

# Nano enabled Biosensors for Early Diagnosis and Continuous Monitoring of Obesity-Related Diabetes

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## ABSTRACT

Obesity-associated diabetes (largely type 2 diabetes mellitus, T2DM) is a global public-health challenge driven by rising prevalence of obesity and metabolic dysfunction. Early diagnosis and continuous metabolic monitoring are essential to prevent complications, personalise therapy and enable timely lifestyle or pharmacologic interventions. Nano-enabled biosensors devices that integrate nanomaterials (gold, graphene, carbon nanotubes, metal oxides, conductive polymers, etc.) with biochemical recognition elements—offer major advances in sensitivity, selectivity, response time, miniaturization, and compatibility with wearable platforms. This review synthesizes recent advances in nanomaterial-enhanced sensing modalities for glucose and complementary obesity-related biomarkers (adipokines, insulin, inflammatory cytokines, HbA1c), highlights non-/minimally-invasive sample matrices (interstitial fluid, sweat, saliva, tears), and examines integrated wearable architectures (microneedles, patches, e-textiles, organic electrochemical transistor-based sensors). We discuss data handling, multiplexing, power strategies, clinical validation requirements and regulatory hurdles, and propose future directions—multiplexed panels for metabolic phenotyping, closed-loop systems coupling sensing to therapeutics, self-powered sensors, and AI-driven analytics. Nano-enabled biosensors hold realistic potential to transform screening, early diagnosis, and long-term monitoring of obesity-related diabetes, but clinical translation will require coordinated progress in standardization, calibration, biocompatibility, and regulatory pathways.)

**Keywords:** nano-biosensor, continuous glucose monitoring, wearable sensors, adipokines, microneedle patch

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## INTRODUCTION

Obesity and its associated metabolic disorders, particularly type 2 diabetes mellitus (T2DM), represent one of the most pressing public health challenges of the twenty-first century[1–3]. At the core of these conditions lies a complex interplay of metabolic disturbances including chronic hyperglycaemia, persistent insulin resistance, and aberrant adipose tissue signaling[4, 5]. In obese individuals, adipose tissue does not simply act as a passive energy storage site but functions as an endocrine organ, secreting a wide range of adipokines and cytokines that modulate insulin sensitivity, appetite, inflammation, and lipid metabolism. Dysregulation of these secretory functions promotes chronic low-grade inflammation and exacerbates insulin resistance, gradually pushing individuals toward glucose intolerance and overt diabetes[6–8]. Obesity.

The clinical burden of obesity-related diabetes is not confined to elevated blood sugar levels but extends to long-term complications such as cardiovascular disease, nephropathy, neuropathy, and retinopathy[9, 10]. Preventing these sequelae requires early detection of dysglycaemia before irreversible damage occurs[11, 12]. Unfortunately, traditional diagnostic approaches such as fasting plasma glucose testing, oral glucose tolerance tests, and HbA1c measurement offer only static, point-in-time data. These methods can confirm the presence of hyperglycaemia but fail to capture the dynamic fluctuations in blood glucose that occur throughout the day and night. More importantly, they are poorly suited for early, continuous risk stratification in obese individuals who may be progressing toward diabetes long before standard diagnostic thresholds are reached. As a result, many patients remain undiagnosed until significant metabolic dysfunction has already set in, limiting the effectiveness of lifestyle or pharmacological interventions[13].

The introduction of continuous glucose monitoring (CGM) systems has marked a significant advance in diabetes management by providing real-time, dynamic glycaemic profiles. These devices, typically worn on the skin with a sensor inserted into interstitial fluid, allow patients and clinicians to observe how glucose levels respond to meals, exercise, medication, and stress. CGMs have been shown to improve glycaemic control, reduce hypoglycaemic episodes, and empower patients through increased awareness of their metabolic state[14]. Yet,

despite their success, most commercially available CGMs remain semi-invasive, relying on microneedles or small subcutaneous probes that require regular replacement. Moreover, their focus is narrowly confined to glucose, leaving out the broader spectrum of metabolic markers that underlie the pathophysiology of obesity-related diabetes[15].

This gap has stimulated growing interest in technologies capable of multiplexed metabolic monitoring. Beyond glucose, parameters such as circulating adipokines, inflammatory cytokines, and metabolic byproducts provide crucial insights into the trajectory from obesity to diabetes[16]. Capturing these signals continuously and noninvasively could enable earlier diagnosis, better risk stratification, and more personalized interventions. Recent advances in nanomaterials have accelerated this vision by enhancing the sensitivity, selectivity, and stability of biosensors. Nanostructured materials such as graphene, carbon nanotubes, quantum dots, and metallic nanoparticles can be engineered to increase surface area for biomolecule binding, improve electron transfer for signal transduction, and enable miniaturization without sacrificing performance[17]. These properties open the door to wearable, portable, and implantable biosensors that are both highly sensitive and user-friendly.

New form factors are also emerging as nanotechnology converges with flexible electronics and smart textiles[18]. Skin patches embedded with nanosensors, microneedle arrays capable of painless interstitial fluid sampling, and e-textiles that integrate biosensing into everyday clothing illustrate the possibilities. Such devices could unobtrusively monitor multiple biomarkers in sweat, saliva, tears, or interstitial fluid, providing a continuous metabolic picture far richer than glucose alone. In the context of obesity and T2DM, this evolution is particularly significant, as early detection of inflammatory or adipokine imbalances could identify high-risk individuals even before hyperglycaemia emerges[19]. Real-time, multi-analyte data could further guide personalized therapeutic strategies, whether in dietary modifications, exercise regimens, or pharmacological interventions[20].

Ultimately, the convergence of nanotechnology, biosensing, and wearable health platforms has the potential to transform how obesity-related diabetes is diagnosed and managed. While current CGM systems have demonstrated the benefits of continuous glucose tracking, the future lies in noninvasive, multiplexed, and user-friendly devices capable of capturing the full metabolic signature of disease progression[21, 22]. Such technologies could shift the paradigm from reactive management of established diabetes to proactive prevention in at-risk obese populations, thereby reducing morbidity, healthcare costs, and the long-term burden of metabolic disorders[22].

## **2. Biomarkers Relevant to Obesity-Related Diabetes and Sensing Targets**

The identification and continuous monitoring of appropriate biomarkers form the foundation of early diagnosis and personalized management of obesity-related diabetes. Glucose remains the central metric in both diagnosis and therapy, as chronic hyperglycaemia is the defining feature of diabetes[23]. However, glucose levels fluctuate substantially in response to meals, stress, and physical activity, which underscores the value of continuous monitoring rather than episodic measurements. Interstitial fluid, sweat, and saliva provide accessible sources of glucose data and are increasingly targeted by noninvasive sensing platforms. Yet glucose alone cannot fully capture the complexity of metabolic dysfunction in obesity, making the inclusion of complementary biomarkers essential[24, 25].

Among longer-term glycaemic exposure markers, HbA1c and glycated albumin offer insights into average blood glucose levels over weeks to months. HbA1c reflects glycation of hemoglobin over a roughly three-month period, making it useful for long-term monitoring, while glycated albumin provides a shorter two- to three-week window[26]. Integrating these markers into biosensing systems could complement real-time glucose data, offering a fuller picture of both acute and chronic glycaemic control[27]. Advances in nanomaterial-based sensors capable of detecting glycated proteins from small fluid samples hold promise for point-of-care or wearable formats.

Another critical dimension involves assessing pancreatic beta-cell function, which can be inferred from insulin and C-peptide measurements. Insulin levels indicate both secretion capacity and exogenous replacement therapy, whereas C-peptide, secreted in equimolar amounts with endogenous insulin, provides a clearer picture of intrinsic beta-cell activity[28]. Monitoring these markers could distinguish between insulin resistance and insulin deficiency, enabling more precise therapeutic strategies. Incorporating insulin or C-peptide sensing into multiplexed biosensors could therefore extend their diagnostic value far beyond glucose tracking[28].

Adipokines such as adiponectin, leptin, resistin, and visfatin are equally important, as they reflect the endocrine dysfunction of adipose tissue that drives much of obesity-related metabolic disease. Adiponectin, which improves insulin sensitivity, is typically reduced in obesity and inversely correlated with T2DM risk. Leptin, conversely, is elevated in obesity, often leading to leptin resistance, while resistin and visfatin are associated with inflammation and impaired glucose homeostasis[29]. Incorporating adipokine monitoring into wearable biosensors could provide early warnings of metabolic imbalance well before hyperglycaemia appears, positioning them as key prognostic markers in obese populations[29].

Low-grade systemic inflammation also plays a decisive role in linking obesity to diabetes, making inflammatory cytokines attractive sensing targets. Interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF- $\alpha$ ), and C-reactive protein (CRP) are among the most relevant. Elevated concentrations of these molecules contribute to insulin

resistance, endothelial dysfunction, and progressive metabolic decline[30]. Early detection of inflammatory upregulation could signal an increased risk of diabetes and related complications, offering opportunities for earlier intervention. Nanostructured biosensors capable of detecting cytokines in sweat or interstitial fluid are under active development and could soon be incorporated into continuous monitoring devices[31].

Finally, metabolic byproducts such as lactate, ketones, and uric acid serve as valuable adjuncts in contextualizing glycaemic data. Lactate reflects tissue oxygenation and exercise response, ketones indicate shifts toward fat metabolism in the context of insulin deficiency, and uric acid levels correlate with oxidative stress and cardiovascular risk. Together, these markers provide contextual depth to glucose readings, offering a more nuanced view of a patient's metabolic status[32].

In selecting biomarkers for early diagnosis and monitoring, several practical considerations arise. Clinical relevance must be balanced against the biomarker's concentration range in accessible fluids and the technical feasibility of detection. For example, while adipokines and cytokines offer early insights, their concentrations are typically low in sweat or saliva, necessitating highly sensitive nanomaterial-based transducers[33]. Meanwhile, glucose and lactate occur at higher levels, making them more amenable to detection with current technologies. Ultimately, the design of effective biosensors depends on aligning the biomarker panel with both clinical needs and the capabilities of the sensing platform[34].

By combining glucose with markers of glycaemic exposure, insulin secretion, adipose tissue dysfunction, inflammation, and metabolic byproducts, next-generation biosensors could provide an unprecedented window into the metabolic health of obese individuals[35, 36]. This multi-analyte approach would not only improve early diagnosis but also enhance personalization of therapy, shifting the clinical focus from reactive management of overt diabetes to proactive prevention and risk stratification.

### 3. Nanomaterials and Sensing Modalities

**3.1 Electrochemical (enzymatic and non-enzymatic) sensors:** Electrochemical sensors are the most widely used platforms for glucose monitoring because they combine sensitivity, reliability, and straightforward design. Enzymatic glucose oxidase (GOx)-based electrodes dominate, with nanomaterials such as gold nanoparticles, carbon nanotubes, graphene, and metal oxide nanosheets enhancing electron transfer, surface area, and catalytic efficiency[37]. These features improve sensitivity, reduce detection limits, and allow faster response. Non-enzymatic alternatives based on noble metals or transition-metal catalysts provide enzyme-free stability, though they remain vulnerable to interference, biofouling, and long-term surface degradation[38].

**3.2 Field-effect and organic electrochemical transistors (FET/OECT):** FET and OECT devices translate small biochemical changes into amplified electronic signals, enabling real-time glucose monitoring with high sensitivity. Their nanoscale channels enhance signal gain, while OECTs' ion-to-electron transduction allows efficient detection of glucose in interstitial fluids[39]. Recent innovations integrate OECTs with microneedles or hydrogel-based sampling platforms, providing low-power, flexible, and compact designs suitable for continuous on-body use. These coin-sized CGM systems are particularly promising for wearable healthcare, combining user comfort, portability, and improved analytical accuracy in minimally invasive formats.[40]

**3.3 Optical (fluorescence, plasmonic) sensors:** Optical nanosensors exploit fluorescence and plasmonic effects of nanostructures for highly sensitive and multiplexed glucose detection. Gold and silver nanostructures enable surface-enhanced Raman scattering (SERS), while quantum dots and fluorescent nanomaterials detect biomolecules with excellent signal-to-noise ratios[41]. These approaches are label-free, rapid, and can simultaneously track multiple analytes, extending beyond glucose to cytokines and metabolites. Integration into smart patches or contact lenses offers noninvasive monitoring, though challenges include miniaturizing optics and ensuring portable readout systems suitable for everyday, real-world clinical and personal healthcare use[42].

**3.4 Microneedles and minimally invasive sampling:** Microneedle-based platforms are gaining traction as a minimally invasive strategy for continuous glucose monitoring. Fabricated from metals, polymers, or hydrogels, microneedles painlessly penetrate the skin to access interstitial fluid, offering stronger correlation with plasma glucose compared to sweat-based monitoring[43]. When combined with nano-modified electrodes or OECTs, they enable real-time analyte detection with high accuracy. These systems support integration into closed-loop devices where sensing is directly coupled with insulin delivery, advancing next-generation wearable therapeutics for diabetes management with improved compliance and patient comfort[43].

**3.5 Self-powered nanogenerators & triboelectrics:** To enhance long-term usability of wearable glucose sensors, energy-harvesting technologies are being incorporated. Triboelectric nanogenerators and biofuel cells convert mechanical movements, body fluids, or biochemical reactions into electrical energy to sustain sensor operation[44]. This eliminates frequent battery replacements, reducing device maintenance and improving patient convenience. Integration of such self-powered systems with nanostructured sensing modules enables continuous monitoring in fully autonomous devices. By coupling power generation with data transmission, these platforms pave the way for next-generation, energy-independent wearable diagnostics for diabetes care[45].

**4. Noninvasive Matrices: Sweat, Saliva, Tears, and Interstitial Fluid:** The use of noninvasive biological matrices such as sweat, saliva, tears, and interstitial fluid (ISF) is increasingly explored in glucose and biomarker monitoring due to their ability to enhance patient comfort and adherence[46]. Sweat is particularly attractive because of its easy accessibility, making it suitable for continuous monitoring through wearable skin patches.

However, sweat glucose levels are typically lower than those in plasma and can be influenced by secretion rate, skin pH, and salt concentration[47]. To address these variables, recent devices employ multi-sensor compensation systems that incorporate temperature, pH, and humidity monitoring. Technologies such as laser-induced graphene and nanocomposite electrodes have shown stability and accuracy for several weeks in sweat glucose tracking. ISF represents another promising matrix since it correlates closely with blood glucose and is already utilized in most commercial continuous glucose monitoring (CGM) systems, often accessed via microneedles or subdermal sensors. In contrast, saliva and tears offer the advantage of minimal invasiveness but present analytical difficulties due to their lower biomarker concentrations, necessitating the use of highly sensitive nanostructured sensors[48]. Ultimately, the choice of matrix reflects trade-offs between invasiveness, biomarker concentration, temporal resolution, and calibration requirements, highlighting the importance of sensor adaptability to physiological variability.

**5. Wearable and Integrated Platforms:** Wearable and integrated sensor platforms are redefining how metabolic monitoring and diabetes management are approached, reflecting a convergence of nanotechnology, flexible electronics, and digital health systems. Skin-mounted patches and e-textiles exemplify this shift, enabling continuous glucose and biomarker tracking with minimal disruption to daily life[49]. These devices incorporate nanostructured electrodes into flexible substrates that conform to the skin, while textile-based sensors can be seamlessly integrated into clothing, supporting long-term lifestyle monitoring. Microneedle-based patches extend functionality by offering minimally invasive access to ISF, coupled with nanoelectrode transduction for precise glucose and insulin measurement. Some innovative designs even integrate controlled thermal or electrochemical actuation to allow on-demand drug delivery, merging diagnostics with therapy[50]. Beyond single-analyte detection, multiplexed panels capable of measuring glucose alongside adipokines or cytokines provide richer insights into metabolic states, enabling early identification of obesity progression to diabetes[51]. These platforms are further enhanced by wireless connectivity, with Bluetooth or near-field communication transmitting data to smartphones or cloud-based systems, where AI algorithms identify glycaemic patterns and predict insulin resistance. While CGM systems are clinically validated and increasingly accessible, noninvasive nano-enabled devices, particularly those using sweat, still face challenges in reproducibility, calibration, and regulatory approval, limiting their widespread clinical adoption.

### **6. Multiplexed Sensing: Why Panels Matter in Obesity-Related Diabetes**

The progression from obesity to type 2 diabetes is rarely a single-marker phenomenon but rather a complex interplay of hormonal, inflammatory, and metabolic signals. Adipose tissue, once considered merely an energy reservoir, becomes an active endocrine organ in obesity, secreting adipokines such as leptin, adiponectin, resistin, and pro-inflammatory cytokines[52]. These biomolecules shift long before overt hyperglycaemia is detected, and their early alterations may herald the onset of insulin resistance and chronic low-grade inflammation. Relying on single biomarker monitoring, such as glucose alone, may therefore miss critical windows of intervention[53]. Multiplexed nano-biosensors, capable of simultaneously quantifying glucose alongside adipokines, insulin, and inflammatory mediators, provide a far richer picture of metabolic dysfunction. By combining evidence of adipokine imbalance with intermittent hyperglycaemic excursions, these systems can flag at-risk individuals before diabetes is clinically manifest, enabling timely lifestyle modifications or targeted pharmacological treatment[53]. Technological innovations drive this capability: nanomaterial functionalization through immobilized antibodies, aptamers, and molecularly imprinted polymers allows selective recognition of diverse analytes within complex biofluids. Microfluidic routing further enables the parallel analysis of multiple biomarkers from a single drop of sweat, saliva, or interstitial fluid, while integration into wearable devices provides continuous, real-time monitoring. Ultimately, multiplexed sensing platforms represent a paradigm shift in managing obesity-related diabetes by moving from glucose-centric to systems-level metabolic surveillance.

### **7. Key Challenges to Translation**

Although multiplexed and nano-enabled biosensors have demonstrated strong potential in preclinical and proof-of-concept studies, translating these devices into everyday clinical use remains challenging[54]. One of the foremost obstacles is analytical accuracy, particularly in noninvasive matrices such as sweat, saliva, and tears, where biomarker concentrations are significantly lower than in blood. In addition, electroactive interferents, pH fluctuations, and ionic strength variations complicate selective detection, demanding sophisticated signal processing and compensation algorithms[55]. A second issue is biofouling and device stability. Prolonged skin contact or continuous exposure to biofluids introduces proteins, salts, and microbial contaminants that can degrade sensor performance over time. Surface modifications, antifouling coatings, and biocompatible materials are critical for maintaining long-term functionality[55]. Standardization and calibration protocols are also lacking, with no universally accepted benchmarks for correlating noninvasive readouts to gold-standard plasma values. This complicates regulatory review and limits the comparability of results across clinical studies. User-related factors further constrain adoption: wearable sensors must balance adhesion, comfort, breathability, and minimal skin irritation while maintaining consistent performance. Beyond technical considerations, regulatory and reimbursement pathways remain underdeveloped. Demonstrating safety, clinical benefit, and cost-effectiveness is essential for obtaining regulatory clearance and securing insurance coverage. Without such validation, clinical uptake will remain slow despite promising laboratory prototypes.

## 8. Opportunities & Future Directions

Despite these challenges, the field of nano-enabled biosensors for obesity-related diabetes is rich with opportunities that could transform management strategies. A major frontier is the integration of sensing platforms into closed-loop therapeutic systems, where continuous biomarker monitoring directly informs automated drug delivery. For example, microneedle-based insulin depots or thermally triggered release systems can be activated in real time according to glucose or multi-analyte signals, tailoring therapy to obese patients' fluctuating insulin sensitivity. Another promising direction is the development of self-powered devices through nanogenerators such as triboelectric harvesters or enzymatic biofuel cells, which harness energy from body motion or metabolic substrates to extend operational lifetime without external charging. Personalized metabolic phenotyping also stands out as a transformative application. By combining streams of continuous biosensor data with individual genomics, epigenetics, and microbiome profiles, researchers can stratify patients into metabolic subtypes and design truly individualized interventions. On the translational side, regulatory science must keep pace, with consensus-driven validation standards for noninvasive biosensors—such as correlating sweat or interstitial fluid measurements with plasma values and establishing calibration frequency. Establishing such frameworks will accelerate clinical adoption and inspire confidence in both regulators and clinicians. Finally, large-scale, affordable manufacturing remains a cornerstone for population-level deployment. Emerging nanofabrication techniques, including roll-to-roll printing of flexible electrodes and laser-induced graphene synthesis, can dramatically reduce costs, making wearable multiplexed biosensors viable for widespread screening and preventive healthcare programs. Together, these opportunities illustrate how the field can move beyond prototypes toward practical, scalable, and patient-centered solutions.

### CONCLUSION

Nano-enabled biosensors are poised to broaden the scope of metabolic monitoring from single-analyte glucose tracking to multiplexed, continuous metabolic phenotyping—particularly valuable for early diagnosis and monitoring of obesity-related diabetes. Advances in nanomaterials, microneedle sampling, OECT/FET amplification, and wearable integration have generated compelling prototypes; however, clinical translation requires coordinated progress on accuracy, durability, validation standards, regulatory pathways and equitable deployment. With rigorous real-world validation and thoughtful systems design, nano-biosensors could enable earlier detection, personalized interventions, and new closed-loop paradigms for managing obesity-related diabetes.

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