Detecting Analytes in Urine for Urinalysis

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Contributor: Chuljin Hwang , Won-June Lee , Su Dong Kim , Sungjun Park , Joo Hee Kim

Human urine samples contain several components that can indicate the health condition of a patient, and therefore aid in the diagnosis of common clinical conditions such as diabetes mellitus (DM), urinary tract infections (UTIs), renal stone disease, kidney disorders, liver problems, obesity, other metabolic disorders, or fetal hypothyroidism. Urine samples also provide evidence of underlying health problems in pre-symptomatic and asymptomatic individuals, which can facilitate early intervention and therapy. These benefits play an important role in encouraging individual access to continuous and regular health monitoring.

urine sensor point-of-care urinalysis clinical application for urinalysis

1. Detection of Glucose in Urine Sample

According to the International Diabetes Federation, diabetes mellitus (DM) is a metabolic disease that affects millions of people worldwide, which is characterized by hyperglycemia with abnormal blood glucose levels [1]. To reduce related complications and manage DM independently, continuous glucose monitoring using various biofluids is needed [2][3]. As opposed to blood glucose tests that require finger pricking to draw blood for each test, which can cause inconvenience and pain to the patient, urine samples can be more conveniently used for glucose measurement. Moreover, the presence of glucose in urine is an indicator of severe DM. Therefore, the use of urine tests for glucose monitoring has attracted substantial attention.

The dipstick test for glycosuria, which is caused by DM, is widely used in clinical practice and public health screening owing to its advantages such as low cost, ease of use, and non-invasiveness; however, its main limitation is low sensitivity [4]. Therefore, for many people, most glycosuria is not diagnosed until severe complications develop, making it more difficult to reduce further deterioration. There has been extensive effort toward developing a biosensor for the detection of glucose in the urine, which would allow patients to track their glucose levels accurately, along with the requirement of frequent glucose monitoring to manage diabetes [5]. For the accurate determination of urine glucose, various detection methods have been employed based on techniques such as fluorescence [6], visible-near infrared spectroscopy [7], surface plasmon resonance [8], and electrochemistry [9]. Among these methods, there has been particularly high interest in the electrochemical sensing technique for urine glucose detection because of its advantages of low cost, fast response time, wide detection range, and ease of use.

A new method was developed to detect glucose based on graphene according to an increasing pH shift due to the enzymatic activity of glucose oxidase (GOx). Fenoy et al. [10] proposed a glucose sensor based on graphene field-

effect transistors (GFETs) coupled with enzymes immobilized by electrostatic interaction. GOx has been the most widely utilized enzyme for this purpose owing to its low cost, bioactivity, selectivity, and stability [11]. Among the various proposed strategies for GOx immobilization, the authors used the electropolymerization technique with poly (3-amino-benzylamine-co-aniline) (PABA) to prepare a GFET glucose sensor. The major advantage of using PABA on GFETs for glucose sensing is the higher quantification ability compared with that possible using conventional glucose sensors that are dependent on electrochemical transduction, allowing for higher reproducibility and the ability to detect glucose in a flow measurement setup. The GOx-PABA-GFET glucose sensor exhibits a wide dynamic range from 10 µM to 1 mM and a low LOD (4.1 µM), enabling the determination of glucose in the urine, as the normal glucose concentration range in urine is between 0 mM (0 mg/dL) and 0.8 mM (15 mg/dL) [12]. In addition, the sensor was able to detect glucose in diluted urine samples with a sensitivity of −13 ± 2 µA per decade of glucose concentration. Although the GOx-PABA-GFET glucose sensor showed good performance in detecting glucose, it presents limitations with respect to the enzyme's activity, which can be influenced by factors such as temperature, pH, humidity, and the harsh purification process of the enzyme [13][14].

Huang et al. [15] recently reported glucose biosensors with high sensitivity and selectivity using a polymer and graphene without an enzyme. The biosensor was functionalized with a poly (acrylamide (Aam)-3-acrylamidophenylboronic acid (AAPBA)-N-dimethylaminopropyl acrylamide (DMAAPA)) for glucose, allowing the covalent bonding of AAPBA to its surface via chemisorption. The resulting functionalized surface was found to exhibit the highest sensitivity toward glucose compared with that of the other components in urine, such as carbamide, creatinine, and l-cysteine (**Figure 2**e). Specifically, the biosensor exhibited a sensitivity of 822 $\mu Acm^{-2}mM^{-1}$, a linear range from 0.04 to 10 mM, and a LOD of 1.9 µM for detecting the presence of glucose in human urine samples. In addition, by the simple process of hydrochloric acid treatment, the biosensor showed excellent reproducibility and repeatability, which was over 93.324% at 0.4 mM of the original value after 20 cycles. The authors claim that their platform serves as a polymer-functionalized glucose biosensor, thus providing new opportunities for the development and application of high-performance sensors.

2. Detection of Hydrogen Ions in Urine Sample

Urine pH, a relatively easily measurable biomarker, is an important indicator of UTI and renal stone disease [16]. In the absence of pathological conditions, the normal range of urine pH is typically between 4.5 and 8, with an average of 6 [17][18]. A urine pH of 8.5 or 9.0 is often suggestive of a UTI-caused urea-splitting bacterium such as Proteus mirabilis or Pseudomonas aeruginosa. At a urinary pH above 6.0, urinary crystallization inhibitors are deficient, leading to calcium phosphate crystals that form insoluble salts as one of the causes of renal stone disease [19], and a urinary pH below 5.5 may induce the formation of anhydrous or dihydrate uric acid crystals when the uric acid concentration is high [20]. Therefore, accurate measurement of urinary pH is essential. Owing to its properties of high accuracy and precision, the gold-standard method for urine pH monitoring is the glass electrode and pH meter [21][22]. However, at present, the urine dipstick is widely used for at-home tests given the various advantages of point-of-care (POC) assessments, such as ease of use, convenience, and cost. Nevertheless, there has been substantial debate about the accuracy of such tests [23][24].

Rabboh and O'Neil [25] developed a novel voltametric pH sensor consisting of three-dimensional (3D)-printed graphene/polylactic acid (G/PLA) filament electrodes, which uses intrinsic functional groups such as quinones on the surface of electrodes for pH sensitivity. Increased quinones that accumulate on the G/PLA electrodes via a multistep pretreatment protocol improved the performance of the sensor, extending the pH measurement range from 2.02 to 11.22. In addition, as the solution pH changes, the anodic and cathodic potential shift was found to be −60 ± 2 mV/pH, which showed good agreement with the theoretical value predicted by the Nernst limit (59.14 mV/pH at 25 °C derived from the Nernst equation). Moreover, G/PLA electrodes show excellent agreement for complex samples such as vinegar, cola, urine, serum, and antacid measured with a glass pH probe which is the gold standard for pH measurement. The major challenge of this biosensor is to achieve the direct sensing of analytes in undiluted complex biological media. To date, only a few biosensor technologies have been developed for the detection of undiluted samples. The authors concluded that their developed electrochemical biosensor has the potential to expand the scope of measuring specified analytes in unadulterated complex samples.

Building upon the invention of the first ion-sensitive field-effect transistor (ISFET) to detect pH values in solution by Piet Bergveld [26], the transistor-based pH sensor was developed, exhibiting promising properties such as high sensitivity, miniaturization, low cost, and long lifetime in various environmental conditions. Many studies have focused on metal oxide transistors for pH measurements such as indium–gallium–zinc-oxide (IGZO) [27], indium oxide (In_2O_3) [28], and zinc oxide (ZnO) [29]. Lee and colleagues [27] reported that electrolyte-gated thin-film transistors were very close to the Nernst limit without any additional settings.

3. Detection of Protein (Albumin) in Urine Sample

Increased urinary protein levels can be a significant indicator of adverse kidney and cardiovascular problems [30][31][32]. Among various proteins, albumin (Alb) is normally found abundantly in the urine; hence, it is standardized as a biomarker for screening proteinuria [33][34]. The Kidney Disease Outcome Quality Initiative of the National Kidney Foundation published clinical practice guidelines for chronic kidney disease (CKD) that recommend initial screening and monitoring of urine Alb [35][36][37]. In the early stage of CKD, the amount of Alb in the urine starts to increase due to reduced kidney function, enabling the progression of the disease to be diagnosed by regular measurements of Alb levels. For example, a urine Alb level above 30 mg/g may indicate kidney disease, even if the estimated glomerular filtration rate is above 60. For this reason, various methods to monitor urine Alb have been developed, such as liquid chromatography [38], capillary electrophoresis [39], fluorescent probes [40], and enzyme-linked immunosorbent assay [41]. Although these methods are reliable, they are limited by the complicated sample preparation, expensive pre-treatment, and time-consuming processes. In recent decades, field-effect transistors (FETs) based on single-walled carbon nanotubes (SWCNTs) have been widely used in the growing field of biochemical sensing applications owing to their advantages of easy miniaturization, label-free detection, rapid response, and integrability.

Kim and Kim [42] reported an SWCNT-FET using the bromocresol green (BCG) dye-binding method, which is based on the specific binding between BCG and human serum albumin (HSA) for the detection in urine. The authors loaded 0.5 wt% of bovine serum albumin (BSA) as a blocking agent before introducing HSA because non-specific

binding can be a significant issue affecting the performance of this type of sensor. As a result, they successfully measured HSA with a LOD of 18.6 µg/L by measuring the electrical conductance of SWCNT-FET, which showed improved sensitivity compared to those of previously developed HSA sensors based on different methods such as total internal reflected resonance light scattering [43], surface-enhanced Raman scattering [44], and zero-current potentiometry [45]. Moreover, the biosensor achieved a real-time response with increasing HSA concentrations from 100 pM to 10 µM in a healthy human urine sample. Overall, this biosensor exhibited the advantages of improved response time and sensitivity; however, the repeatability and reproducibility for continuous monitoring remain to be investigated.

In 2019, Zhang et al. [46] proposed an electrochemical biosensor using a dual-signal strategy, including a current change of the substrate and solution probe. This biosensor is based on a molecularly imprinted polymer (MIP) for the measurement of HSA in urine using 3D cavities on the surface formed by an HSA template. The authors claimed that optimization of various factors and the dual-signal strategy (ΔIsubstrate and ΔIprobe) for detecting HSA in urine offer an opportunity to improve sensing performance; indeed, their biosensor exhibited a wider detection range from 0.1 ng/L to 0.1 mg/L and a lower LOD of 30 pg/L compared with those of previously reported methods for HSA detection. In addition, the biosensor showed acceptable repeatability with a relative standard deviation (RSD) of 4.4%; a lifetime longer than 20 days; and low interference toward other biomolecules such as glycine, glutamate, cysteine, tryptophan, histidine, dopamine, ascorbic acid, hemoglobin (Hb), and BSA.

Karim et al. [47] reported the first FET immunosensor that was based on a high aspect ratio of ZnO nanorods NRs for HAS detection. The linearity and selectivity of the immunosensor were enhanced with the addition of the antibody (Ab) that facilitated the immobilization of HSA on the surface of the device. The Ab also acted as an exclusion membrane, simultaneously excluding some interferents such as small molecules, protein fragments (gamma globulin, glycoprotein, ribonuclease, lysozyme, hemoglobin, Tamm–Horsfall mucoprotein, and Bence–Jones protein), and other residues. To detect the presence of albumin, a functionalization process is required on the immunosensor surface. The most commonly used cross-linking process for an immunosensor is the APTES method because its amino group is in one end, and three ethoxy silanes groups covalently attach to surfaces in the other end. The albumin immobilized to the surfaces of the immunosensor to induce a larger signal as an electric double layer (EDL) at the surface–electrolyte interface determines the minimum sensing distance, which leads to a V_{TH} shift in the transfer characteristic according to each binding interaction. Their results demonstrated a high sensitivity of 0.826 mA (g/mL) with a LOD value of 9.81 µg/L in a linear range from 10 µg/L to 100 mg/L. In addition, their sensor showed good storing stability at 4 °C in the dark for up to 360 days (Figure 6f). Moreover, other proteins in urine such as cytokines, chemokines, and growth factors are also being studied as the biomarker of disease determination [48][49].

4. Detection of Ketone Bodies in Urine Sample

Urinary ketone bodies are composed of three small compounds, acetoacetic acid (AcAc), 3-β-hydroxybutyric acid (3β-HB), and acetone, which play an important role as indicators of metabolic health status, aiding in the diagnosis of metabolic conditions such as obesity, central obesity, metabolic syndrome, dyslipidemia, and type 2 DM. The

normal concentration of ketone bodies in the urine is less than 1 mg/dL. In diabetic ketoacidosis (DKA), due to reduced insulin levels, the increase in ketone bodies in the blood leads to their excretion via the urine, thereby increasing the concentration of ketone bodies in the urine, which is known as ketonuria. Unlike ketone bodies in the blood, 3β-HB is absent and AcAc is relatively abundant in the urine. Therefore, the detection of AcAc in urine could be a clinically useful method to monitor and diagnose DKA. Compared to obtaining blood samples, urine monitoring is a simpler, less expensive, and less invasive method for confirming the presence of AcAc. Despite these advantages, continuous monitoring of AcAc in urine has rarely been studied.

Recently, Go et al. [50] reported a new biosensor with a multi-layer enzyme [NAD+ and a mixture of d-β-hydroxybutyrate dehydrogenase (HBDH) and nicotinamide adenine dinucleotide (NADH)]-modified electrode, which can quantify AcAc in the urine, and is reusable and more accurate compared to the conventional dipstick test. 3β-HB is transformed from AcAc by catalyzing a reaction between HBDH and NADH, which allows for the transduction of the concentration of AcAc into the current peak at 0.073 V. The sensitivity of the biosensor for detecting the AcAc concentration in phosphate-buffered saline (PBS) solution was experimentally confirmed to be 6.27 mg/dL and a LOD was 6.25 mg/dL in the range of 6.25–100 mg/dL, which was equally able to identify ketone bodies in patients diagnosed with DKA as the urine dipstick test (+++: up to 100 mg/dL; ++: up to 50 mg/dL; +: up to 10 mg/dL; trace 5: 10 mg/mL, and–as the normal level). Moreover, the biosensor was reusable after simple cleaning steps, and a change in the current value of less than 5% was maintained even after 10 uses. The measurements of urine samples of 20 patients with DKA showed an excellent correlation with the detection of ketone bodies in the same patients using a commercially available dipstick test. This represented the first attempt to detect ketone bodies in urine using a biosensor in a clinical test.

5. Detection of Hemoglobin in Urine Sample

One of the most important substances for assessing the physiological condition of the human body is Hb, which is responsible for carrying 97% of the oxygen in the blood; changes in Hb levels in the blood may indicate several diseases [51]. The typical blood Hb level for males and females is 140–180 mg/mL and 120–160 mg/mL, respectively [52]. When the Hb level in the blood is too high (i.e., over the renal threshold), Hb begins to appear in the urine. People who suffer from hematuria show a concentration of ~1.0 mg/mL of Hb in the urine. The presence of Hb in the urine causes a change in the color of the dipstick pad to green/dark blue, which can be associated with kidney stones, renal carcinoma, and other disorders [53]. However, since the dipstick test is based on the presence of peroxidase-like activity and not Hb itself, the presence of myoglobinuria or hypochlorite in urine may cause false-positive results. Thus, a microscopic examination of the urine is required to confirm the presence of Hb and exclude a false-positive result.

To overcome the issue of the false-positive result due to interferential components in urine, Anirudhan and Alexander [54] developed a potentiometric biosensor for the determination of Hb directly in urine using surface-modified multiwalled carbon nanotubes (MWCNTs)–MIP. Because of the highly porous and hollow structure of MWCNTs–MIP, it is possible to directly immobilize Hb inside the matrix during sample loading. A potentiometric signal was observed with a linear correlation in the range of 1.0–10.0 mg/L and a LOD of 1.0 mg/L. In a real urine

sample test, the performance of the biosensor was comparable with that of the conventional high-performance liquid chromatography method (97.5% recovery and RSD < 1.0). Furthermore, the selectivity of the MWCNTs–MIP sensor was verified using other proteins such as HSA, myoglobin, and cytochrome C, showing a negligible change compared to Hb. The authors claimed that since the Hb concentration in urine for people with hematuria is 1 mg/mL, the accuracy of the biosensor with a LOD as low as 1.0 µg/mL is sufficient to determine Hb in urine. Although this study reported promising results for the measurement of Hb, it did not demonstrate the ability for continuous monitoring of Hb concentrations in real urine samples. Han et al. [55] performed another study for Hb determination using a disposable electrochemical sensor, which was based on the reversible redox reaction. They built an electrode modified with Fc [CO-Glu-Cys-Gly-OH] (Fc-ECG) and Fc [CO-Cys-(Trt)-OMe]$_2$ (Fc (Cys)$_2$) for the detection of Hb in biological fluids. They confirmed the morphological structure of the electrode by scanning electron microscopy images. This sensor showed a linear response for Hb in the concentration range of 0.1–1000 mg/L and had a LOD of 0.03 mg/L. To evaluate the selectivity of the sensor towards other biomolecules, differential pulse voltammetry in the presence of potentially interfering molecules such as HSA, glucose, ascorbic acid, IgE, and dl-cysteine was conducted under optimized conditions. Moreover, recovery studies demonstrated that the electrochemical biosensor had high reproducibility with an RSD lower than 2.8% and good recovery of 95.5–103.2% in detecting Hb in human serum. The authors claim that the results of the reproducibility and recovery tests are consistent with the clinical requirements for Hb analysis.

6. Detection of Nitrite in Urine Sample

UTIs are among the most common bacterial infections seen in the general population. Even though UTIs are rarely fatal, if left untreated, the infection could spread from the kidneys into the bloodstream, causing bacteremia. Although the gold standard for a diagnosis of UTIs is to perform a bacteriological urine culture and physical examination, dipstick tests are widely used in clinical practice owing to their aforementioned advantages of convenience, low cost, and quick response. The parameters of the dipstick test to diagnose UTIs include nitrite, LE, and pH. Among them, nitrite detection relies on the ability of bacteria such as *Escherichia coli*, *Pseudomonas aeruginosa*, *Enterobacter*, *Serratia*, *Citrobacter*, and *Proteus* to convert nitrate to nitrite in the urine; positive results of a dipstick test indicate the significant presence of such bacteria (at least 10^5 colony-forming units per milliliter) [56]. To date, many studies have been carried out to improve the accuracy of nitrite detection, and the sensitivity and specificity of nitrite detection for UTIs are ~50% (45–60%) and ~95% (85–98%), respectively [57].

Zou et al. [58] reported a graphene electrochemical transistor (GECT) biosensor based on a gold nanoparticles modified reduced graphene oxide (AuNPs/rGO) nanocomposite. The detection and measurement of their sensor could be employed as gate voltage induced by the electrooxidation of nitrite at gate electrodes. By using this approach, their sensor achieved an excellent LOD of 0.1 nM and exhibited the response over a wide concentration range from 0.1 nM to 7 µM and from 7 to 1000 µM linearly. In addition, to confirm the high selectivity toward nitrite, they added various interfering species such as K^+, Li^+, Ca^{2+}, Mg^{2+}, NH_4^{3+}, Cl^-, NO^{3-}, SO_4^{2-}, PO_4^{3-}, CH_3COO^-, SO_3^{2-}, I^- and glucose in PBS solution. Due to the difference in electrocatalytic reaction mechanisms, the response to the addition of each species except for nitrite was negligible. Although this study reported promising results for

the measurement of nitrite using the GECT biosensor, it did not demonstrate the ability for detecting nitrite in real urine samples.

Cardoso et al. [59] were the first to introduce 3D-printed G/PLA sensors for detecting nitrite in biological samples using multiple-pulse amperometry combined with batch-injection analysis (BIA-MPA). The electrochemical performance of nitrite detection was accomplished by mechanical polishing and solvent immersion of the 3D-printed G/PLA sensor surface [60][61]. The BIA-MPA sensor exhibited high performance in detecting nitrite with a LOD of 0.03 µM. Moreover, the highly linear behavior of the sensor was shown over a wide concentration range of nitrite from 0.5 to 250 µM. Estimated recovery values by the standard addition method were between 70% and 90% for nitrite in a urine sample, which is within the allowable range for the analysis of biological fluids [62]. For the clinical test, they measured nitrite levels of approximately 5 mM, which is higher than the level of ~1 mM typically detected in patients diagnosed with UTIs [56]. Overall, this study showed that the 3D-printed-G/PLA sensor exhibited superior analytical characteristics for the detection of nitrite in biological samples; however, more experiments and tests are required for its development for selectivity enhancement.

7. Detection of Bilirubin in Urine Sample

Bilirubin is mainly formed from the degradation of Hb in the reticuloendothelial system [63], which is transported in the circulation in a form bound to Alb traveling through the blood to the liver. After entering the liver, bilirubin is transported into hepatocytes and conjugates with glucuronic acid. Conjugated bilirubin is also called direct bilirubin, as it directly reacts with diazotized sulfanilic acid [64]. The direct bilirubin concentration in the blood is typically 1–5 µM (0.06–0.3 mg/dL), whereas the bilirubin in urine is not usually detectable [65]. When the liver is damaged, bilirubin can leak out into urine; thus, an excess accumulation of bilirubin in urine, which is called bilirubinuria, can help in the diagnosis or monitoring of problems in the liver. Therefore, screening for bilirubin in urine is useful in detecting liver damage or disease even before other clinical symptoms manifest.

The detection of bilirubin using a dipstick test involves a coupling reaction of a diazonium salt in an acidic medium, producing a diazotization color reaction in the presence of bilirubin. However, these chemical reactions on dipsticks can cause a high rate of false-positive results due to interference of various components in urine, such as indoxyl sulfate, high vitamin C, and nitrite [66]. Accordingly, a positive test result from the dipstick test should be verified with a confirmatory test such as the bilirubin tablet test (Ictotest) [67].

Thangamuthu and coworkers [68] proposed electrochemical sensors for a POC assay to detect bilirubin using MWCNTs and electrochemically reduced graphene oxide (Er-GO) separately deposited on SPEs. Their sensing system consists of a carbon working electrode with a sensitive surface in which the electrochemical reaction occurs. The sensitivity using MWCNT-SPE and Er-GO-SPE showed a linear range over 0.5–500 µM and 0.1–600 µM with a detection limit of 0.3 ± 0.022 nM and 0.1 ± 0.018 nM, respectively. Moreover when applied to real human serum samples, the recovery value was found from 94% to 106.5% that represents a very good accuracy.

Rahman et al. [69] were the first to develop an enzyme-free electrochemical biosensor for detecting bilirubin in urine using a glassy carbon electrode (GCE) modified with iron-doped antimony oxide nanorods and Nafion to improve the electrical conductivity and chemical stability owing to the high surface area. To confirm the accuracy of the biosensor, they first demonstrated that varying bilirubin concentrations (0.1 nM to 0.01 M) in PBS solution can quantitatively change the I–V response, and an extremely low LOD of 16.5 ± 0.05 pM was achieved compared with those previously reported using other methods [70][71][72]. The repeatability, which represents the performance of the biosensor, is the most frequently evaluated parameter of accuracy. The repeatability was investigated by successively detecting 0.1 µM bilirubin in seven experiments, achieving similar current results (RSD = 4.24%, n = 7). Finally, the authors demonstrated excellent quantitative (~100%) recovery of the bilirubin concentration from 0.1 nM to 0.1 mM using clinical urine and blood serum samples, indicating that the biosensor does not require re-calibration to improve accuracy. Therefore, the authors concluded that their technique for detecting bilirubin is efficient and reliable.

8. Detection of Leukocyte Esterase (LE) in Urine Sample

LE is a protein released by white blood cells, thus serving as a biomarker for these immune cells. As an enzyme released by neutrophils, LE is also a widely used conventional biomarker for predicting or differentiating UTIs with the dipstick test. A positive result for LE in a dipstick test indicates an elevated number of leukocytes (a condition known as pyuria), which is often caused by UTIs. Many studies have been carried out to evaluate the accuracy of the dipstick test for detecting UTIs; however, the accuracy remains controversial without an adequate explanation of the cause. Moreover, the dipstick test provides only limited qualitative and semi-quantitative information depending on the concentration. Ho et al. [73] reported a paper-based electrochemical biosensor to detect LE (LE-PAD), which was deposited with mixed 3-(N-tosyl-l-alaninyloxy)-5-phenylpyrrole (PE) and 1-diazo-2-naphthol-4-sulfonic acid (DAS) on an Ag film, exhibiting excellent performance and reliability. This biosensor provides quantitative measurement through increased resistance due to non-conductive azo products produced by LE in the reaction areas of the PE and DAS. For analysis of real samples, urine samples collected from 16 patients with suspected UTIs were tested using the biosensor. For a UTIs diagnosis, the resulting biosensor exhibited promising sensitivity and specificity of 87.5% and 92.3%, respectively, with higher accuracy compared with those of 62.5% and 76.9% obtained in the dipstick test. Moreover, the biosensor did not cause a resistivity change from the interfering molecules in urine, such as uric acid, glucose, urea, or ascorbic acid. Although this study demonstrated an efficient chemiresistive method for improving the detection accuracy of LE in urine with a reliable clinical test, there are still challenges to achieving the continuous, real-time monitoring of LE.

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