

Glucose and Hydration Monitoring Techniques: Current Trends and Future Frontiers

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Diabetes is one of the most prevalent health diseases that is characterized by elevated blood glucose levels. It is considered a primary cause of morbidity and mortality, affecting approximately 425 million people worldwide. This paper discusses recent studies about currently available and utilized techniques for glucose and hydration monitoring. It aims to highlight the advantages and disadvantages of existing devices and methods and identify future advancements in improving processes involved in glucose and hydration monitoring. Various glucose monitoring techniques are classified as invasive, minimally invasive, and non-invasive. Proper hydration is essential for improving physical performance and lowering the risk of dehydration, which can lead to severe diabetes-related emergencies. Numerous approaches for hydration monitoring include thermal, colorimetric, and piezoresistive sensing. Due to the need for accurate and precise blood glucose control in diabetes management, biosensors are widely employed. 3D printing is primarily used to manufacture components with precise dimensions and smooth surfaces, which are crucial for developing highly sensitive sensors. These improvements are expected to offer high-accuracy results and show real-time readings, marking an opportunity for future breakthroughs in monitoring technologies.

1. Introduction

Diabetes is one of the most prevalent health diseases worldwide, with projections of approximately 693 million by 2045. It is estimated that almost half of the global population (49.7 %) living with diabetes remain undiagnosed (Cho et al., 2018). Diabetes mellitus is a lifelong and severe condition characterized by excessively increased blood glucose levels caused by a failure in insulin production. Dehydration exacerbates the likelihood of increased blood glucose levels (Singh, 2023). Patients diagnosed with diabetes with low hydration are more likely to develop excessive amounts of sugar present in the blood. Low hydration leads to more severe cases of diabetes, such as diabetic coma (Brutsaert, 2023). Glucose and hydration monitoring techniques have constantly improved through major technological and scientific advancements over the years. Modern glucose and hydration sensing devices offer minimally invasive to non-invasive processes to limit conventional invasive methods that induce pain and discomfort and pose risks of infection (Gonzales et al., 2019). While these approaches exhibit exceptional potential in biosensing in the medical field, process optimization is still needed to address its limitations. Despite having real-time quantitative monitoring, these devices are prone to contamination and provide less accurate readings (Wu et al., 2023). Optimizing these sensors to improve accuracy and sensitivity, similar to standard invasive methods, presents an avenue for better glucose and hydration monitoring. The objective of this review paper is to evaluate and synthesize the existing methods for glucose and hydration monitoring. By comparing and analyzing the advantages and disadvantages of these techniques, this paper aims to identify future developments in improving the processes involved in detecting glucose and hydration levels.

2. Methodology

An initial scope was set to outline the limitations of this review paper. This was done by searching the keywords glucose monitoring, hydration monitoring, biosensor, or 3D printing only on Scopus and Google Scholar. This paper includes studies regarding available glucose and hydration monitoring techniques and potential improvements for diabetes management. Studies discussing the most known and utilized methods were selected. The advantages and disadvantages of each technique were analyzed.

3. Glucose and hydration monitoring

The current glucose and hydration monitoring allows the integration of process analyses to detect possible improvements for new and innovative sensing devices. These process analyses include medical treatment, training, and exercise to enhance further and develop existing techniques.

3.1 Glucose monitoring

Blood glucose monitoring facilitates the identification of trends in blood glucose fluctuations resulting from dietary changes, physical activity, medication, and pathological processes like diabetes mellitus. This information is crucial for healthcare providers to make evidence-based treatment decisions. Blood glucose monitoring can be classified as invasive, minimally invasive, and non-invasive.

Invasive methods are considered the gold standard and serve as the benchmark for other monitoring approaches. These include self-monitoring blood glucose (SMBG) and laboratory assays such as the hexokinase method. SMBG is a point-of-care testing method that requires finger pricking, typically involving a glucometer and a test strip (Matteucci and Giampietro, 2011). After a drop of blood is added to the strip, an enzyme oxidizes the glucose, producing a current proportional to the glucose level, which the meter converts to a voltage. Devices may use glucose oxidase (GOx) or glucose dehydrogenase (GDH) with coenzymes like flavin adenine dinucleotide (FAD) or pyrroloquinoline-quinone (PQQ) (Gonzales et al., 2019). Hexokinase is a photometric method where the concentration of NADPH, which absorbs light at 340 nm, is proportional to the glucose level, and traditional spectrophotometry quantifies this absorption (Burrin and Price, 1985).

Minimally invasive glucose monitoring methods, such as continuous glucose monitoring (CGM) and flash glucose monitoring (FGM), eliminate the need for drawing blood samples. CGM systems are sensors that automatically monitor blood glucose levels day and night using an electrochemical approach. They measure glucose concentration in the interstitial fluid (ISF) and convert it to blood glucose concentration. CGM devices consist of a sensor, transmitter, and wireless receiver. The sensor, inserted into subcutaneous tissue, detects glucose in the ISF, and the transmitter sends the data to the receiver, where it is displayed on a monitor (Lee et al., 2021). FGM employs wired enzyme glucose sensing technology to detect glucose automatically and uses the same chemical glucose oxidase process as CGM, but its disposable sensor is attached to the skin using a tiny needle (Hirsch et al., 2019).

Lin et al. (2022) introduced a hydrogel patch with a non-invasive electrochemical glucose sensor for detecting natural sweat. This patch efficiently collects hand sweat without external stimulation and detects glucose via chronoamperometry. The sensor uses a Prussian blue-doped poly (3,4-ethylenedioxythiophene) nanocomposite (PB-PEDOT NC) electrode, providing a cost-effective and stable solution with excellent electrocatalytic activity for measuring sweat glucose. Chang et al. (2022) integrated a glucose patch into a watch for continuous, non-invasive blood glucose monitoring using reverse iontophoresis and electrochemical detection. The watch includes an LED screen, rechargeable battery, PCB circuit, circular watchband, and a flexible glucose sensor patch that extracts and detects glucose from ISF. A calibration algorithm corrects the sensor's readings, displaying real-time glucose levels on the LED screen and a connected smartphone app. Table 1 summarizes the accuracy and response times of various methods for glucose monitoring.

Table 1: Accuracy and response times of glucose monitoring techniques

Methods	Accuracy (%)	References	Response time	References
SMBG	≥ 80	Kirk and Stegner (2010)	within seconds	Pleus et al. (2022)
Hexokinase	98	Ayyanar and Pichandi (2018)	5 min	Yudhana et al. (2021)
CGM	95	Freckmann et al. (2019)	within seconds	Freckmann et al. (2019)
FGM	-	-	within 3 s	Bailey and Gavin (2021)
Highly Integrated Watch	84.34	Chang et al. (2022)	17 min	Chang et al. (2022)

Invasive methods induce pain and discomfort after prolonged usage in addition to the possibility of infection (Gonzales et al., 2019). It has been reported that there is a 15 % inaccuracy rate found in 19 % of patients using SMBG because of the lack of knowledge in interpreting and reading results, improper handling of control solutions and test strips, and uncleaned hands (Klonoff, 2007). Minimally invasive methods may lead to tissue damage due to problems with insertion, adhesion, and removal. These approaches may also face challenges related to cost, accuracy, and reproducibility (Karakuş et al., 2021). CGM devices are limited to measuring real-time glucose levels, which does not correlate to interstitial fluid glucose levels at the same time where a lag time is considered before measuring (Sun et al., 2021). These devices only last up to 7 days and entail calibration twice or thrice a day. Glucose sensor patches pose risks of contamination and may encounter issues with sample mixing and pH changes, affecting the accuracy of measurements (Liu et al., 2021).

3.2 Hydration monitoring

Effective diabetes management includes regular hydration assessments. Recent studies suggest that hydration needs to be addressed and prioritized (Garcia-Garcia, 2022). Proper hydration is essential for preventing elevated blood sugar levels, maintaining normal kidney function, and preventing medical emergencies like diabetic ketoacidosis and hyperosmolar hyperglycemic state (McPherson, 2023). Hydration level monitoring approaches use body fluids such as sweat, saliva, and urine to measure hydration levels. Thermal, colorimetric, and piezoresistive approaches are utilized for hydration monitoring, enabling tracking and maintaining proper hydration levels.

Thermal hydration monitoring utilizes the thermal transport characteristics of the skin to measure the water content of the skin through thermal conductivity measurements. The plane source (TPS) technique, integrating resistive heating and temperature sensing, enables hydration level measurements. Shin et al. (2023) stated that improvements in interconnect design and skin-sensor interfaces enhance sensitivity by 135 %. Utilizing an improved protocol with acclimatization periods, rapid measurements, and a skeletal applicator increases repeatability by 36 %. Jose et al. (2021) developed a sensor system that provides consistent and repeatable moisture volume measurements that can measure as low as 0.5 μL of sweat. It effectively tracked and measured the sweat solution volume, with varying NaCl concentrations of 0.005 and 0.1 M, without any interference. The TPS measurement system can track the temperature of the medium and the textile sensor with a sensitivity of 0.158 $\Omega/^\circ\text{C}$.

Colorimetric sensors operate on the relationship between analyte concentrations and color intensity. Zhou et al. (2016) developed a sensor using acid-capped gold nanoparticles (AuNPs) to detect hydration levels by reacting with sodium cations, showing color changes from red to purple to grey, indicating overhydration, normal hydration, and dehydration. Three distinct colors were observed upon adding 26.5 mM, 40 mM, and 47.9 mM of NaCl to AuNP solutions. Optimal performance was achieved using a 0.35 g/L AuNP solution with a 5:1 ratio of artificial sweat to AuNP solution. Color changes are observed within 5 min. Visual experiments, UV-spectra, and Zeta-potential measurements confirmed the simplicity and accuracy of this colorimetric sensor. These sensors offer simple detection, high stability, and rapid response times, aiding hydration monitoring and health assessment.

Embedded piezoresistive microcantilevers (EPM) sensors are vital for monitoring devices that measure volumetric changes responding to human saliva osmolality, allowing real-time hydration monitoring. The sensors had varying response times from 2000s to 3000s to come to equilibrium depending on the thickness of the polymer layer (Gunter et al., 2005). Recent advances include 3D-printed graphene-filled sensors, exhibiting exceptional stretchability (1,960 % strain), and excellent stability (over 2,000 cycles). With high sensitivity (175.57 kPa^{-1} at pressures <300 Pa) and rapid mechanical response (105 ms) and recovery times (66 ms), these sensors hold promise for immediate health monitoring, including hydration levels (Ma et al., 2021).

Hydration monitoring approaches face challenges. The effectiveness of thermal sensing is limited by epidermal depth variations of approximately 100 μm (Madhvapathy et al., 2020). Colorimetric sensing experiences sweat rate constraints of 1.526 $\text{mg}/(\text{cm}^2/\text{min})$ in 90 min of usage, declined dye retention, and material longevity issues (Jain et al., 2019). Piezoresistive sensors may suffer from hysteresis and sensitivity to temperature changes (Zhang et al., 2022). Present hydration monitoring methods require clinical trials for better and more accurate data on the relationship between varying skin permittivity and hydration levels (Kilpijarvi et al., 2020).

Skin electrical impedance is the most reliable and well-established method due to its ease of use and cost-effectiveness (Matsukawa et al., 2020). This is due to the correlation between hydration levels, increased conductivity, and dielectric constant. Increased skin water content leads to higher conductivity and dielectric constant. Reduced contact and epidermal impedance may cause a decrease in measured skin impedance values (Yao et al., 2017). Ichikawa et al. (2018) stated the average internal resistance of the human body is 500 Ω . Humans can perceive an electric current of 1 mA, while currents exceeding 50 mA can be lethal. The safe exposure limit for tissue is 1 mA/cm^2 , suitable for frequencies ranging from direct current up to 1,000 MHz (Schwan, 1971). Smartwatches employ bioimpedance, requiring users to remain still for accurate readings.

Patch sensors use sweat for electrochemical analysis, offering real-time data transmission via Bluetooth (Manimegala et al., 2021).

4. Potential improvements

Monitoring techniques still need to be fully optimized. Available glucose and hydration monitoring devices do not offer 100 % accuracy, and some cannot show real-time readings. Improvements can be made to better the available methods instead of creating a new one. The potential improvements in existing glucose monitoring techniques include biosensor development, sensor fabrication via three-dimensional (3D) printing, and potentiostat utilization.

Biosensors are analytical instruments crucial in medical science for monitoring illnesses, drug discovery, and identifying contaminants and disease markers in physiological fluids like blood, urine, saliva, and sweat. Bhalla et al. (2016) discussed the effect of nanotechnology on biosensing technology advancements that utilize the field of miniaturization to fabricate micro or nano-scale biosensors with exceptional signal-to-noise ratio and lower limits of detection, enabling single-molecule detection. Glucose biosensors are widely employed for diabetes diagnosis due to the need for precise blood glucose control (Scognamiglio et al., 2010). Biosensors offer advantages such as less susceptibility to interference, faster response times, higher sensitivity, and more stable output for minimally invasive or non-invasive constant monitoring of physiological chemicals (Tetyana et al., 2021).

3D printing is extensively used in engineering to create components with high dimensional accuracy and smooth surface finish, which are crucial for developing highly sensitive sensors (Khosravani and Reinicke, 2020). A notable advancement is the fabrication of a highly sensitive enzyme-immobilized reactor that employed a 3D printing technique called Fused Deposition Modeling (FDM) with Acrylonitrile Butadiene Styrene (ABS) material to monitor lactate and glucose among rat subjects. Results showed that 3D printing technology can extend the adaptability and diversity of existing analytical configurations (Su et al., 2016). Mass et al. (2021) found that the composition of aqueous ink, particularly with Single-Walled Carbon Nanotubes (SWCNT), significantly impacts printability. Printability in bioprinting refers to the ability of a bioink to form well-defined 3D structures with controlled dimensions and morphology (Zhang et al., 2018). The printability of a sensor can be compromised by unoptimized ink concentrations, resulting in low-quality prints that affect biosensor sensitivity.

A potentiostat is a vital tool in electrochemical analysis that requires an electrochemical cell with three electrodes. The working electrode is responsible for voltage and current measurement, while the reference electrode maintains a constant potential (Beasley, 2023). This analytical instrument controls the voltage of the working electrode in a multi-electrode setup, ensuring a constant voltage between it and the reference electrode. Lopin and Lopin (2018) found potentiostat applications in various experiments like cyclic voltammetry and amperometry that accurately measure substances such as Vitamin C, glucose, and lead. The potentiostat exhibits possible improvements as it was built with a single commercially available integrated circuit (IC) that does not require any external electronic components, making it cost-effective and viable in resource-limited environments.

5. Conclusion

The available glucose and hydration monitoring techniques have been reviewed revealing that they have unique characteristics and limitations. The advantages and disadvantages of these methods were utilized to determine the gaps and potential improvements in fabricating glucose and hydration monitoring devices. These include the development of biosensors, sensor fabrication via 3D printing, and utilization of biopotentiostat. Hydration monitoring technologies are important for detecting and alleviating dehydration that can lead to diabetes. Both the processes of glucose and hydration monitoring were analyzed to identify future improvements in existing approaches. The process analyses also allow the evaluation of potential health risks and the prevention of detrimental effects. This paper involves the optimization of blood glucose monitoring devices from invasive to non-invasive, as well as hydration monitoring devices by measuring sweat through 3D printed patch biosensors. Quality control can be applied in the innovation of new sensing devices ensuring product quality and process efficiency. The fabrication of a non-invasive approach for a cost-effective and innovative electrochemical sensor measuring both the glucose and hydration levels can be further explored and analyzed. This will increase medical 3D printing applications that will unfold opportunities in disease monitoring, such as diabetes.

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