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Nanodiagnostics for Early Detection of Metaflammation in Obesity-Associated Diabetes

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ABSTRACT

Obesity-associated type 2 diabetes is now recognized as a state of chronic, low-grade metabolic inflammation, or metaflammation, driven by adipose tissue immune activation, ectopic lipid deposition, gut dysbiosis, and oxidative stress. This inflammatory tone often precedes overt hyperglycemia and structural complications, suggesting that early detection of metaflammation could refine risk stratification and enable preventive intervention. However, current clinical markers such as fasting glucose, HbA1c and standard lipid panels are relatively insensitive to early inflammatory shifts and provide limited spatial or temporal resolution. Emerging nanodiagnostic technologies leverage the unique optical, electrical, magnetic and catalytic properties of nanomaterials to detect inflammatory biomarkers at ultra-low concentrations in small, minimally invasive samples. Metal, carbon, polymeric and hybrid nanostructures can be integrated into biosensors, imaging probes and wearable devices to quantify cytokines, adipokines, acute-phase proteins, microRNAs, exosomes and oxidative stress products associated with metaflammation in obesity and diabetes. These platforms offer high sensitivity, multiplexing capacity and potential for real-time monitoring in blood, interstitial fluid, saliva, sweat and breath. This review outlines the biological basis of metaflammation in obesity-associated diabetes, the evolving biomarker landscape, and the main classes of nanodiagnostic platforms. It highlights preclinical and early translational evidence, discusses technical and regulatory challenges including specificity, standardization and nanotoxicology, and explores future directions such as point-of-care multiplex panels, integrated wearables and AI-assisted interpretation. By enabling earlier and more precise detection of metaflammation, nanodiagnostics may support personalized prevention and more efficient management of obesity-associated diabetes.

Keywords: Metaflammation; obesity-associated diabetes; nanodiagnostics; inflammatory biomarkers; nanobiosensors

INTRODUCTION

Obesity-associated diabetes is not merely a disorder of glucose homeostasis; it is a chronic immunometabolic disease in which excess nutrient load, adipocyte hypertrophy and insulin resistance drive a persistent, low-grade inflammatory response termed metaflammation[1–3]. Metaflammation differs from classical acute inflammation in both amplitude and chronicity. It is subtle yet sustained, emerging within metabolic organs such as adipose tissue, liver, skeletal muscle and pancreatic islets, and spilling into the circulation as a modest elevation of inflammatory cytokines, adipokines and acute-phase proteins[4]. This state is increasingly recognized as a causal driver of insulin resistance, β-cell stress and vascular dysfunction rather than a mere epiphenomenon.

Longitudinal and mechanistic studies show that markers of low-grade inflammation, including interleukin-6 (IL-6), C-reactive protein (CRP) and tumor necrosis factor-α (TNF-α), are elevated in individuals with obesity long before diabetes is clinically diagnosed and independently predict incident type 2 diabetes[5–8]. Adipose tissue macrophages, particularly pro-inflammatory subsets that secrete IL-1β, TNF-α and osteopontin, accumulate early as adipocytes enlarge and become stressed, providing a local inflammatory source that is reflected in circulating biomarkers. Parallel changes occur in liver, muscle and gut, where immune cells and stromal elements undergo metabolic reprogramming toward a pro-inflammatory phenotype. Collectively, these processes precede and promote the transition from obesity to overt diabetes. Detecting metaflammation at this

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pre-diabetic stage could therefore identify high-risk individuals who might benefit most from targeted lifestyle or pharmacologic interventions[9–12].

Conventional diagnostics in obesity-associated diabetes remain dominated by glycemic indices such as fasting glucose, oral glucose tolerance tests and HbA1c. While useful, these parameters capture the glycemic consequence of underlying immunometabolic disruption rather than the inflammatory process itself[13, 14]. They may remain within the "normal" or borderline range while subclinical metaflammation is already active, especially in younger individuals or those with intermittent weight cycling. Traditional inflammatory markers like CRP offer better coverage but lack specificity for metabolic inflammation and are influenced by infections and other comorbidities. A growing list of candidate biomarkers, including adipokines, microRNAs (miRNAs), exosomal cargo and metabolomic signatures, has been proposed to complement classical measures and improve early detection[15, 16]. However, many of these are present at very low concentrations, require multiplex quantification and exhibit subtle changes over time, which challenge conventional immunoassays and clinical chemistry platforms.

Nanodiagnostics offer a compelling solution to these limitations. Nanomaterials display size-dependent quantum, plasmonic, catalytic and magnetic properties that dramatically boost signal generation and transduction in biosensors and imaging agents[17–19]. Gold nanoparticles, quantum dots, carbon nanotubes, graphene derivatives, polymeric nanospheres and metal–organic frameworks can be engineered to present large surface areas for biomolecule immobilization, facilitate electron transfer and generate intense optical or electrical signals upon analyte binding[20]. As a result, nanobiosensors routinely achieve femtomolar to picomolar detection limits for proteins, nucleic acids and metabolites, far surpassing conventional ELISA and often enabling label-free, real-time measurements.

For metaflammation in obesity-associated diabetes, this means that subtle rises in IL-6 or TNF-α, shifts in miRNA expression or changes in oxidative stress markers could be detected earlier and from smaller sample volumes, including capillary blood, saliva or sweat. Furthermore, the modularity of nanomaterials supports multiplexed detection: different capture probes can be attached to distinct nanoparticles or spatially separated on a single platform, allowing simultaneous profiling of complex inflammatory signatures[21, 22]. Wearable or minimally invasive devices incorporating nanosensors in patches, microneedles or textiles make continuous or high-frequency monitoring feasible in free-living individuals, capturing dynamic patterns rather than single time points.

The concept of early nanodiagnostic detection of metaflammation fits well within a precision prevention framework for obesity-associated diabetes. Individuals could be classified according to inflammatory risk signatures that reflect adipose tissue stress, gut–liver axis perturbation or islet immune activation, even when glycemia remains in the prediabetic range[23]. This would inform intensity of lifestyle interventions, selection of anti-inflammatory or incretin-based therapies, and frequency of monitoring. In established diabetes, nanodiagnostics could support more granular phenotyping of the inflammatory state, guiding adjunct immunomodulatory treatments and monitoring response[23]. They might also be deployed in weight-loss programs or bariatric surgery follow-up to gauge resolution of metaflammation independent of weight change alone.

Nevertheless, enthusiasm must be balanced with a clear understanding of the current evidence base, technical hurdles and safety considerations. Nanomaterials themselves can elicit inflammatory or oxidative responses if not carefully engineered, and regulatory pathways for diagnostic nanodevices remain evolving. In the following sections, we examine the biological underpinnings of metaflammation in obesity-associated diabetes, the biomarker landscape that nanodiagnostics seek to capture, and the main technological platforms being developed to measure these signals in a clinically relevant, scalable fashion.

2.Molecular and Cellular Basis of Metaflammation in Obesity-Associated Diabetes

Metaflammation arises when nutrient excess, particularly from high-fat and high-sugar diets, overwhelms the storage and buffering capacity of adipose tissue and other metabolic organs[24]. Adipocytes expand in size, outstripping their vascular supply and developing local hypoxia, oxidative stress and endoplasmic reticulum stress. These stress signals, in combination with lipotoxic metabolites such as ceramides and diacylglycerols, activate intracellular inflammatory pathways including JNK, IKK/NF-κB and inflammasomes. The result is increased production of chemokines and cytokines that recruit immune cells and reinforce inflammatory signaling[25].

Adipose tissue macrophages are central effectors in this process. In lean adipose tissue, macrophages are relatively sparse and skewed toward an anti-inflammatory profile[11, 26, 27]. With obesity, macrophages accumulate, often forming crown-like structures around dying adipocytes, and adopt a more pro-inflammatory phenotype characterized by secretion of TNF-α, IL-1β and IL-6, as well as expression of markers such as osteopontin and CD163. These mediators interfere with insulin signaling in adipocytes and systemic metabolic organs, disrupting glucose uptake and promoting hepatic gluconeogenesis. Other innate and adaptive immune cells, including neutrophils, B cells and T helper subsets, join this inflammatory niche, creating a complex cytokine milieu that sustains metaflammation[28, 29].

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Similar immunometabolic changes occur in liver, skeletal muscle and pancreatic islets. In the liver, accumulation of triglycerides and lipotoxic species triggers Kupffer cell activation, stellate cell engagement and production of inflammatory mediators that exacerbate insulin resistance and promote progression to metabolic dysfunction–associated steatotic liver disease[30]. In skeletal muscle, lipid accumulation and mitochondrial stress induce local cytokine and myokine changes that impair insulin signaling. Islets experience β-cell stress from glucolipotoxicity, with local immune cell infiltration further accelerating dysfunction. The gut–liver axis adds another layer: dysbiosis and increased intestinal permeability expose the immune system to microbial products that activate pattern-recognition receptors and contribute to systemic inflammation[30, 31].

These tissue-specific events are reflected in circulating biomarkers. Modest elevations in IL-6, TNF-α, IL-1 receptor antagonist, CRP, serum amyloid A, adipokines such as leptin and adiponectin, and chemokines such as MCP-1 form a systemic signature of metaflammation[32]. Oxidative stress markers, including malondialdehyde and advanced glycation end products, further indicate disturbed redox balance and glycotoxicity. Over time, these biomolecular signals correlate with impairments in insulin sensitivity and β-cell function, predicting progression from obesity to overt diabetes and the emergence of cardiovascular complications[32].

Importantly, metaflammation is heterogeneous. Sex, age, fat distribution, genetics, weight history and environmental exposures all shape immune and metabolic responses[33]. Some individuals with obesity maintain relatively low inflammatory tone and preserved insulin sensitivity, while others exhibit marked metaflammation and rapid progression[34]. This heterogeneity underscores the need for diagnostic tools capable of capturing nuanced differences in inflammatory signatures rather than relying on single markers or general surrogates such as BMI. Nanoscale diagnostics, with their high sensitivity and multiplexing ability, are well positioned to dissect these patterns and support more refined risk stratification[34].

3. Biomarker Landscape for Early Detection of Metaflammation

Early detection of metaflammation requires biomarkers that change before overt hyperglycemia and structural complications, while also being stable enough for reliable measurement and reasonably specific for metabolic inflammation[35]. Classical inflammatory markers such as high-sensitivity CRP and IL-6 have strong epidemiologic links to incident type 2 diabetes and cardiovascular events, and they are elevated in obese individuals with impaired glucose tolerance. However, their lack of tissue specificity and susceptibility to acute infections limit their stand-alone utility for early, obesity-focused risk assessment[35].

Adipokines are attractive candidates because they originate largely from adipose tissue, the primary site of metaflammation. Leptin levels rise with adiposity and reflect energy stores, but leptin resistance blunts its anorexigenic effects and fluctuations may primarily indicate mass rather than inflammatory tone[36]. Adiponectin, in contrast, typically decreases with obesity and insulin resistance, and low levels are associated with higher diabetes risk. Novel adipokines such as resistin, visfatin and omentin provide additional nuance but remain less well validated. Panels combining adipokines with cytokines and chemokines may better capture the complexity of adipose tissue inflammation[10, 37, 38].

Circulating miRNAs have emerged as particularly promising biomarkers. Specific miRNAs implicated in insulin signaling, lipid metabolism and inflammation show altered expression in obesity and prediabetes, and some correlate with measures of insulin resistance and β-cell stress[39]. Because miRNAs are often packaged in exosomes or protein complexes, they are relatively stable in blood and other fluids. Exosomes themselves, derived from adipose tissue, liver or immune cells, carry proteins, lipids and nucleic acids that reflect the state of their tissue of origin. Profiling exosomal cargo could provide organ-specific windows into metaflammation[39].

Metabolomic and lipidomic signatures also show promise. Branched-chain amino acids, acylcarnitines, ceramides and other lipotoxic species are consistently linked to insulin resistance and may change early in the disease course. Combined with inflammatory proteins, these metabolites can form integrated risk scores capturing both metabolic overload and immune activation[40]. Oxidative stress markers, such as malondialdehyde, 8-iso-PGF2α and oxidized LDL, further enrich this picture by indicating reactive oxygen species–driven damage downstream of chronic metabolic stress.

Translating this rich biomarker landscape into clinically useful diagnostics faces several challenges. Analytes are often present at low concentrations, particularly in early disease or in non-blood fluids. Biological variability, including diurnal patterns and responses to meals or exercise, complicates interpretation[41]. Conventional laboratory assays lack the multiplexing capacity and sensitivity needed to capture complex panels in small sample volumes with rapid turnaround. Nanodiagnostics directly address these issues by enabling ultrasensitive, multiplex detection in point-of-care or even wearable formats. For example, nanostructured electrodes and plasmonic surfaces can simultaneously detect multiple cytokines and adipokines in a single microliter of serum, while nanoparticle-enhanced nucleic acid probes quantify miRNA panels with high specificity[41].

4. Nanoscale Biosensing Platforms and Signal Transduction Strategies

Nanodiagnostic platforms for metaflammation can be broadly categorized by the primary readout they generate, including electrochemical, optical, piezoelectric and magnetic signals. Electrochemical nanosensors often employ nanostructured electrodes composed of gold nanoparticles, graphene, carbon nanotubes or metal oxides

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to increase surface area and enhance electron transfer[42]. Capture probes such as antibodies, aptamers or nucleic acid sequences are immobilized on these surfaces to recognize target cytokines, adipokines or miRNAs. Binding events modulate current, potential or impedance, with nanostructuring improving detection limits into the femtomolar range for analytes like IL-6.

Optical nanodiagnostics harness localized surface plasmon resonance, fluorescence, chemiluminescence or surface-enhanced Raman scattering. Gold and silver nanoparticles, quantum dots and upconversion nanoparticles can be functionalized with biomolecular recognition elements. Target binding shifts plasmon resonance peaks, alters fluorescence intensity or generates characteristic Raman signatures[43]. These approaches support both label-free detection and multiplexed readouts through spectrally distinct probes. For example, distinct quantum dot colors can be assigned to different cytokines or miRNAs in a single assay, enabling simultaneous quantification from minimal sample[43].

Magnetic and piezoelectric nanodiagnostics provide alternative transduction strategies less sensitive to optical interference. Superparamagnetic nanoparticles can be used as labels or capture agents, with binding events detected via changes in magnetic relaxation or resonance[44]. This is particularly attractive for integration into compact point-of-care devices and for use in turbid samples such as whole blood. Piezoelectric and microcantilever systems detect mass changes or surface stress upon analyte binding, with nanostructuring improving sensitivity[44].

Across these platforms, the choice of recognition element is critical. Antibodies remain widely used due to their high affinity and specificity for protein biomarkers but can be expensive, temperature-sensitive and prone to batch variability[45]. Aptamers, short oligonucleotides selected for high-affinity binding, offer better stability and easier synthesis, making them attractive for repeated measurements in wearable devices. Molecularly imprinted polymers can serve as synthetic recognition sites for small metabolites and lipids. For nucleic acid biomarkers such as miRNAs, complementary DNA probes with nanomaterial-based signal amplification provide high specificity even for closely related sequences[45].

Signal amplification strategies are central to nanodiagnostics. Enzymatic labels, catalytic nanomaterials, redox mediators and plasmonic coupling are routinely employed to convert low-abundance analyte binding into robust, measurable signals[46]. Hybrid nanostructures combining metal, carbon and polymer components can be tailored to improve sensitivity, reduce noise and enhance biocompatibility. Integrating microfluidics with nanobiosensors enables precise sample handling, on-chip preconcentration and automated calibration, which are essential for reliable deployment in clinical or home settings[46].

5. Body Fluid–Specific Nanodiagnostic Approaches and Wearables

Blood remains the primary matrix for assessing metaflammation, but venous sampling is invasive and poorly suited to high-frequency monitoring[47]. Nanodiagnostic development therefore increasingly targets alternative biofluids, including interstitial fluid, saliva, sweat and exhaled breath condensate, each with distinct opportunities and challenges[47].

Interstitial fluid closely mirrors plasma composition and is accessible via minimally invasive microneedles. Nanosensors embedded in microneedle patches can continuously sample interstitial fluid, detecting cytokines, adipokines or miRNAs with little discomfort to the user. Integration with flexible electronics allows real-time data transmission and on-patch processing[48]. Such platforms are well suited for capturing dynamic changes in metaflammation during meals, exercise or weight-loss interventions. Saliva offers a non-invasive alternative, with several inflammatory markers and miRNAs detectable at measurable levels. Nanostructured strips or microfluidic chips can concentrate analytes and amplify signals, though lower concentrations and variable flow rates pose challenges[48].

Sweat-based wearables have gained significant attention, especially for monitoring electrolytes and metabolites. Chronic inflammation markers, including certain cytokines and oxidative stress products, can be excreted in sweat, albeit at low levels[49]. Nanomaterial-based sensors integrated into skin patches, textiles or wristbands enable continuous sampling and real-time readouts. For metaflammation, sweat-based nanodiagnostics could provide an accessible modality for large-scale screening and behavioral feedback, particularly when combined with physical activity tracking. However, more work is needed to clarify correlations between sweat and plasma biomarker levels in obesity-associated diabetes[49].

Exhaled breath condensate is another attractive matrix, containing volatile organic compounds and condensed droplets reflecting systemic oxidative stress and inflammation. Nanostructured gas sensors and surface-enhanced Raman substrates can detect disease-specific volatile signatures linked to metabolic dysfunction and inflammatory status. Breath-based nanodiagnostics could offer fully non-invasive screening tools for community-level risk assessment, though standardization and validation remain early-stage[49].

Across these fluids, nanomaterial-enabled wearables play a central role. Flexible, stretchable substrates incorporating graphene, metal nanowires or conductive polymers host nanosensors while conforming to body contours[50]. Low-power electronics, energy harvesting and wireless communication support long-term, ambulatory monitoring. For obesity-associated diabetes, combining inflammatory nanodiagnostics with sensors

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for glucose, heart rate, physical activity and sleep could yield rich multimodal data to understand the interplay between behavior, environment and metaflammation[50].

6. **Preclinical and Translational Evidence in Obesity-Associated Diabetes**

Preclinical studies have begun to explore nanodiagnostics for inflammatory markers in obesity and diabetes, often in parallel with nanotherapeutic interventions. Rodent models of diet-induced obesity and insulin resistance display elevated levels of cytokines, adipokines and oxidative stress markers that can be tracked using nanoparticle-enhanced immunoassays and biosensors[51]. For example, nanostructured electrochemical platforms have measured IL-6 and TNF-α at femtomolar levels in small-volume samples, capturing changes associated with high-fat diet exposure and weight-loss interventions[21].

Human studies, though still limited, increasingly document the link between obesity, inflammatory biomarkers and diabetes risk[52]. Obese individuals with and without diabetes typically show higher levels of TNF-α, IL-6 and CRP, with these markers correlating positively with BMI and measures of insulin resistance. Prospective cohorts have confirmed that elevated IL-6 and CRP predict incident type 2 diabetes independently of traditional risk factors. Nanotechnology-focused diabetes reviews highlight that nanobiosensors and nanomaterial-enhanced assays can detect these biomarkers at much lower thresholds than standard methods, opening the door to earlier detection in high-risk but normoglycemic individuals[52].

Recent work has extended nanodiagnostic applications to emerging biomarkers such as miRNAs and exosomes. Nanoparticle-based nucleic acid sensors have profiled miRNA panels associated with β-cell stress and insulin resistance in plasma samples, distinguishing individuals with prediabetes from those with normal glucose tolerance[53]. Nanoparticle-assisted exosome isolation improves yield and purity, enabling detailed analysis of adipose- or liver-derived exosomal cargo that reflects tissue metaflammation[53]. These approaches are beginning to be tested in clinical cohorts of obese and diabetic patients, though large-scale validation is still pending.

In parallel, wearable nanodiagnostics for inflammation are being piloted in broader chronic disease contexts. Flexible patches and wristbands capable of tracking inflammatory cytokines, oxidative stress markers and metabolic parameters are under investigation in patients with cardiovascular disease, rheumatologic conditions and obesity. Lessons from these early translational studies, including issues of sensor fouling, calibration drift, inter-individual variability and user acceptability, will be directly relevant for applications in obesity-associated diabetes.

7. **Challenges, Safety and Future Directions**

Despite rapid progress, several obstacles must be overcome before nanodiagnostics for metaflammation can be widely deployed in obesity-associated diabetes. Analytical validation is a primary concern. Many nanobiosensors are demonstrated in idealized laboratory conditions with spiked samples rather than in heterogeneous clinical specimens. Matrix effects, non-specific binding and biological variability can degrade performance. Rigorous, multi-site validation against reference methods is essential to establish reliability, reference ranges and clinically meaningful cut-offs[54].

Nanotoxicology and safety represent another critical dimension. While diagnostic use generally involves lower doses than systemic nanotherapeutics, repeated exposure to nanoparticles via implants, patches or sampling probes could still pose risks[55]. Some nanomaterials, particularly certain metal or metal oxide particles, can induce oxidative stress, organ accumulation and immunotoxicity. Choosing biodegradable, biocompatible materials and minimizing systemic exposure are key design principles. Regulatory frameworks are still adapting to such hybrid devices that combine nanomaterials, biological recognition elements and electronics[55]. Clear guidance on risk assessment, manufacturing quality and post-market surveillance will be needed.

Implementation challenges include cost, infrastructure and equity. Advanced nanodiagnostic platforms may initially be expensive and require specialized readers or consumables. Without deliberate design for affordability and robustness, they risk exacerbating existing disparities in diabetes care, particularly in low- and middle-income settings where obesity and diabetes are rising rapidly[56, 57]. Conversely, simple, low-cost lateral flow assays enhanced with nanoparticles, or robust electrochemical strips compatible with portable readers, could democratize access to metaflammation testing if thoughtfully developed.

Looking ahead, the most impactful applications will likely involve multiplex, longitudinal monitoring integrated with digital health tools. Panels combining cytokines, adipokines, miRNAs and metabolic markers could define individualized metaflammation fingerprints. Continuous or high-frequency tracking via wearable nanodiagnostics would generate large data streams, well-suited to machine-learning models that can identify patterns predictive of diabetes onset, response to lifestyle interventions or impending decompensation. This vision aligns with a shift from episodic, clinic-based care toward proactive, data-driven management, in which nanodiagnostics serve as the sensing layer of a broader precision health ecosystem.

Conclusion

Nanodiagnostics offer a powerful and increasingly practical route to detect metaflammation at its earliest stages in obesity-associated diabetes. By exploiting the unique properties of nanomaterials, these platforms achieve ultra-sensitive, multiplexed and potentially continuous measurement of inflammatory and metabolic biomarkers

across diverse biofluids. Such capabilities could transform risk stratification, enabling identification of high-risk yet normoglycemic individuals, refining phenotyping of obese patients and guiding personalized preventive and therapeutic strategies. Current evidence from preclinical and early translational studies is encouraging but remains preliminary, with key challenges in analytical validation, safety, standardization, cost and equitable deployment. Future work should prioritize biocompatible materials, robust point-of-care formats, integration with wearables and digital analytics, and rigorous evaluation in diverse clinical populations. If these hurdles can be addressed, nanodiagnostics for metaflammation may become an essential component of precision prevention and management of obesity-associated diabetes.

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