning algorithms will be used for predicting temporal trends and supporting efficient decision-making towards tailored, accurate and timely insulin dosing and efficient personalized glucose regulation[83,94–96]. Data privacy and security remains a major concern in closed-loop-system health-care services. With the increase in data management platforms, multilayered security strategies are critical for preventing privacy data leakage and remote hacking[97]. Overall, the robustness and effective operation of such closed-loop systems will rely on the effective integration of all of the above-mentioned technologies. Our envisioned artificial intelligence-assisted next-generation closed-loop system would help with tracking the insulin dynamics in the body for providing tailored optimal insulin dosages.

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