A mini-review on non-enzymatic electrochemical biosensing techniques for creatinine determination

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Abstract. The escalation of industrial activities over the past century has significantly heightened human exposure to heavy metals, posing grave threat to the health as well as the environment. Cadmium, mercury, and lead are few of the many heavy metals. They are prevalent pollutants and are absorbed, retained, and accumulated within the human body. On the basis of the absorbed dosage, exposure route, and duration, the range of the toxicity fluctuate. While these metals are essential in limited quantities, excessive exposure can lead to severe health complications and disorders. This review examines the mechanisms and adverse effects of cadmium, mercury, and lead on human health when present in exceedingly large amounts.

1 Introduction

Creatinine (2-amino-1-methyl-5H-imidazole-4-one) is an amino acid compound (figure (Fig.) 1) and it is produced in the muscles from the breakdown of creatine phosphate [1]. It is normally excreted out of the body through the blood filtering mechanism of kidneys [2]. The creatinine range in the body serum in healthy male/female 0.7 and 1.3 ppm and 0.5 and 1.1 ppm, respectively may be used as access the kidney function [3]. The kidney function is measure by the glomerular filtration rate (GFR) to eliminate waste products from the blood. In progressive renal failure, the GFR becomes reduced to $< 15$ ml/min, which is a severe reduction in kidney function [4] Advancements in CKD and the resulting cardiovascular diseases is projected to directly contribute to 1.2 million fatalities, 19 million disability-adjusted life-years, and the loss of 18 million years of life [5]. Furthermore, creatinine plays a crucial role in the early identification of muscular diseases, the monitoring of renal function post-surgery, and serves as a direct indicator of the body’s hydration status [6]. Due to its profound clinical significance, creatinine has been firmly established as a vital diagnostic biomarker [7].
There are several methods for measuring creatinine levels in biological fluids, including Jaffé method [8], colorimetry [9], spectrophotometry [10], high-pressure liquid chromatography (HPLC) [11], and mass spectrometry [12]. Each of these methods has their merits or demerits, depending on the specific application and the required sensitivity, accuracy, and precision. For instance, colorimetry and spectrophotometry are relatively simple and inexpensive, but they may be less sensitive and specific than HPLC or mass spectrometry [13]. On the other hand, HPLC and mass spectrometry are more complex and expensive, but they offer higher sensitivity and specific analysis, and multiplexed detection [14].

Compared to these reported methods, the biosensor technology offers significant benefits for regular serum creatinine analysis. This can be attributed to the simplistic design, ease of operation, specific and sensitive detection, fast response time with reduced cost, and personalized monitoring [15]. In both enzymatic and non-enzymatic sensors, electrochemical approaches are one of the primary trends for the detection of creatinine; due to their excellent selectivity, enzymatic systems are the most widely used electrochemical creatinine sensors [16]. There are electrochemical sensors for creatinine detection functioning with enzymes in the literature [15,17,18]. It is important to note, nonetheless, that these systems exhibit poor stability, sensitivity, and repeatability because of the denaturalization of enzymes.

To address these drawbacks, nanomaterials (NMs) has efficient property for a variety of applications, including immobilization and sensing, because of their tiny size as well as high surface to-volume ratio. Recent research has shown that metallic nanoparticles (NPs) are an effective substitute for creatinine detection [19]. Due to the strong affinity between electron rich creatinine (Owing to the nitrogen on the imidazole ring of creatinine) and electron deficient metal atoms, (e.g., gold, silver, iron, and copper), affinity complexes are formed between these reactants. This affinity interaction serves as a basis for the detection of creatinine in numerous studies. The formation of this complex can be readout by various modes including electrochemistry, colorimetry, and many more. Among these, electrochemical detection of creatinine is the most exhaustively studied technique. Accordingly, this article summarises the current state of NMs-based electrochemical biosensors for creatinine detection.

2. Electrochemical biosensors

The first biosensors were developed by Clark and Lyons in 1962 for quantification of glucose [20]. Electrochemical sensors rely on the chemical reactions that occur at the surface of an electrode when it is exposed to the target analyte [21]. There are several types of electrochemical creatinine sensors (amperometric, potentiometric, and conductometric
sensors) depending on specific signal types (Fig. 2) [22]. A biosensor made up by two closely elements such as a biological recognition element and a signal conversion unit [23]. The potentiometric sensors, Due to charge transfer reactions mediated by biocatalysts, the biosensor can be used to determine open circuit voltage between a working electrode and reference electrode presence of creatinine [24]. Conductimetric biosensors are a type of biosensor that detect analytes through changes in electrical conductivity [25].

The development of novel materials in recent years, including metal and metal oxide NMs, carbon-based NMs, and metal-organic frameworks, has resulted in an exponential increase in the analytical performance of electrochemical biosensors.

![Fig. 2. The several types of electrochemical sensors with its own principle of operation. With the approval from reference[15]. Copyright 2018 Elsevier B.V.](image)

### 3 Nanomaterial-based electrochemical creatinine biosensors

Nanomaterial-based electrochemical creatinine biosensors utilize variation in the electrochemical signals generated as a chemical or biochemical interaction between the CKD specific biomarkers and their substrates [26]. For instance, metallic NMs, such as gold nanoparticle (GNPs) or silver nanoparticle (SNPs), can be used to modify the electrode surface and improve the sensitivity and selectivity of the biosensor and its absorption coefficients increase the sensitivity of optical detection methods in comparison to ordinary dyes [27]. The GNPs and SNPs can also be used to amplify electrochemical signal and increase the detection limit (DL) of the biosensor [28]. The carbon nanotubes (CNTs) and graphene can increase the surface area of the electrode, which allows for more enzyme immobilization and enhances electrocatalytic activity of the enzyme[29]. Creatinine biosensors based on NMs provide several benefits over standard enzyme based biosensor, including excellent sensitivity, selectivity, and stability [30]. In a specific study, an electrochemical sensor was constructed for creatinine detection in human body fluids [31]. For sensor fabrication, the dendritic nanofibers of poly(methylene blue) (PMB) were synthesised on the surface of Cu-carbon dot with the help of cyclic voltammetry technique. The constructed electrode displayed DL, sensing accuracy, and linear detection range values of 0.2 ng/mL, 0.133 A ng/mL\(^{-1}\) and 0.5 to 900 ng/mL, respectively [31]. In another report, an electrochemical biosensor was developed for detecting creatinine in urine [32]. The biosensor was developed by modifying a carbon paste electrode (CPE) with SNPs, CNTs, and folic acid...
The electrode displayed great selectivity, stability, and rapid response (1.5) with a DL of 8000 nM [32]. Li et al. developed a microfluidic biochip to evaluate the levels of creatinine in body serum [33]. The biochip was fabricated using a screen-printed carbon electrode (SPCE) and polydimethylsiloxane (PDMS) sheets with the help of microfluidic components. Gold nanoflower (GNFs) were carboxylated and subjected to reaction to change multi-walled carbon nanotubes (MWCNTs). A portable biodevice was created by accommodating the microfluidic biochip with a smartphone-based to determine creatinine at the point of care.

The biosensor was effective in creatinine recognition across a wide analytical scale of 0.01 to 1 μM and DL of 0.5 μM [33]. In a recent work, Teekayupak et al. created an electrochemical sensor based on modified CuO-IL/rGO nanoparticles for the detection of creatinine in urine samples [34]. Without the requirement for enzymes, the modified 3D-printed electrodes (3DE) provided electrocatalytic activity for creatinine. In ideal conditions, the modified 3DE directly linked with a portable smartphone potentiostat demonstrated a linear detection range of 0.5-35.0 mM and a DL of 37.3 M [34].

4 Conclusion

The significance of creatinine as a diagnostic molecule has led to the rise of numerous novel technologies for its detection in clinical samples. Compared to conventional diagnostic methods, NM-based electrochemical sensors offer significant benefits for regular serum creatinine analysis. These include — improved sensitivity, reliability, portability, low fabrication cost, and point-of-care detection. Moreover, interfacing of electroactive probes with NMs increases the performance of electrochemical sensors owing to increased surface area of electrode, enhanced immobilization of the biological ligands over the probe material, thereby leading to enhanced electrocatalytic activity of the biological ligands. However, electrochemical creatinine sensors also have some limitations, including the need for calibration to ensure accurate measurements, and the potential for interference from other molecules in biological samples. Future studies on the development of electrochemical creatinine sensors should focus on comprehending the mechanism of creatinine interaction with the NMs. Further, the performance of electrochemical nanosensors must be validated under clinical samples with focus on personal care and mass scale reproducibility.

References

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