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A Review on Non-Invasive Renal Function Assessment Technologies

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Abstract

The prevalence of renal diseases is becoming a pressing problem and induces stress on global health expenditure. Late diagnosis may lead to further complications and increases the mortality rate. The existing gold standard techniques for renal function assessment do not support early diagnosis even though with high accuracy. Hence researchers are focused on developing alternate technologies for early diagnosis of renal diseases. Moreover, the invasive nature of the existing techniques hinders the public for regular monitoring. Yet the development of non-invasive methodologies paves way for regular monitoring and proper control of diseases. This review is dedicated to disseminate emerging non-invasive diagnostic technique for the assessment of kidney function. Initially, the causes of the renal failure are discussed in coherence with kidney anatomy and its physiology. Next, current clinical practice using blood, urine and biopsy tests were conferred. Finally, we provide emphasis on the non-invasive imaging techniques and renal failure biomarkers from other sources of samples to achieve non-invasive detection.

1. Introduction

Kidneys are complex organs that are vital for the normal body functions. Its primary functions involves in regulating the fluid, electrolyte and acid-base balances of the body in order to create a stable environment for the tissue and cell metabolism through accomplishing crucial functions like balancing the metabolic waste excretion, nutrient conservation and solute-water transport [1]. Other predominant functions of the kidneys comprise of erythropoietin production that in turn regulates blood pressure and the production of red blood cell inside the bone marrow and. In a human body, the renal-urologic system consists of a pair of kidneys, a urinary bladder, pair of ureters and urethra. The bean shaped organ is located below the ribs towards the middle of the back. The right kidney is located slightly lower than that of the left kidney due to the displacement of liver. The kidneys are enclosed by the fibrous capsule and consist of inner layer called medulla and an outer layer cortex. The inner layer is further divided into renal pyramids which then lead to the renal calyces. The tiny filtering units in kidney called nephrons remove urea from the blood. The nephrons are the basic functional units of kidney. Each kidney contains approximately 1.2 million nephrons. Each nephron has glomerulus which is formed of specialized small blood capillaries. Urea and other substances form as urine as they pass through the nephrons. The ureters are narrow tubes, that are around 27 cm to 30 cm in length and 1 to 5 mm in width that passes the urine from the kidneys to the bladder by the peristaltic contractions. They serve as a reservoir for the urine. In the case of urine back up or allowed to stand still, it may lead to kidney infection. The triangular shaped hollow organ located at the lower part of the abdomen is bladder. Ligaments attach them to the other organs and as well as the pelvic bones. The bladder's function is to relax and expand to store the urine. The bladders contract, flatten and empty them through the urethra. The sphincter muscles help in holding the urine by closing and opening them. The urethra are around 4 cm in length in female and 21 cm in male that helps in allowing the urine to be expelled outside the body [2].

The loss or decline of renal function is termed as kidney failure and classified in to acute and chronic. The acute kidney failure is potentially reversible and chronic failure progress slowly over time that leads to permanent failure. It can be further categorized into five different types such as chronic pre-renal kidney failure, acute intrinsic kidney failure, chronic `intrinsic kidney failure, acute pre-renal kidney failure and chronic post-renal kidney failure. Kidney failure contributes significantly to mortality and morbidity from non-communicable diseases [3].

According to the study conducted by global burden of disease in 2010, approximately, 10% of the population worldwide is affected by chronic kidney disease and ranked 27th that caused total number of deaths worldwide in 1990 and moved to 18th in 2010. The global prevalence of the kidney failures was estimated to be around 697.5 million cases as suggested by an analysis conducted in 2017. The kidney failure has reportedly caused around 1.2 million deaths in that year [4]. In developing countries like India and China, the number of kidney failure cases is

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estimated to increase disproportionately. By 2030, it is estimated that 2 million people in the United States would require a kidney transplantation or hemodialysis [5].

The early kidney disease does not usually exhibits any symptoms. The functions of the kidney can only be assessed through tests. A person with conditions such as diabetes, elevated blood pressure, cardiac disease should get checked for the kidney disease. In order to detect a kidney disease, two type of tests are used such as blood test and urine test. The blood test consists of a glomerular filtration rate (GMR) test that checks the ability of the kidneys to filter the blood. A GMR of 60 or more is considered to be in the normal range. GMR of less than 60 indicates that there is a problem associated with the kidneys. When the GMR drops down below 15, it is called as a kidney failure where the patient needs a kidney transplant or dialysis. The urine test is done to check for the albumin. The protein named albumin pass through urine when kidneys are damaged and can be estimated through urine test. A damaged kidney is likely to let more albumin into the urine. Two types of albumin tests are prevalent such as Dipstick test for albumin and Urine albumin-to-creatinine ratio (UACR) test [6].

2. Causes of Renal Failure

The causes of the renal failure have been classified into three categories such as pre-renal, intrinsic and post renal (Figure 1).

2.1 Pre-Renal Failure

The pre-renal failure is a reversible form of acute renal dysfunction and occurs due to the low perfusion of nephrons thus causing low GFR [7]. Any imbalance or inadequacy in the delivery of proper nutrition and oxygen to the nephrons leads to poor GFR. It can otherwise be described as the decreased filtration through glomerulus, thus leading to an increase in the creatinine and imbalance in the electrolytes and fluids.

The cause of the failure includes intravascular volume depletion, systematic vasodilation, macro vascular and microvascular kidney level alterations in the blood flow, hypotension, sepsis, cardiac failure, solitary functioning kidney, over diuresis and shock. [8] The most common cause is the intravascular volume depletion and it can be due to poor oral intake or enormous fluid loss. The disproportionate fluid loss can be attributed to the diarrhea, vomiting, excessive sweating, urination and hemorrhage. In case of systematic vasodilation, the major causes are hypotension, shock from trauma, gastrointestinal bleeding etc. In the local level, the blockage in the flow through kidneys can be at microvascular and macrovascular level. Renal artery stenosis that results from the fibromuscular dysplasia and atherosclerosis cause the obstruction at the macrovascular level, whereas in microvascular level, majority of the blockage is induced due to excessive medication intake. Pre-renal failures often occur due to extra renal process and the structure of the kidney is intact. The kidneys recover in most cases, as soon as the courses are reversed [9]. The management of pre-renal failure includes correction of fluid and electrolytes, avoiding nephrotoxins and kidney replacement therapy [10].

2.2 Intrinsic Renal Failure

Intrinsic renal failure is also known as organic or inter-renal failure [9]. It is usually caused due to structural damages within the kidneys, leading to sudden loss in kidney functions. The most common causes include acute interstitial nephritis (AIN), acute glomerulonephritis (AGN) and acute tubular necrosis (ATN). When the small filtering tubes inside the kidneys are injured, acute tubular necrosis occurs. This is considered to be the most common cause of intrinsic renal failure, and may occur due to infections, abdominal or cardiovascular surgeries, burns, and muscle injuries or severe physical excretion. The causes can be categorized into ischemic such as prolonged hypotension and nephrotoxic, the agents that are toxic to the tubular cells. With the help of proper therapy, both ischemic and nephrotoxic necrosis can be resolved over time.

When the tiny blood vessel in the kidneys has acute inflammation or damage, leading to improper filtration of blood, acute glomerulonephritis (AGN is developed. It is majorly caused by abnormal immune system response. Certain conditions such as bacterial infections, vasculitis and systemic lupus erythematosus can cause the renal failure. The management often involves in administration of immunosuppressive or cytotoxic medications.

The inflammation in the kidneys leads to acute interstitial nephritis due to the overdose of certain medications such as anti-biotic and nonsteroidal anti-inflammatory drugs. Infections such as viral, streptococcal and legionella can be the causative agents of the kidney failure. Discontinuing the offending medications, administration of steroids are beneficial to address the early course of disease [11].

2.3 Post Renal Failure

The post renal failure usually stems from the blockage in the urinary flow and prostatic hypertrophy below the kidney causes the waste to build up in the kidneys. This may lead to blockage in one or both the kidneys, thus preventing the normal flow of urine. The conditions that may lead to this post renal kidney failure are kidney stones that develop in ureters or urethra, enlarged prostate, improper emptying of the bladder, formation of blood clots in the urethra or ureters, colon, cervix and prostate cancer.Urinary obstruction may occur as anuria or intermittent urine

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flow (such as polyuria alternating with oliguria) but also occur as nocturia or nonoliguric [12]. In comparison to the other renal failures, post renal failure requires immediate treatment. Before any damage is done to the kidney, this condition can be reversed by proper treatment such as removing the blockages or bypassing them. To remove or destroy the blockage, extracorporeal shock wave lithotripsy can be done. This procedure uses sound waves to destroy the stone. In case when the stones cannot be removed, usages of catheter or stent facilitates in rerouting the urine around the blockage. Timely reversion usually leads to proper recovery of function. If the obstruction is not relieved, the kidney tissues may be irreversibly damaged due to the waste build up and pressure [13].

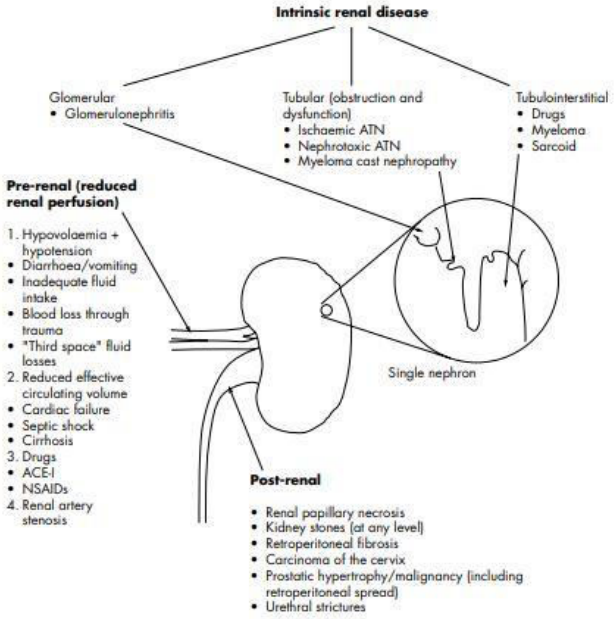

Figure 1: Etiology of Renal failure reproduced with permission from [3].

3. Traditional Methods for Renal Diagnosis

3.1 Blood test

Creatinine clearance estimation has been considered as a gold standard assessment and still acts as a primary method of stratifying the kidney function. Serum creatinine, the most commonly used biomarker depends largely on the muscle mass remains entrenched in modern day kidney patient care. It examines the buildup of creatinine in the blood. Since the kidney is supposed to completely filter out the creatinine, an elevated level of creatinine suggests that the kidney is at malfunction. National kidney foundation suggests that a creatinine level of 1.2 milligrams/decilitre (mg/dL) for female and 1.4 milligrams/deciliter (mg/dL) for male suggests that the kidney is affected. Many clinics now use glomerular filtration rate GFR, for the identification of kidney failure. Any result lesser than 60 milliliters/minute/1.73m^2 is an indication of kidney disease. Screening for proteinuria can be done as a preliminary test prior to GFR. These traditionally used tests that detects the functional abnormalities are inexpensive and readily available laboratory tests [14]. The validation of these assessments has been a point of debate for many years because, it is not certain that which biomarkers and equations yield the most accurate estimates of GFR, and opinions and practices are still varying. These tests have the disadvantage of relying on endogenous biomarkers, which are also disconcerted by non-GFR determinants such as muscle mass, drugs, age, diet and sex.

Blood urea nitrogen test (BUN) is the measure of amount of urea in blood. A low BUN indicates that there is lesser amount of protein in the body and a high BUN is indicative of affected kidney. Other factors such as bleeding in the gut, cardio vascular disease may affect the BUN.

Qualitative tests such as urinalysis, biopsy and radiographic assays are also advantageous assessment in the detection of kidney functional imbalances that determines the pathology and etiology of the disease [15, 16]. However, creatinine is no longer the only method of assessing the renal function since other markers for renal functions have been discovered, developed and validated.

3.2 Urinalysis

A damaged kidney may leak microscopic amounts of protein in the urine and hence proteinuria may be done to assess the kidney function. There are two types of urine test such as dipstick urine test and urinine albumin to creatinine ratio test. Dipstick urine contains a chemically treated strip reveals a change in color depending on the

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presence of protein, blood, pus and sugar. This test reveals the amount of microprotein in the urine whereas the urinine albumin to creatinine ratio test detects the ratio of the protein to wastes in the urine that are secreted by the body due to the wear and tear of the body.

3.3 Kidney biopsy

This kidney biopsy is slicing a small piece of kidney tissue using thin needle with a sharp cutting edge for examination under a microscope and is used to evaluate the amount of damage that has been done to the kidney and helps in determining whether the kidney will respond to a particular treatment. A local anesthesia is usually administered to the patient undergoing the test. This test utilizes light immunofluorescence and electron microscopy for examination. Usually the lower pole of the left kidney is preferred to reduce the risk of inadvertent injury to a major vessel. However, if the patient is obese or has breathing difficulty, then a supine anterolateral position (SALP) may be more suitable. Bleeding is the most common complications that can arise out of the kidney biopsy. One major disadvantage of this technique is the possible infection such as bowel perforation after biopsy. If the sterile conditions are used, the complications can be reduced [17].

4. Imaging Tests for non-invasive renal diagnosis

Presently, radiology imaging is a non-invasive diagnostic tool has only limited role to play in the detection of kidney disease. There are various methods such as radioactive methods, ultra sound methods and MRI.

4.1 Ultra Sound Imaging

The sonography serves as an essential tool in nephrology both for diagnosis and also serves as guidance for invasive procedures. Imaging tests uses sound waves to take a series of pictures of kidneys to create a more in depth, 3D picture of the kidneys and helps in characterizing the abnormalities such as size, echogenicity, position, urinary space, masses, density, vasculature, crude markers and the parenchymal damage of the kidneys or possible occurrence of stones and tumors [18]. This method emits ultrasound waves at high frequencies impossible to hear. When the transducer is brought in to contact with the skin, the sound waves propagate through body and reaches organs and the structures within. The sound waves are reflected and bounced off by the organs much similar to an echo and is received back by the transducer, where they are processed and then converted into an image of the respective organs or tissues by the computer. Depending upon the type of the tissue or organ encountered by the sound waves, their speed is altered. These sound waves travel at their maximum speed through the bones and in the minimal speed through air. The returned sound waves are analyzed by the transducer.

While performing the scan, an ultrasound gel is placed on both the transducer as well as skin to allow for proper and smooth movement of the transducer on the skin and also to get rid of the air between both medium. This also enables best sound conduction. This ultrasound scan can be able to detect cysts, tumors, fluid retention, infection and obstructions such as stones. It also facilitates in assisting the placement of needles to obtain biopsy, to remove the fluid from a cyst and to position a drainage tube [19].

4.2 CT scan

CT scan uses x-ray to detect the structural abnormalities in kidney and also detect the obstructions. They use an intravenous contrast dye that enhances the radiographic visibility of structures. These imaging probes are used to detect only specific biologic process or uses x-ray to detect the structural abnormalities in kidney and also detect the obstructions. They use an intravenous contrast dye that enhances the radiographic visibility of structures [20]. These imaging probes are used to detect only specific biologic process or molecules.

4.3 Radioactive methods

Renal scintigraphy/renal scan is a method that utilizes very small amounts of radioactive materials termed as radiopharmaceuticals, with the aid of a specialized camera and integrated computer to evaluate the kidney's structure and function. This technique is capable of providing information that are difficult to obtain through other imaging methods. Various types of renal scans are used to examine the different functions of the kidney. This procedure involves in injecting a radio tracer which emits a small amount of radioactivity into the patient. The interaction of the radiotracer is different for the different tissues and organs of the body and thus helps in examination of the kidney. It can also be used in the evaluation of kidney transplant. The injected radiotracer travels throughout the body and reaches kidney and emits in the form of gamma rays. This energy is then detected by gamma camera which is integrated with a computer to produce special pictures that details about morphology and functionality of the organs and tissues. There are four types of renal radioactive imaging such as renal cortical scintigraphy that uses the images from the gamma camera and analysis the amount of renal cortical tissue that is functioning. Renal perfusion and functional imaging analyses the blood flow rate in the kidneys and detects the narrowing of renal arteries. The images are required to be taken in series after 30 minutes of radioactive injection to obtain the kidney functionality. Any obstruction in the flow of the urine in the kidneys can be detected by diuretic renal scintigraphy. This is achieved by intake of diuretic, that moves through the kidneys. The narrowing of the renal arteris, due to high blood pressure that emerge out from the kidneys can be detected by ACE-inhibitor renal

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scintigraphy. Blood pressure medication called as ACE-inhibitor should be taken, in order to perform the analysis [18].

4.4 Magnetic Resonance Imaging (MRI)

Magnetic resonance imaging (MRI) used for the analysis of kidney function holds a great value due to its capability in providing anatomical and functional characterization in non-invasive mode.

MRI uses a magnetic field to align the patient's free water protons along a magnetic field axis. A coil otherwise called as radiofrequency antenna, is kept over the area to be imaged and made to release pulses of energy to disrupt the protons alignment. When the pulses are stopped, protons release energy and they realign with the magnetic field and hence this released energy can be captured as an image. The sensitivity of MRI for stone imaging is variable factor. The MRI has the ability to probe infiltrative kidney disorders. This helps in assessment of both acute and chronic renal failure. These include renal vascular structure and function such as tissue oxygenation (blood oxygen level-dependent MRI), renal metabolism (chemical exchange saturation transfer, spectroscopic imaging), contrast-enhanced MRI, molecular events (targeted-contrast imaging), renal tissue injury and fibrosis (diffusion or magnetization transfer imaging, MR elastography) and nephron endowment (cationic-contrast imaging) [21]. Initially the usage of MRI for kidney disease was limited due to the lengthy acquisition time, low spatial acquisition when compared to other imaging methods and low availability. But with advent of technological developments, ultra-short acquisition is made possible. Although there are several MRI techniques available, the most important ones are plain multi-contrast MRI and contrast enhanced MRI [22]. MRI exhibited high sensitivity (82%) in comparison with ultrasonography and radiography but lesser than CT imaging. MRI is conventionally used in adjunction with ultrasonography in pregnant patients. MRI is used as the second line modality, in cases where there is a suspicion of obstruction in nephrons but cannot be imaged and visualized by ultrasonography. MRI has been found to exhibit improved sensitivity, specificity and accuracy.

5 Alternative sources for non-invasive renal diagnosis.

5.1 Salivary source

The integrity of oral tissues is preserved by the saliva. It is considered to be a best medium to be analyzed for health diagnosis which contains oral fluid from salivary glands. It serves as a good tool when compared to the serum and tissues. The pathology due to kidney dysfunction and the dialysis treatment adversely the oral health and salivary composition. A damaged renal system might have systematic alterations in the composition of saliva and its flow rate. The oral problems associated with the patients of renal dysfunction involve enamel hypoplasia, xerostamia, uremic order and huge amount of calculus. Salivary flow rate, concentrations of magnesium, phosphorus and potassium varies from a healthy person from a person who has kidney damages. This results in oral cavity too. Numerous markers such as uric acid, chloride, sodium, nitrite, lactoferrin, pH and amylase are associated with end stage renal failure (Figure 2). Colorimetric test strips can be used to detect the markers and monitor the changes in case of treatments such as dialysis. It has been suggested that the salivary test could be done to decide the need of dialysis. A significant change in the amount, concentration and flow rate of markers has been observed before and after the dialysis [23]. It is observed that salivary NO_2^- and UA could be used in addition to the current gold standard blood tests such as BUN and creatinine. However salivary sources cannot provide signs for early diagnosis yet feasible for monitoring advanced stages of renal diseases. The test strip method may be useful for patients with progressive renal failure or undertaking peritoneal dialysis. The analyte concentrations can be monitored routinely by the patients at their comfort. The major goal of saliva usage in clinical practice is easy, home monitoring of renal health by using dipstick. Any visible change in the color of saliva indicates the changes in the concentration of saliva. Thus it is hypothesized that saliva is a suitable marker for qualitatively estimating renal health, dialysis efficacy and the patient can be informed with the health status of their kidney [24].

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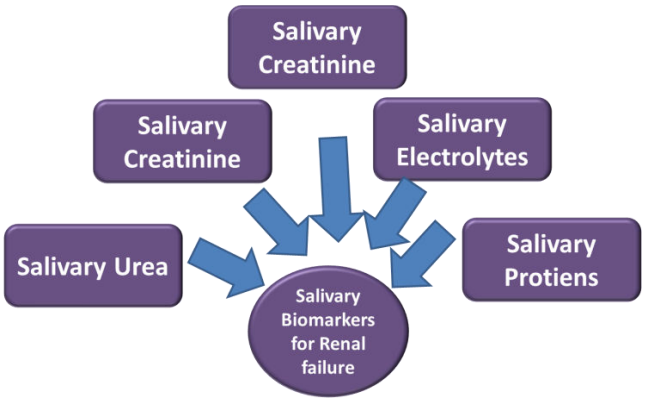

Figure 2: Salivary biomarkers for renal failure diagnostics.

5.2 Breath source

Analysis of exhaled breath volatile organic compounds (VOCs) is a type of non-invasive method that provides information about health status. Breath analysis facilitates early detection of renal failure as it replicates the fundamental body metabolism and eliminates complex analysis. Usage of multisensory system to analyze exhaled breath proves to be simple, rapid and reliable method for the renal failure diagnosis and is also a promising technique for early detection. Compared to the other analytical techniques, the breath analyzers do not provide information from the composition of the breath, rather from the digital smell print. The inability to filter urea gets converted to ammonia and being a volatile compound escapes through lungs and appear in breath. Volatile organic compounds such as ammonia are associated as biomarker for renal failure because of the high nitrogen content in the breath. Ammonia is a potential biomarker that can be used to track changes in the dialysis process. Diabetic patients are most commonly prone to the kidney failure and it proves that there is a clinically important relationship between upper breath ammonia and renal damage. Therefore, the presence of breath ammonia and its measurement helps in validating the need for kidney treatments thus potentially improving the quality of renal health care [25]. Numerous nanomaterial-based ammonia sensors such as conducting polymer nanojunctions sensor, polypyrene nanowires sensor, polyaniline nanofiber sensor and chemiresistor sensor arrays proved their reliability for detection of ammonia and is used for the detection of renal damage and hemodialysis. Conventional analytical techniques including laser-based spectroscopy, selected ion flow tube mass spectroscopy, proton transfer reaction mass spectroscopy (PTR-MS) and ion mobility spectrometry can provide real time measurements online or through off-line breath sample collection in a suitable tedlar bag. Although the commercial market is still in the process of developing reliable instruments for swift diagnosis. However, breath analyzer is more advantageous than blood and urine analysis because of the quick detection and requirement of low quantity of breath samples. Tolerance, retention, reliability is considered to be some of the limitations of this method [26, 27].

5.3 Sweat Source

Sweat contains a wide range of biomarkers such as metal ions, metabolites, amino acids, that are relevant to health status. The sweat is considered to be a best source of renal failure analysis due to the easy of collection and non-invasive procedure. Healthy kidneys regularly remove creatinine and urea from the blood via glomerular filtration. An estimation of glomerular filtration rate can be obtained by the concentration of creatinine in the serum. It is estimated that the parameters such as sweat PH, creatinine and urea concentrations have connections with the chronic kidney disease. One of the key challenges in establishing relationships between biomarkers in sweat and different stages of chronic kidney disease stems from difficulties in collecting sweat samples. It is equally challenging in quantifying the sweat rate and volume simultaneously and avoid the effects that are related to sweat evaporation and compensatory sweating [28] Sweat collection is done passively by using sweat patches and can be actively induced by medical grade sweat collecting devices. Various proportions of sweat glands such as holocrine, apocrine and eccrine are present in different areas of skin, and they exhibit their own secretion mechanisms. Hence, it is evident that each type of sweat gland excretes a varied quantity and quality of biomarker. Therefore, the detection of specific metabolites and drugs largely depends on the location of the sample that is collected from the body. The sampling is mostly done on the volar lower arm including the eccrine sweat glands of the skin. The laboratory analysis of the sweat comprises of two most commonly observed methods called mass spectrometry that helps in detecting a broad range of metabolites simultaneously and a relatively cheaper enzyme –linked immunosorbent assay that has distinctly defined target molecule. A number of physiological states for an individual can be determined for an individual using the kidney biomarker concentrations, ratios and trends, thus helping in deciding the trends in ongoing therapy. Using the wearable sweat sensing device, it is preferable to measure more

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than one biomarker and develop a kidney functional profile or injury profile. Additionally, it is desirable to have devices and methods for measuring and indicating an individual's sweat concentrations of kidney biomarkers, and interpreting those concentrations, ratios, and trends to inform a health condition for the individual [20].

6. Conclusion

Non-invasive diagnosis of renal failure is one of the foreseen healthcare advancements. The credibility of various imaging sources to monitor renal parameters has made them a promising alternative to assess the kidney function. To this direction radioactive, ultrasound, CT and MRI imaging were presented in the current review. These techniques do not only facilitate non-invasive diagnosis but also provides deeper insights compared to the traditional methods. Imaging techniques may allow mass screening at rapid time;however it is still in its infancy and further research on various aspects are progressing. On the other hand, identifying biomarkers associated with renal dysfunction from saliva, sweat and breath is gaining momentum due to the development of advanced Nano sensor array system capable of detection trace level concentration that may provide accurate diagnostics and assists early diagnosis as these sources reflect the fundamental cellular metabolism. This review has provided an overview of various futuristic kidney function assessment tests.

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