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Conventional and nanotechnology based sensors for creatinine (A kidney biomarker) detection: A consolidated review

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ABSTRACT

There is an increasing demand for developing the novel methods for the detection of clinically important metabolites. One among those metabolites is creatinine (2-amino-1-methyl-5H-imidazol-4-one), a waste product, produced by the catabolism of phosphocreatine from muscle and protein metabolism. It is very important to measure the creatinine level in human blood and urine as it reflects the muscular and thyroid functions. Importantly, the elevated level of creatinine is considered to be as impairment of the kidney. There are numerous methods existed to measure the concentration of creatinine in blood and urine. In this review, we consolidated the different conventional methods (chromatography, spectroscopy, immune sensor and enzyme-based detections) and their shortcomings. On other hand, we also dissertated the various nanomaterials (chemiluminescence, voltametric, amperometric, conductometric, potentiometric, impedimetric and nano polymer) based creatinine detection methods and their advantages. Finally, we also focussed on the point-of-care detection methods of creatinine determination. This review can conclude the low cost, more efficient and reliable nanotechnology-based new sensors for the detection of creatinine.

1. Introduction

The creatinine is a waste product of creatine phosphate derived from muscle and protein metabolism. It is constantly excreted from the body depending on the mass of protein and muscle metabolism [1]. Kidneys purify blood by filtering its contents and are released into urine. Creatinine is one among the metabolites expelled from the body by the function of kidneys. Its level in body can be checked through blood sample and the high level determines the impairment of kidneys. Protein and muscle mass are also the determining factors of creatinine content in human body; hence men have relatively higher muscle mass and usually contain higher creatinine than woman and children. The creatinine formed in the muscle transported to kidney for the excretion as illustrated in Fig. 1. Creatinine test can be conducted by various methods, some of the commonly exploited methods includes BUN (blood urea nitrogen) test or comprehensive metabolic panel (BMP or CMP). If CMP tests are observed to be abnormal then there may be relative risk of kidney related diseases. Estimated glomerular filtration rate (eGFR) is the blood filtered per minute by the kidneys. This test can screen and detect early kidney damage (EKD), this in turn can diagnose kidney health status and prevent from chronic kidney diseases (CKDs). CKDs are notified one of the most prevalent and cost consuming disease facing worldwide [2]. The prevalence of CKDs in global scenario existed between 11% and 13% [3].

Creatinine determination can be performed by several methods, varying from conventional to modern methods. Conventional methods employed are chromatography or enzyme-based methods. On other hand, modern methods namely nanotechnology-based methods, molecular imprinting (MIP), electrochemical methods, amperometric biosensors, potentiometric biosensors, conductometric biosensors, impedimetric sensors and chemiluminescence sensors have been developed in recent past for the detection of creatinine. Conventional

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methods are relatively simple and cost effective, however, in certain cases the results produced are low in reproducibility, low accuracy, low reliability and low specificity [4,5]. On other hand, nano-based methods offers great advantages and has potential capability to address major disadvantages associated with conventional methods.

2. Pros and cons of the different approaches for the creatinine detection

The most commonly exploited conventional methods of creatinine detection are spectrophotometry [4], colorimetry, high pressure liquid chromatography (HPLC) [5], mass IR spectroscopy [6], spectroscopy [7], capillary zone electrophoresis [8], enzymatic assays and nuclear magnetic resonance (NMR) [9]. One of the oldest methods of creatinine detection is chromatography method, where it separates molecules from a complex mixture. However, these methods encounter a number of limitations such as low rate of reproducibility, stability (creatinine stability) and sensitivity. Moreover, conventional methods do not address the interventions occur by numerous biological metabolites (ascorbic acid, cephalosporins, fructose, glucose, ketone bodies) which causes the inaccurate results either may be quantitatively or qualitatively. Such hindrances create inaccuracy in creatinine determination. Reliability of the interpreted results is much lower than those derived from modern techniques such as molecular or nano-based studies.

The modern and novel methods of creatinine detection is made possible with the development of nanoscale materials. Nanoparticles (NPs) are small building blocks operating exceptional applications and developments made through nanotechnology. Creatinine determination methods employing nanoparticles offers great advantages like higher sensitivity, improved stability, better absorbability, cost effective, simple procedure and higher accuracy. Specially, metallic nanoparticles are widely exploited in the estimation of creatinine concentration and extensively used in early detection of chronic kidney disorders (CKD) [10]. It is very interesting that nanoparticles have been successfully synthesized using various methods namely, UV mediated, sunlight mediated, sonocatalytic, plant mediated, temperature assisted and using some biological materials [11–23]. These nanoparticles exhibit many unique properties such as high surface volume ratio, higher absorption ability and enhanced catalysis makes them highly fit to utilize as sensors in medical study to detect several ailments at initial stages. The main advantage of these nanoparticles includes the application in electrochemical reactions to enhance the electron transport in enzyme active site for creatinine detection [24].

3. Conventional methods employed in the detection of creatinine

The most frequently employed conventional methods for detecting

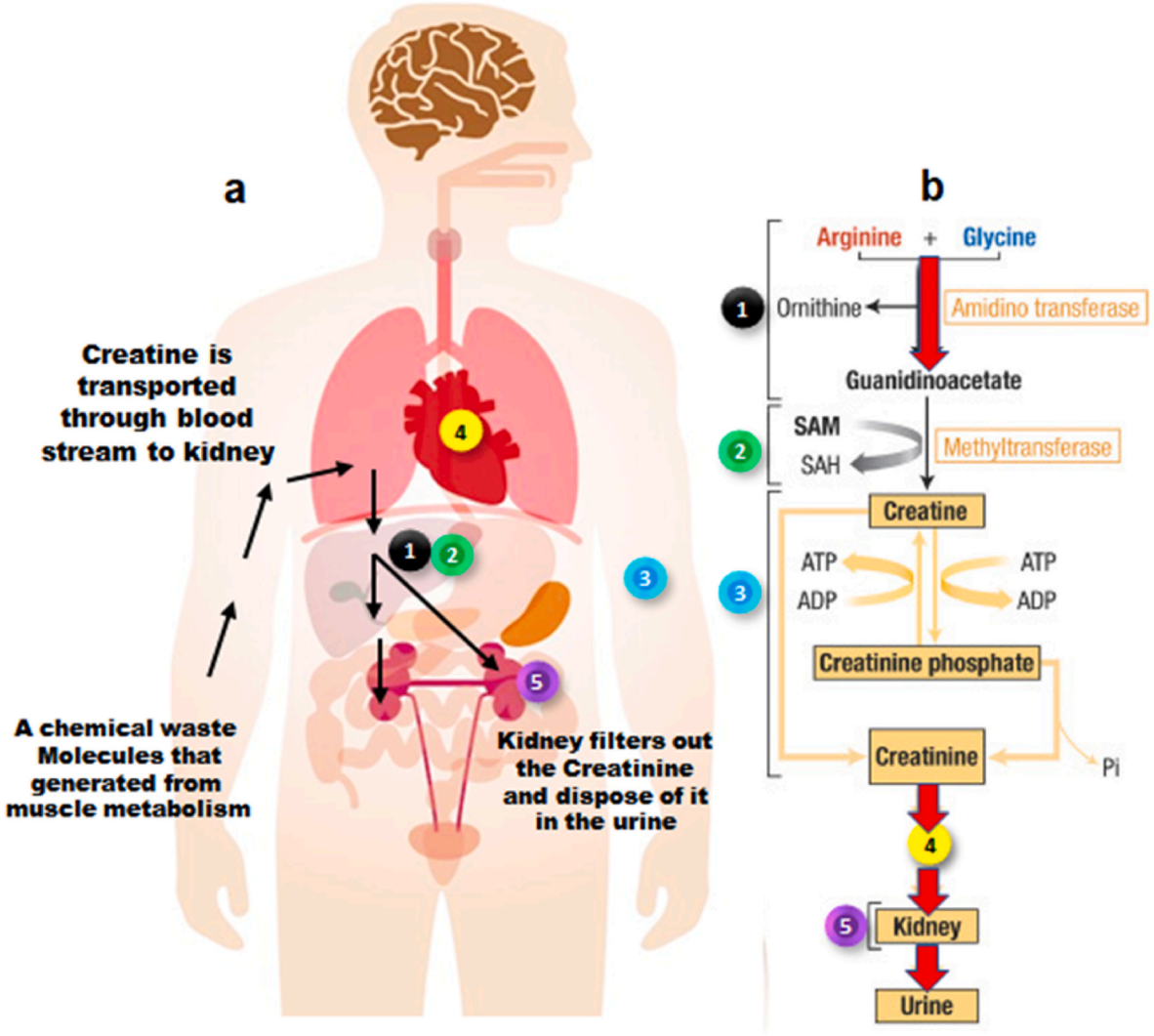

Fig. 1. (a) Creatinine, a waste product, transport into kidney through vascular system (b) The process of metabolism of creatinine in different organs.

the levels of creatinine includes spectrophotometry, HPLC, mass spectroscopy, immunological and enzyme assay methods. Basic mechanism behind the functioning of various types of electrochemical sensors is illustrated in Fig. 2.

3.1. Chromatography-based methods

HPLC (High performance liquid chromatography) is one of the most sensitive technique which is employed not only to separate but also to quantify the serum levels of creatinine by measuring absorbance at 234 nm using cation exchange chromatography [25]. The sensitivity of HPLC based detection method is found to be 0.28 nM [26]. GC-MS can also be considered for the quantification of creatinine in the given sample. However, the method is very laborious, time consuming and require separation step before the sample is subjected for analysis. On other hand, the samples containing creatine should be removed from the samples to prevent the derivation of creatine to creatinine, otherwise causing the false quantification of creatinine. This is very important step in determining the creatinine using gas chromatography [27]. LC-MS is considered to be much faster method to determine the creatinine as compared to HPLC and GC-MS and does not require any derivation step of the sample before its analysis [27]. In LC-MS based detection solvent protein precipitation is used for cleaning the samples. To minimize the loss of creatinine during sample preparation, deuterated creatinine was added before treating with ethanol. The use of isotopic creatinine as reference material helps in quantifying the creatinine accurately in the unknown samples [28].

3.2. Spectroscopy based methods

The normal spectroscopy method involves the treatment of samples (blood/urine) with picric acid which forms red colour whose absorbance can be measured in the range of 470–550 nm with absorbance maxima at 520 nm. The reaction mechanism is illustrated in Fig. 3. However, the reaction was found to be non-specific and depends on several factors such as pH, temperature, sample purity, RBC and other proteins in the blood sample which may give erratic results [29,30]. In addition, spectroscopic measurements require more sample volume (up to 2.0 ml).

The advanced spectroscopic detection of creatinine involves both absorbance and emission of fluorescence in the presence of chalcone PTP ((E)-3-(pyrene-2-yl) - (3,4,5 tri methoxy phenyl) prop-2-en-1-one. It displayed two absorbance peaks at 297 nm and 407 nm at low pH, depending on the concentration of creatinine. Dal Dosso et al. (2017), developed the point-of- care sensor comprising of multilayer polymeric cartridge with multi enzyme system (involved in hydrolyzing creatinine) integrated with microfluid pump for sampling and detection of creatinine at 570 nm. This point-of-care sensor works on the change in colour due to the release of H_2O_2. The sensitivity of the above detection method was found to be up to 1 nM concentration [31,32].

3.3. Infrared and Raman spectroscopies

Molecules with polar bonds contribute to infrared absorption from 700 nm to 2500 nm [33]. Analysing the biomolecules using IR is very

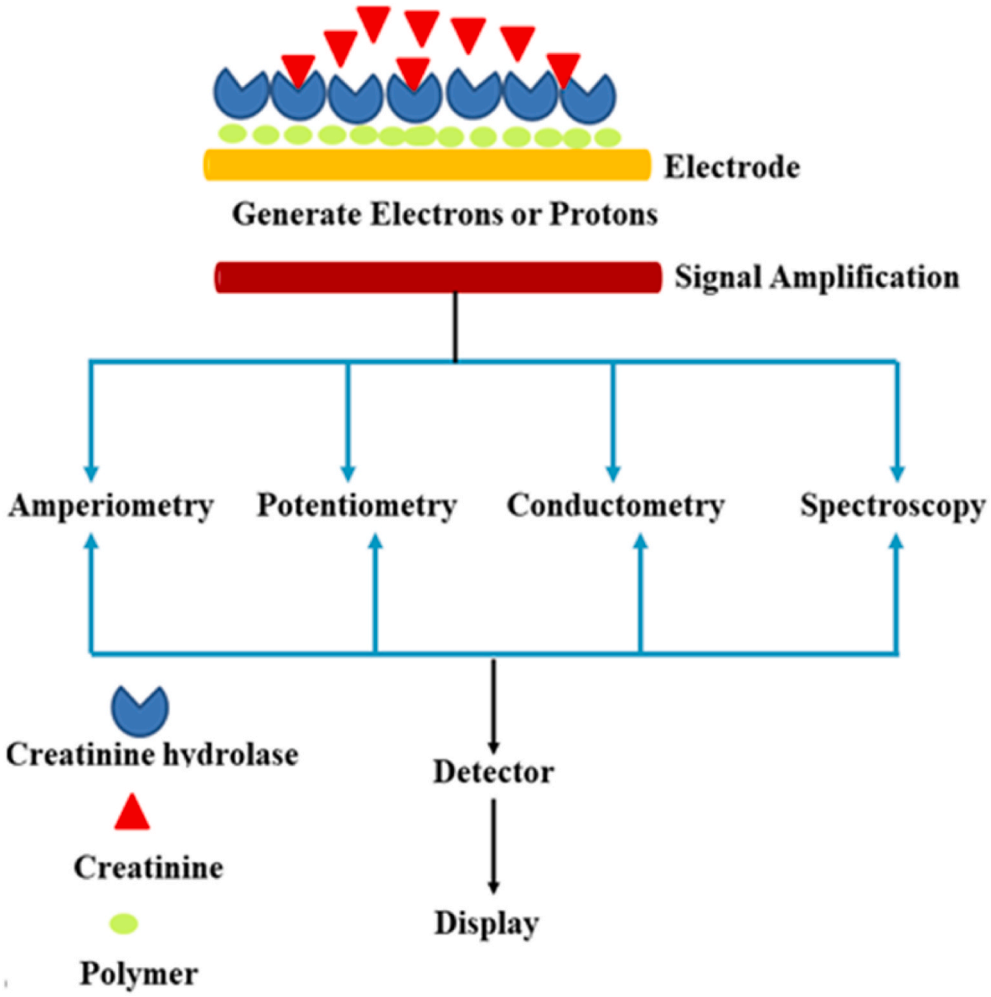

Fig. 2. Mechanism involved in different chemical sensors available for the detection of creatinine.

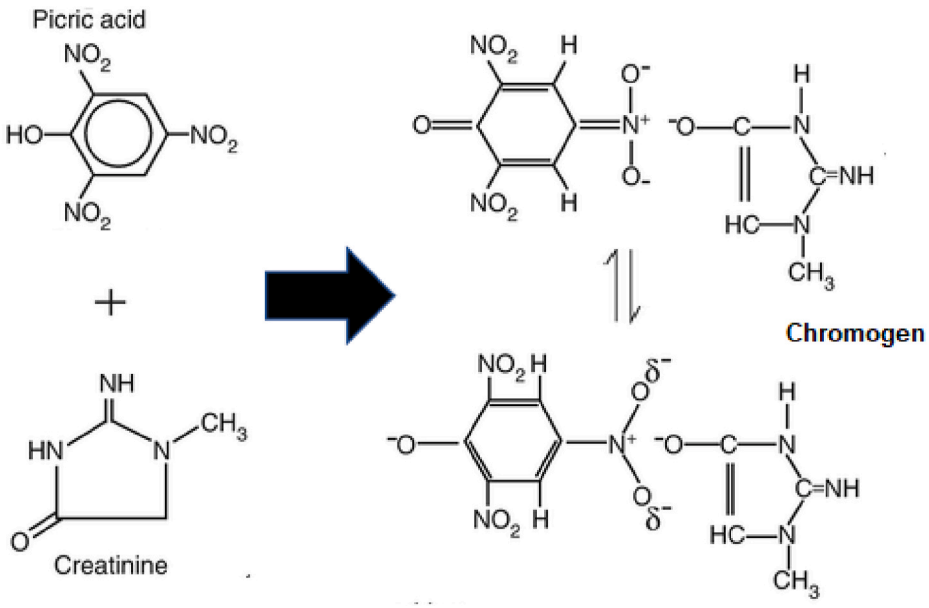

Fig. 3. The creatinine reacts with picric acid forms the chromogen; a colour compound spectroscopically measured at 520 nm.

difficult as they are very complex in nature with several overlapping bands. The IR spectra for organic molecules is often predicted in two regions (i) functional group (>1500 cm^{-1}) and (ii) fingerprint region (<1500 cm^{-1}) [34]. Raman spectroscopy determines the structural finger prints of biomolecules based on the vibration modes of molecules [35]. To minimize the sensitivity issues associated with IR and Raman methods, the urine samples were analysed by surface enhanced Raman spectroscopy. The signature peaks for creatinine were observed at 888 cm^{-1}, 958 cm^{-1} and 1444 cm^{-1} due to C═O, C–C and CH_3 [36]. Excitation of wavelength is the key factor to minimize the fluorescence of urine sample and reduce the signal to nose ratio. The sensitivity of Raman spectroscopy was found to be 0.2–15 mg/L [37,38].

3.4. Immune sensor

Detection of compounds/molecules based on the immunological (antibodies) reaction are called immune sensors. For detecting the creatinine levels in the given samples indirect method is used, where the signal is generated by the emission of light (fluorescence or luminescence). The sensor is made of creatine modified platinum electrode (electrochemical cell) [39]. The test sample is mixed with anti-creatinine antibodies and mouse anti-IgG conjugate placed in the modified electrochemical cell. After washing the sample, glucose was added and the generated H_2O_2 will be measured by amperometric sensor. The detection limit of the above sensor ranges from 0.09 to 90 μM. The method is very reliable, less interference and very sensitive [40].

3.5. Enzyme based detection of creatinine

The enzyme mediated creatinine detection can be broadly divided into three types (1) H_2O_2 (2) NH_4^+ (3) Electrical potential difference [41]. In case of H_2O_2 based detection, creatinine is treated with creatine amido/aminido hydrolase in presence of water to produce either creatine or sarcosine. The H_2O_2 released during the above enzymatic reaction will be detected by oxygen-based electrodes using amperometric sensors. In the second type, the amount of ammonia released during the enzymatic reaction of creatinine deiminase which converts creatinine to *N*-methyl hydantoin in presence of water and releases NH_4^+ which is detected either by pH/potentiometric sensors as mentioned in Fig. 4. The levels of NH_4^+ is directly proportional to the creatinine concentration. However, the sensitivity of the reaction is hampered by the NH_4^+ present in blood/urine sample [42]. While, in third type creatinine is hydrolyzed to creatine/sarcosine in presence of creatinine amidohydrolase/aminido hydrolase and water. In this sensors, the creatinine concentration is measured in terms of change in electrical potential and is measured by using potentiometric sensors [43]. The efficiency of the above system greatly depends on the complexity and sensitivity of enzymes being used [44]. Based on the number of enzymes being used for the detection of creatinine, they are classified into first,

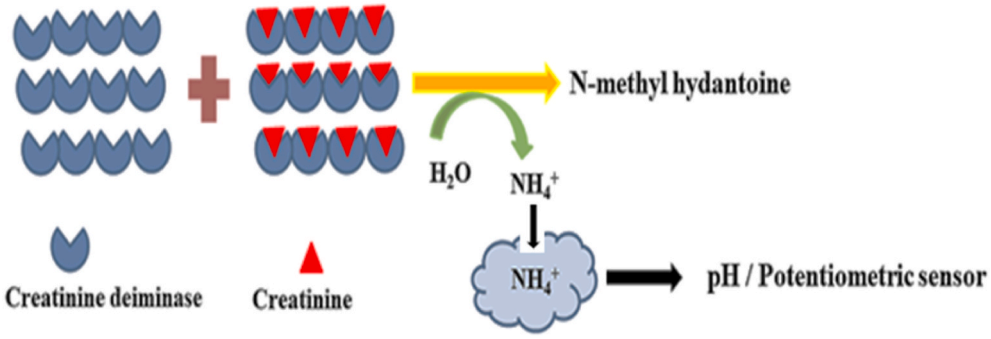

Fig. 4. Ammonia released during the enzymatic reaction of creatinine deiminase which converts creatinine to *N*-methyl hydantoin in presence of water and releases NH_4^+ which is detected either by pH/potentiometric sensors.

second and third generation biosensors. In case of first-generation, creatinine deiminase is immobilized on the membrane along with nitrifying bacteria (Nitrosomonas/Nitrobacter species) on to dissolved oxygen (DO) meter. The NH_4^+ ions thus produced by the enzymatic reaction with creatinine is used by the Nitrosomonas and Nitrobacter species and decrease in oxygen levels at platinum electrode (DO sensor) [45,46]. The conventional methods described above have several short comings such as low reproducibility, require large sample volume, sample analysis time, stability and cost [23,44].

4. Nanoparticle mediated sensors for the detection of creatinine

In order to overcome the flaws in conventional methods for detecting creatinine, scientists have developed advanced detecting techniques to determine the creatinine concentration in the sample (blood/urine) by employing nanomaterials in their analysis. Silver nanoparticles (AgNPs) coated with picric acid is treated with the test sample to generate red colour by performing centrifugation step and quantifying the creatinine levels [47]. On other hand, AgNPs coated with citric acid was reported to cause creatinine aggregation in urine sample at pH 12 [48]. A concentration-based creatinine detection method was developed by coating Hg^+ on AuNPs in urine sample which change the colour from red to blue [49]. The above nanomaterial-based detection methods are rapid and fast, but the precision is not accurate and can be considered for qualitative detection. It was reported that even three creatinine hydrolyzing enzymes were co-immobilized on the membrane. Creatinine amidohydrolase converts creatinine to creatine, which is subsequently converted to sarcosine by the action of creatinine aminido hydrolase. The resulting sarcosine is finally converted to glycine and the decrease in oxygen levels are detected in the third step of enzymatic reaction [50]. The limitation of the above detection is the interference of atmospheric oxygen. In second generation, three enzymes are coupled (covalently immobilized) on the membrane. The first enzyme (creatinine deiminase) will hydrolyze creatinine to produce NH_4^+, followed by the synthesis of glutamate and finally formation of 2-oxoglutarate in presence of glutamate oxidase. The decrease in oxygen levels during the above reaction cascade is detected by the oxygen electrode. In case of third generation system, three creatine hydrolyzing enzymes were co-immobilized on to the membrane. The first enzyme (creatinine amidohydrolase) will convert creatinine to creatine which is converted to sarcosine in presence of second enzyme (creatinine aminido hydrolase), finally glycine is produced from sarcosine in presence of third enzyme (sarcosine oxidase). The constant decrease in the oxygen levels in the sample is detected by oxygen electrode. Amperometric detection is used for the detection of oxygen levels in the above enzymatic methods [43,51].

4.1. Chemiluminescence based systems for creatinine sensing

In this chemiluminescence based systems, the analyte or test sample will be detected by chemical reaction between the analyte and the substrate by excitation and deexcitation of molecules to ground state and release energy either in the form of heat or light. The sensitivity of the above sensors for creatinine detection is 72 nM [52]. In another method, creatinine in serum samples is detected by using palladium-naphthalimide fluorescence (FCP) probe by incubating the sample for 30 min. The creatinine palladium complex will allow the release of the FCP which in turn increases the fluorescence intensity. The above method was validated with Jaffe method with efficiency of 95–99% respectively [53]. A photoluminescence sensor was developed by functionalizing bovine serum albumin (BSA) with carbon-gold

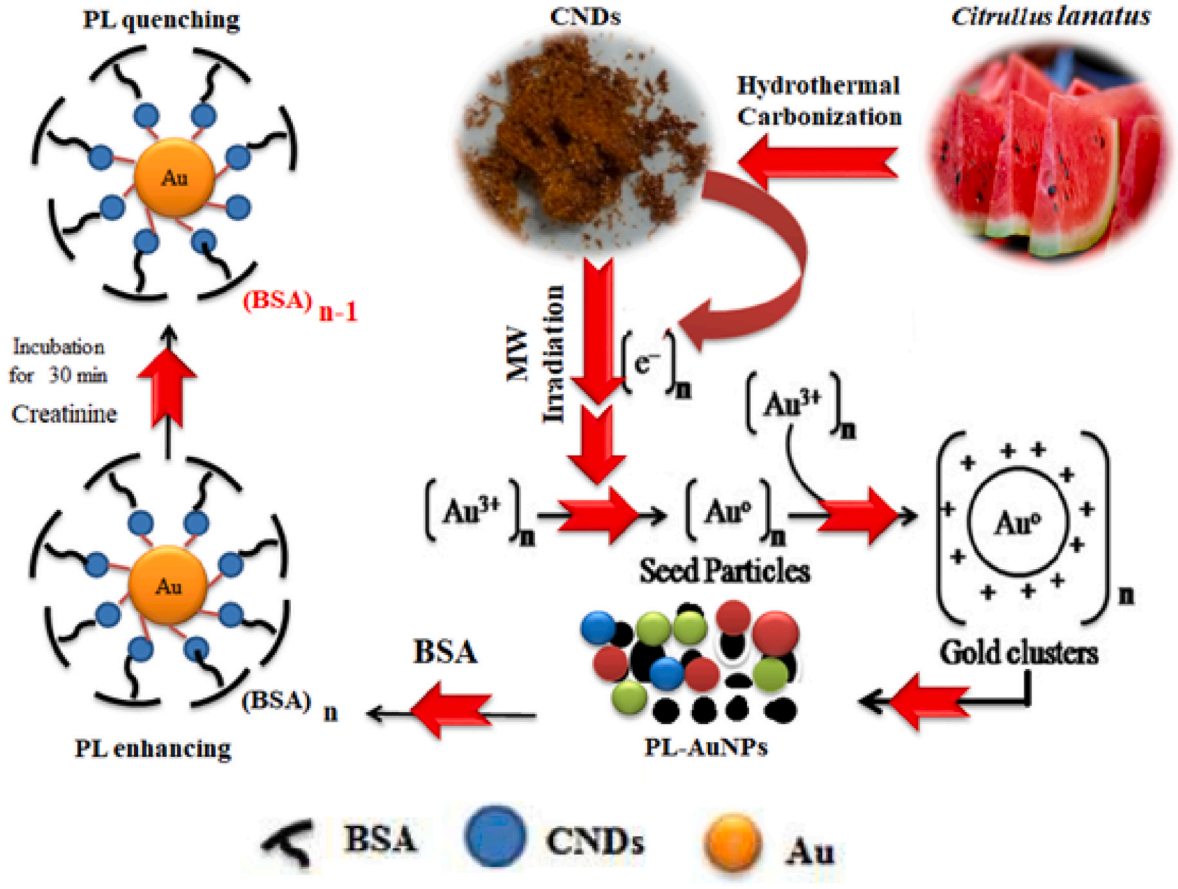

Fig. 5. Synthesis of C–Au nanocomposite from *Citrullus lanatus* and photoluminescence of colloidal solution decreased due to attachment of creatinine with BSA thereby sensing the creatinine.

nanocomposites. In this sensor, the luminescence will decrease with increase in concentration of creatinine, as the nanocomposite forms complex with creatinine which causes the release of BSA from the composite as illustrated in Fig. 5. The sensitivity of the above sensor ranges from 17 μM to 1.7 M in all test samples [20].

4.2. Nanomaterials based voltametric method of creatinine sensing

In this method, the polymers made of carboxylic polyvinyl chloride, polyaniline or cotton fiber membrane are imprinted with Au nanoparticles by electro polymerization. The sensitivity of the above sensors ranges from 0.14 nM to 0.35 nM. However, the disadvantage with the above method is duration of sample analysis ranges from 3 to 5 h [54]. In another method, molecular imprinting of polypyrrole film doped with phosphomolybdate on glassy carbon electrode could able to record creatinine levels by differential voltammetry [55]. Voltametric detection of Cu-creatinine complex was enhanced by treating the serum sample with PbO_2 which prevented the interference of uric acid. Also, Molecular imprinting of carbon electrode with $FeCl_3$ cotton fiber membrane was used to detect the creatinine concentration in the given test sample. Creatinine forms complex with Fe^{3+} leads to gradual decrease in Fe^{3+} ion concentration resulting the decrease of current which will recorded by the voltameter as mentioned in Fig. 6. The above method does not require any pre-treatment step and does not interfere with serum albumin [56]. An indirect method for detection of serum cysteine C (another biomarker for Chronic Kidney Disease, CKD) was developed by imprinting cysteine protease, papain on multiwalled nanotubes. The amino terminal of papain is covalently linked to electrode. The interaction between papain and cysteine C is monitored electrochemically by the electrode. The detection limit of the above electrode was found to be 0.006 nM [57]. Molecular imprinted glassy carbon electrode was developed by the functionalization with Ag nanoparticles or polyoxometalate to detect creatinine in the sample with detection limits of up to 1.5×10^{-11} M [58].

4.3. Nanomaterials based amperometric methods for the detection of creatinine

In this method, the sample is detected by the chemical reaction occurring between analyte and electrode. Creatinine is detected either by employing single or multi enzyme system in presence of three electrodes [59]. The working electrode is made of Ag which is used to sense the creatinine, while the other two are counter and inert electrodes. The amount of oxygen (H_2O_2) released by the enzymatic reaction will be detected by the working Ag electrode. However, the sensitivity of the sensor is greatly affected due to the complexity of enzymes and the use of multiple sensors [60]. Covalent immobilization of creatinine amidohydrolase or sarcosine oxidase with zinc oxide nanoparticles on to either multiwalled carbon nanotubes/chitosan/polyaniline/could able to detect the creatinine levels up to 0.5 μM in 10 s at pH 7.5 and 30 °C [61]. The above creatinine biosensor could able to retain 85% of its activity when stored at 4 °C for 4 months. Co-immobilization of creatinine amidohydrolase or creatinine amindino hydrolase by covalent interaction with *N*-ethyl-*N*-(3-dimethylaminopropyl) carbodimide (EDC) and *N*-hydroxy succinimide on polyaniline or carboxylated multi-walled carbon nanotube nanocomposite on the surface of platinum electrode as mentioned in Fig. 7. The above biosensor showed optimum activity at pH 7.5 and 35 °C with response time of 5 s. The nano biosensor retained 85% of its activity even after 180 days of storage or 150 times of regular use [24]. Co-immobilization of creatinine hydrolyzing enzymes (creatinine amidohydrolase or creatinine amindino hydrolase) on to Fe_3O_4 nanoparticles in presence of chitosan-polyaniline complex. When this complex is polarized with Ag/AgCl, the biosensor displayed optimum activity (1–800 μM) at pH 7.5 and 30 °C with response time of 2 s. The above biosensor could retain 90% of its activity when stored at 4 °C (120 uses; 200 days) [44]. Similarly, enzyme nanoparticles (creatinine amidohydrolase or creatinine amindino hydrolase) were immobilized on glassy carbon electrode for amperometry detection of creatinine in blood samples in 10 s at pH 7.2 and at 34 °C with limit of detection up to 50 μM. The biosensor was stable up to 30 days when stored at 4 °C [62]. An improved amperometric biosensor was developed by modification of

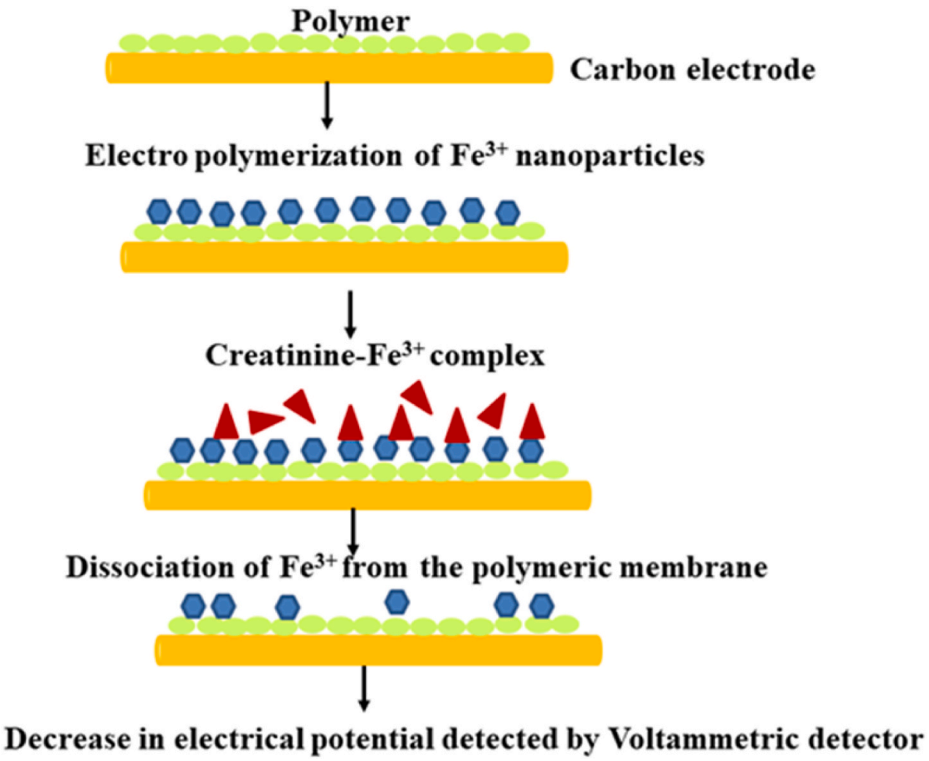

Fig. 6. Polymer and iron based voltametric detection of creatinine.

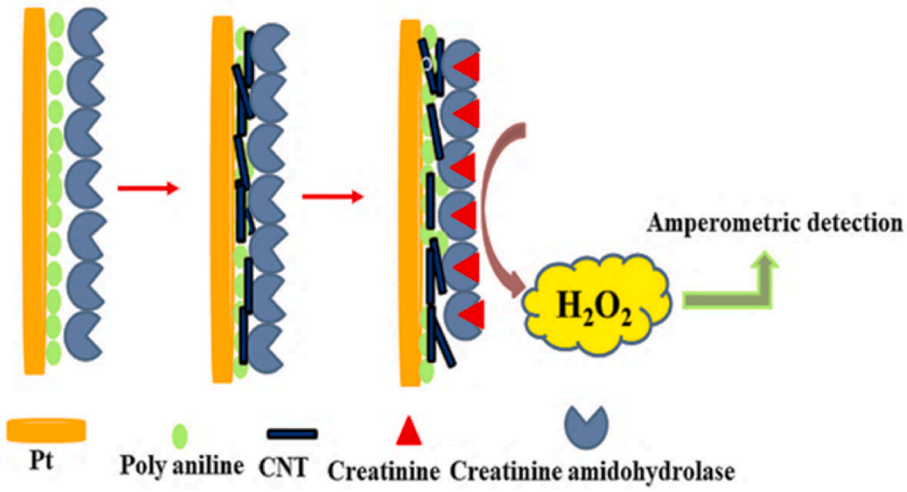

Fig. 7. Amperometric detection of creatinine using platinum and carbon nano tubes.

glassy carbon electrode co-immobilized with creatinine hydrolyzing enzymes and when polarized against Ag/AgCl at pH 6.0 and 25 °C with response time of 2 s. The efficiency of the above biosensor was found to be around 90% (240 days of continues usage) when stored at 4 °C [63]. Creatinine in the given test sample is monitored by amperometric measurement of the Fe-creatinine complex formed and detecting the levels of free Fe^{3+} which causes alteration in current generated as described by Kumar et al. (2018). Thus, the above method does not require any pre-treatment step and can abort the interference or interaction of albumin with the test sample [64]. As compared to potentiometric or conductometric biosensors, amperometric biosensors offers great advantages in terms of sensitivity, cost, rapid testing and easily disposable.

4.4. Nanomaterials based conductometric methods for sensing of creatinine

In this method, the creatinine levels in the sample will be detected my measuring the ions present or released during the reaction. Creatinine hydrolyzing enzyme was covalently immobilized on to glutaraldehyde with ammonia sensor. Test sample containing creatinine is placed on the sensor which produces the ammonium ions creating a change in electrical resistance which is detected by the ammonium sensor. The detection limit is 2×10^{-6} M, response time of 10 s, pH 7.0 and storage stability of 1 month at 4 °C [65]. Ammonium sensitive conductometric biosensor can be developed using polyvinyl chloride-NH_2 membrane [65]. Conductometric sensor developed by immobilizing creatinine deiminase on to polymeric nanocomposite (polyvinyl alcohol/polyethyleneimine with AuNPs) can be used for the detection of creatinine [66]. The above method can be employed to determine the concentration of various unknown samples which are not light sensitive, compatible and no need of any reference electrode with good limit of detection [65,66].

4.5. Nanomaterials based system for the detection of creatinine

Creatinine levels are detected based on the variation in potential difference or pH or the release of NH_4^+ ion during the reaction. Molecular imprinting of creatinine hydrolyzing enzyme (creatinine deiminase) by either ionic/covalent/cross linking on to a polymeric support (chitosan/carboxylated polyvinyl chloride/tetrahydrofuran) or Ag nanoparticles are very popular for detecting the creatinine levels in the samples. Certain electroactive materials made of creatinine molybdo phosphate, creatinine picrolonate and creatinine tungsto phosphate were developed to integrate with poly vinyl chloride membranes to promote the diffusion of creatinine to the enzyme layer to enhance the signal generation [67]. A wired potentiometric electrode was developed to detect the creatininium ion in urine and plasma samples [68]. The results were validated with Jaffe gold standard method. The disadvantage with the above potentiometric biosensor is, the test samples need to be buffered at pH 3.8 to convert neutral creatinine to creatininium ion [69]. The detection limit of the above sensors varies from 5 μM −0.1 mM concertation [49,70]. However, the stability of enzymes is a big concern for this type of sensors [71]. High purity metallic sensors with polyvinyl chloride membrane were produced to sense the levels of creatinine in blood and urine samples [72]. Molecular imprinting of polymeric materials (polyvinyl chloride) was used to dope the electrode to detect the creatine levels, an indirect evaluation of creatinine. The exchange of ionic charge take place across the membrane by binding of creatine to the membrane receptors which produces extra surface charge based on ionic and electronic conductors [73].

4.6. Nanomaterials based impedimetric/capacitive systems for the detection of creatinine

In this system, the creatinine detection greatly depends on the thickness and the amount of sample absorbed to the receptor present on the electrode. Lesser the thickness of molecular imprinting of polymeric membrane (methylene diacryl amide or alkynyl alcohol or acryl amido methyl propane sulfonic acid), more will be the efficiency of sensor. Molecular imprinting of carboxylic polyvinyl chloride on to gold plated electrode followed by polymerization with N, N'-methylene bisacrylamaide to cover the free space such that creatinine will bind specific to the surface of gold-plated electrode. The levels of creatinine were qualitatively detected by using either differential pulse voltammetry, UV–visible spectroscopy or cyclic voltammetry with detection limit of up to 0.08 ng/ml [54]. The concentration of analyte (i.e) creatinine is determined by change in capacitance of the electrode [67]. Since, there is no chemical or enzymatic reaction involved in this system as a result there will be no change in pH. Thus, the response time is slightly higher as compared to amperometric or potentiometric system. In addition to the above, the electrode fouling and signal to noise ratio is higher in these sensors [74,75].

4.7. Nano-polymer based detection of creatinine

The world of medical science has undergone a drastic improvement upon discovery of polymeric nanoparticles (PNPs) over recent years. Properties of PNPs such as small in size has allowed controlled release of chemicals and effective reach of target sites. Hassanzadeh and Ghaemy,

2017 recently conducted an experiment to detect creatinine by magnetic molecularly imprinted polymer NPs [76]. In this study, they have developed a novel method to detect and separate creatinine based on molecular imprinted polymer nanoparticles (MCMIPNs). It was prepared by polymerising methacrylic acid (MAA) in presence of magnetic Fe_3O_4 NPs functionalised with 3-(trimethylsilyl)propyl methacrylate (TMSPMA) and in presence of a cross-linker; ethylene glycol di-methacrylate (EGDMA). The polar carboxylic acid groups in MAA were supplied to the molecularly imprinted polymers in order to improve the interaction of functional monomers and template molecules which plays a crucial role in selection. Detailed characterization of MCMIPNs were done for adsorption or desorption course, size, selectivity, structure, reusability, magnetic and thermal properties. Other factors effecting adsorption like interaction period, pH, Fe_3O_4 NPs amount and initial concentration of creatinine present prior to treatment are also studied. The MCMIPN of 25 nm size records, an outstanding affinity for creatinine with a percent of 99 efficiency of loading. The MCMIPN nano-polymer showed tremendous recognition and binding capability of creatine when compared to *N*-hydroxysuccinimide (NHS) and L-tyrosine. In another study conducted by Nanda et al., 2015 developed a novel method creatinine detection using nano-polymer based sensors. Sensor employed are poly-lactic-co-glycolic acid (PLGA) and 1-butyl-3-methylimidazolium (BMIM) chloride, in the existence of 2′,7′-dichlorofluorescein diacetate (DCFH-DA) [77]. Functional porous polymer like structure (FPPS) were formed from PLGA and BMIM. Creatinine entrapped in FPPS gets rapidly hydrolyzed and releases hydroxyl ions. These ions get converted from DCFH to DCF^{+}, giving out green colour. This conversion leads to in enlargement of FPPS and improves solubility. Detection of creatinine levels of even 5 μM and also from blood can be measured by DCFH-based nano sensor. This novel method developed could be employed in investigative applications for observing individuals with kidney disorders.

5. Nanomaterials based point-of-care methods for the detection of creatinine

Samples which cannot be analysed by colorimetric or electrochemical methods can be analysed by advanced sensing devices. The creatinine in blood samples can be detected by paper-based sensors which allow the separation of plasma and blood. Several point-of-care devices has been developed recently which works by enzymatic hydrolysis of creatinine to produce H_2O_2 and NH^{4+} can be detected by amperometric or spectrophotometric methods. However, the accuracy and efficiency of the sensors are hampered by the complexity, sensitivity and stability of enzymes. Stat/Roche-Reflotron/Abaxis-Piccolo based sensors exhibit greater potential and offers a great scope to be considered as point-of-care device for measuring the creatinine levels in blood samples with low sample volume, high sensitivity and lesser time for analysis. Immobilization of multiple enzymes which can hydrolyze the creatinine to generate H_2O_2 can be detected by colorimetric sensor can be considered for point-of-care device. As immobilized enzymes are quite stable, long lasting and can analyze the sample in less time. However, the cost incurred in developing such enzyme-based sensors is rather expensive. Regeneration of biosensors after its biosensing activity are very important in point-of-care diagnosis process. The regeneration of biosensors can be performed by altering the composition of solvent by either chemical/thermal modifications to promote the unbinding of analyte and the sensor or minimizing the ionic/covalent interactions between the sample and sensing probe or altering the hydrophobic interactions and enhancing the negative potential by electrochemical modifications. Employing the above strategies, we can recover the biosensors for further use and applications [75]. A non-enzyme-based point-of-care sensor developed by Kumar et al. (2017a) were the complex formed between Fe^{3+} with creatinine, helps in analyzing the urine samples with greater efficiency and sensitivity [56]. The sensor is stable to temperature (20–40 °C) and even minimal interference of albumin. Any point-of-care device developed should be selective, easy to handle, generate reliable results (sensitivity should be high), minimal detection time and easy disposal. At laboratory scale level several point-of-care devices were developed to detect the creatinine levels in blood and urine samples but no accurate biosensor which can considered for point-of-care detection. There is a great need to develop biosensors in the form of wearable devices such as diapers or bags or microneedle to sense the levels of creatinine using advanced technologies. The other key factors to be considered while developing biosensors includes cost, shelf-life, fouling, disposability, calibration/recalibration frequency and finally validation using either Jaffe method/HPLC based gold standard techniques. Finally, we have listed various creatinine detection methods

Table 1
Various methods used for the detection of the creatinine (For creatinine, 1 mM is equal to 0.113 g/L).

Method	Lower Limit of Detection (Sensitivity)	Specificity	Time/ Interference	Reference
Uric acid/Hg 2+ -AuNPs system	0.019 μM	High		[49]
Potentiometric sensor	0.6 μM	High		[68]
Amperometric sensor	0.6 μM	High	Uric acid	[78]
AgNPs on poly (pyrrole) thin film-based SPR sensor	0.19 μM	High	20 min	[79]
AuNPs colorimetric probe	80 μM	High	24 min	[80]
Capillary-gravitational chip	900 μM	Low	10 min	[81]
Conducting-polymer electrochemical sensor	40.4 μM	High	<5 min	[82]
Electrochemical sensor	0.27 mM	Low	5 min	[83]
Enzyme-amperometric sensor	5.3 μM	High		[84]
AuNPs based colorimetric sensor	12.7 nM	High	<5 min	[85]
AuNPs	121.2 μM	Low	3 min Bovine serum albumin, cationic components	[86]
Ion mobility spectrometric sensor	5.3 μM	High	7 min	[87]
Tandem mass spectrometry	3.5 μM	High	1 min	[88]
Multichanllel kinetic spectrometric sensor	6.7 μM	High	7.1 min	[89]
PEG/ Hg2+–AuNPs Colorimetric sensor	9.68Nm	High	<5 min	[90]
Photonic crystal sensor	6 μM	High	30 min	[91]
Portable microfluidic sensor	29.2 μM	Low	2 min Glucose, carbonyl compounds, haemoglobin, human serum albumin, transferrin, IgG	[92]

in Table 1.

6. Conclusion

Creatinine is a waste metabolic bi-product filtered out of the body by kidneys. The high values of the creatinine concentration in blood/urine can be treated as malfunctioning of kidneys. There are quite number of methods namely conventional methods (chromatography, spectroscopy, Infrared and Raman spectroscopy, immune sensor, enzyme-based detection of creatinine) and nanoparticle-based sensors (chemiluminescence, voltametric, amperometric, conductometric, potentiometric, impedimetric/capacitive systems, nano-polymer based and point-of-care detection) are available for the detection of creatinine. Biosensor and nano-based detection techniques become popular as they shown high sensitively and less reactive time. Recently, several point-of-care biosensors are being developed to measure the levels of creatinine using blood and urine sample. Overall observations suggested that the cost, sensitivity, specificity and reproducibility of many detection methods are still challenging. Specially, cost of chemiluminescence based biosensors are quite high which restricts its usage for the creatinine detection. The identification and use of other biological sample/fluids to determine the levels of creatinine should be given more emphasis rather than depending only on blood and urine-based analysis. In conclusion, any device developed can be calibrated easily to determine the creatinine concentration difference between healthy and diseased subjects.

Declaration of interest

Authors declare no conflict of interest.

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