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A Review on Biomarkers of Kidney Dysfunction in Orthopaedic Cases

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Abstract: *Kidney dysfunction in orthopaedic cases may be as a result of kidney injury due to fracture, burns, osteomyelitis, spinal injury, spinal tuberculosis, sickle cell disease and various forms of arthritis among others. Kidney injury may be acute or chronic. The overall incidence of kidney dysfunction after elective or emergency surgical procedures is reported to reach 9.1%. The risk of acute kidney injury in surgical patients has been estimated to be approximately 1% of all hospitalized patients.However, biochemical markers play an important role inaccurate diagnosis and also for assessing risk and adopting therapy that improves clinical outcome. The markers of renal function include serum Urea, Creatinine, Uric acid and electrolytes used for routine investigation. Serum Malondialdehyde, calcium, phosphate and vitamin D are used for further analysis and confirmation.*

Keywords: *Acute, Biochemical Markers, Chronic, Diagnosis, Incidence, Kidney injury and Orthopaedic*

I. Introduction

Kidney injury (KI) has traditionally been defined as a loss of kidney function with resultant accumulation of nitrogenous waste and dysregulation of electrolytes and blood volume.[1]In most cases, renal diseases areasymptomatic; until in its clinical cause. Laboratory tests are often employed to evaluate glomerular and tubular functions. [2, 3]As Glomerular filtration rate (GFR) declines, a wide range of disorders develops, including fluid and electrolyte imbalance such as hyperkalemia, metabolic acidosis, volume over load and hypophosphatemia.[4]As glomerular function deteriorates, substances that are normally cleared by the kidneys accumulate in the plasma. The biochemical investigations of renal function can be used to diagnose the presence of renal dysfunction or the severity of the disorder and response to treatment. [5]Kidney dysfunction (KD) is known to be an independent predictor of poor in-hospital outcome .[6] Biochemical markers play an important role in accurate diagnosis and also for assessing risk and adopting therapy that improves clinical outcome. Over the decades, research and utilization of biomarkers has evolved substantially. Markers of renal function such as creatinine, urea, uric acid and electrolytes are for routine analysis.[3]

Patients that undergo major orthopaedic procedures can also be at high risk for kidney disease due to severe electrolyte disturbances, development of perioperative infection or sepsis, and presence of several co-morbidities that may impair renal function (i.e. diabetes, heart failure, severe arrhythmia, pulmonary embolism etc). In addition, pre- or post-operative KD is one of therisk factors for postoperative complications, including acute renal failure and cardiovascular disease, leading to increased mortality and morbidity.[6]

1.1 Kidney Injury

Kidney injury has traditionally been defined as loss of kidney function with resultant accumulation of nitrogenous waste and dysregulation of electrolytes and blood volume.[1]Nephrons are lost via toxic, anoxic, or immunological injury that may initially injure glomerulus, the tubule or both. The kidneys have considerable ability to increase their functional capacity in response to injury. Thus, a significant reduction in renal mass (50%-60%) may occur before the onset of any significant symptoms or even before any major biochemical alterations appear. The GFR is reduced even before the minor signs and symptoms are observed. This increase in workload per nephron is thought to be an important cause of progressive renal injury itself .[9] As the kidney functions deteriorate, a progressive disruption of mineral homeostasis leads to skeletal and extraskeletal complications with impact on the quality of life and survival of patients . [10]Renal failure is also defined as acute or chronic decline of the renal function. [9]

1.2 Acute Kidney Failure

Acute kidney injury (AKI) has been defined as an abrupt loss of kidney function with resultant accumulation of nitrogenous waste and dysregulation of electrolytes and blood volume. [1] It most commonly occur in a hospital setting frequently as a result of ischemic or nephrotoxic insult and also known to be an

independent predictor of poor in-hospital outcome which carries a high mortality. [9, 11] AKI isa common complication of varieties of critical illnessesand independent risk factors for hospital mortality and is associated with longer intensive care unit (ICU) stay, increased morbidity, utilization of resources, and higher mortality at six months, [1, 12]it is also an important prognostic marker for complications during hospitalization in the elderly.[1]Efforts have been made to elucidate the underlying mechanisms of the development of AKI, based on which preventive or therapeutic strategies can be developed to control this devastating complication. Although there are numerous strategies for the prevention and treatment of AKI including optimization of hemodynamic status, use of vasodilators (e.g. dopamine and fenoldopam), early initiation of continuous renal replacement therapy and use of natriuretic peptides, most of them failed to show a beneficial effect.[12] Most of the data on perioperative AKI are from patients with cardiac surgeries. [1]

1.2.1Causes Of Acute Kidney Disease

The causes of AKI are often divided into three groups: pre-renal, intrarenal and post-renal. Pre-renal failure, also called prerenal azotaemia (PRA), is described as a reversible increase in serum creatinine and urea concentrations resulting from decreased renal perfusion, which leads to a reduction in the GFR. On the other hand, intrarenal diseases affect structures of the nephron such as the glomeruli, tubules, vessels or interstitia, and the most common cause of intra-renal (intrinsic) disease is thought to be acute tubular necrosis (ATN). These two causes have been reported to account for 66 to 75% of all cases of AKI. Early recognition of the cause of AKI, especially distinguishing PRA and ATN are widely considered clinically important as fluid resuscitation may improve PRA but can cause tissue edema and worsen ATN. Furthermore, ATN has a much worse prognosis. [12]

1.3 Chronic Kidney Disease

Chronic Kidney Disease (CKD) is defined as a disease characterized by alterations in either kidney structure or function or both for a minimum of three months duration. [14]Chronic Kidney diseaseis also defined as the presence of kidney damage, manifested by abnormal albumin excretion or decreased kidney function, quantified by measured or estimated glomerular filtration rate (GFR) that persists for more than three months.[8] The disease includes conditions that damage the kidneys and decrease their ability to keep them healthy. If kidney disease gets worse, wastes can build to high levels in the blood and make individual feel sick. It may result to complications like high blood pressure, anemia (low blood count), weak bones, poor nutritional health and nerve damage. Also, kidney disease increases the risk of having fluid overload, heart and blood vessel disease. These problems may happen slowly over a long period of time. [15] Earlier recognition of CKD could slow progression, prevent complications, and reduce cardiovascular-related outcomes. However, current estimates of CKD awareness on both patient- and provider-level awareness remain unacceptably low.Further research is necessary to design and refine awareness campaigns aimed at both patients and providers, but there is an immediate need for dissemination of basic CKD information, given both the high prevalence of CKD and its risk factors and the low estimated awareness of CKD. [16]

1.3.1 Causes ofChronic Kidney Disease

Chronic kidney disease may be caused by diabetes, high blood pressure and other disorders. Early detection and treatment can often keep chronic kidney disease from getting worse. The progressionof kidney disease may eventually lead to kidney failure which requires dialysis or a kidney transplant to maintain life. [15]
People are exposed to various potentially toxic agents and conditions in their natural and occupational environments. These agents may be physical or chemical, may enter the human body through oral, inhalational, or transdermal routes, and may exert effects on all organ-systems. Several associations exist between CKD and both environmental agents and conditions, such as heavy metals, industrial chemicals, elevated ambient temperatures and infections. The effects of these agents may be modulated by genetic susceptibility and other co-morbid conditions which may lead to the development of acute and chronic kidney disease. [17] Nalado *et al.* [18] reported the prevalence of risk factors for CKD among civil servants in Kano with high Positive history of use of the traditional medicines among the civil servants, and this is important as most of these herbal preparations were not studied and accurately characterized, hence the active ingredient is not known. Some of these herbal preparations in some parts of the country were actually reported to be Nephrotoxic. The use of analgesic drugs, alcohol ingestion or use of bleaching creams where also recognized as risk factors for kidney disease.
With early identification and treatment of anaemia, renal osteodystrophy, uremic malnutrition, hyperlipidaemia and cardiovascular disease, primary care physicians and nephrologists together are making significant strides toward extending and improving the lives of patients with CKD.[8] It is also knownthat diabetes, hypertension and glomerulonephritis are the main causes of CKD in Nigeria, while in the United States, diabetes and hypertension are the commonest causes of CKD meanwhile glomerulonephritis plays a less important role. [19, 20]

1.4 Epidemiology of Kidney Disease

End-stage renal disease (ESRD) is the final event of a sequence that begins with an initial insult and progresses towards total loss of renal function.[22] The incidence of CRF and ESRD in any specified area may be influenced by the prevalence of specific disease entities resulting in CRF and by the availability of funds, sophisticated modalities of treatment and expertise required in the care of the varied types of renal diseases. [22]The incidence and the prevalence of ESRD are good indicators of the burden of renal disease in a country. The prevalence is influenced by the number of new patients and the number of deaths. The poor socio-economic status of most patients with renal disease precludes access to care in the tertiary health institutionswhere most of the data is generated. [23]

Chronic kidney disease has become a major health problem with about one in ten adults affected worldwide. [10] However, it is estimated that over 20 million Americans have chronic kidney disease. [21]

The overall incidence of kidney dysfunction after elective or emergency orthopaedic surgical procedures is reported to reach 9.1%. The risk of acute kidney injury (AKI) in surgical patients has been estimated to be approximately 1% of all hospitalized patients. [6]

The increased prevalence of ESRD among blacks in the United States and South Africa compared with other races also suggest that ESRD may be more prevalent in Africa than in the United States and other developed nations. [19]In Nigeria, the actual incidence and prevalence of ESRD is not clearly known with the incidence of CKD ranging between 1.6 and 12.4% as shown by various studies. [19, 23]

1.5 Kidney Function Tests

In most cases, the symptoms of renal disease do not show initially until in its clinical cause. Kidney function tests are those evaluating glomerular and tubular functions. [2, 3]As glomerular function deteriorates, substances that are normally cleared by the kidneys accumulate in the plasma. [22] Biochemical markers play an important role in accurate diagnosis and also for assessing risk and adopting therapy that improves clinical outcome. Over the decades, research and utilization of biomarkers has evolved substantially. As markers of renal function, creatinine, urea, uric acid and electrolytes are for routine analysis. [3]

Chronic kidney disease typically increases with age and therefore there is an increased risk in older adults. It is found that females are less prone to the risk of the disease. [20]

1.5.1 Serum Urea

Urea is manufactured in the liver from carbon dioxide and ammonia resulting from the breakdown of amino acids. It constitutes almost half of the total of the non protein nitrogenous substances of the blood. It is the major execratory product of protein metabolism. Urea is carried by the plasma to the kidney where it is filtered by the glomerulus. About 40% of the urea in the glomerular filtrate is reabsorbed by the renal tubules. Most of the urea in the filtrate is excreted in the urine while small amount are excreted through the gastrointestinal tract and the skin. [22]

Blood urea nitrogen (BUN)is directly related to the excretory function of the kidney and measuring the amount of urea nitrogen in the serum is an indirect and rough measurement of renal function. [25] Serum BUN levels, however, may provide supplemental information in regards to renal function as renal proximal tubule cells may increase BUN reabsorption in the setting of increased neurohormonal activation.[74]

The amount of urea in the blood is affected by the protein in the diet. When the amount of the urea becomes excessive, the condition is known as ureamia. This condition is usuallyas a result of impaired kidney function.In the elderly, the urea level may be a little higher than normal; and low values are found during pregnancy and in full term infants, whereas premature infants may have slightly higher values than the adult range. [24]

1.5.2 Serum Creatinine

Creatinine is a nitrogenous product produced from the metabolism of creatine in the skeletal muscles; it is an amino acid derivative with a molecular mass of 113 D. It is filtered by the kidneys and excreted in the urine. Unlike urea, creatinine level is not affected by protein intake. The measurement of creatinine level is a test of renal function. [24, 26] Many studies support the similarity of creatinine clearance to GFR and its reciprocal relationship with the serum creatinine level. [26]Renal functionshave routinely been assessed with an estimated creatinine clearance, serum creatinine or an estimated glomerular filtration rate (eGFR) derived from the serum creatinine. Creatinine tests diagnose impaired renal function and measure the amount of creatinine phosphate in the blood. [25] The loss of kidney function may easily be quantified by measuring the serum creatinine. [1] The formation of creatinine is constant and is a direct relationship to muscle mass, for this reason,it varies with age and sex.[24] Serum creatinine also originates from dietary sources such as cooked meat, it's generation from the muscles is proportional to the total muscle mass and muscle catabolism. In people with a relatively low muscle mass, including children, women, the elderly, malnourished and cancer patients, the serum creatinine is lower for a given GFR. There is a danger of underestimating the amount of renal impairment in these patients, as their

serum creatinine is also relatively lower. For example, the GFR may be reduced as low as 20-30 mL/min in a small elderly woman, while her serum creatinine remains in the upper range of normal. Creatinine is an imperfect filtration marker, because it is secreted by the tubular cells into the tubular lumen, especially if renal function is impaired. When the GFR is low, the serum creatinine and creatinine clearance overestimate the true GFR. Some drugs (such as cimetidine or trimethoprim) have the effect of reducing tubular secretion of creatinine. This increases the serum creatinine and decreases the measured creatinine clearance. Therefore when these drugs are used, a more accurate measurement of GFR is obtained as it is largely free from the error contributed by the physiological tubular secretion of creatinine.[7]Evidence suggests that even a mild increase in serum creatinine will have significant negative impact onthe kidney. [12]Creatinine clearance provides a more accurate assessment of renal function. [7]

1.5.3 Serum Uric acid

Uric acid, the product of the xanthine oxidase–catalyzed conversion of xanthine and hypoxanthine, is the final metabolite of endogenous and dietary purine nucleotide metabolism. It is a weak acid, with a p K_a of 5.75; at a physiologic pH of 7.40 in the extracellular compartment, 98% of uric acid is in the ionized form as urate. In the collecting tubules of the kidneys, where the pH can fall to 5.0, uric acid formation is favored. [27]It is problematic because humans do not possess the enzyme uricase, which converts uric acid into the more soluble compound (allantoin). [28] Because acute gout attacks are painful, attention had been directed towards the pathogenic role of uric acid and evidence was provided that uric acid stone formation is responsible for renal colic. [29]

Three forms of kidney disease have been attributed to excess uric acid: acute uric acid nephropathy, chronic urate nephropathy, and uric acid nephrolithiasis. These disorders have different clinical features but common element of excess uric acid or urate deposition. [28]

Recent evidence however, supports the view that uric acid may not be an active player in the pathogenesis of renal disease by causing endothelial dysfunction, intrarenal impairment. Most compelling evidence comes from animal models in which induced hyperuriceamia in healthy rats caused renal cortical vasoconstriction and glomerular hypertension that was prevented by allopurinol treatment. In rats with pre-existing renal disease, hyperuriceamia increase renal vascular damage. [30]

The precipitation of uric acid in the renal medulla with formation of characteristics tophi was believed to evoked an inflammatory response leading to fibrosis, a loss of nephron and ultimately to chronic irreversible renal failure. Some emphasized that nearly 100% of the patients with chronic gout also have renal involvement, however, based on the investigation of autopsy cases, chronic uric acid deposit in the kidney (renal tophi) hardly cause irreversible renal failure because, in significant number of cases, renal tophi were also found without evidence of renal involvement . [31]

1.5.4 Serum Malondialdehyde

Malondialdehyde (MDA) is an end-product generated by decomposition of arachidonic acid and larger Poly Unsaturated Fatty Acids (PUFAs), through enzymatic or non enzymatic processes. It has also been proposed that MDA could react physiologically with several nucleosides (deoxyguanosine and cytidine) to form adducts to deoxyguanosine and deoxyadenosine, and the major product resulting is a pyrimidopurinone.MDA is an important contributor to DNA damage and mutation. The MDA-DNA adducts may lead to mutations (point and frameshift), strand breaks, cell cycle arrest, and induction of apoptosis. [32]

Chronic kidney diseaseis a pro-oxidant state and the degree of intracellular and extracellular oxidative stress is related to the severity of renal failure. The oxidative stress depends on the excess production free radical coupled with low concentration of antioxidants. It is also has been observed that, free radical induced lipid peroxidative tissue damage has played a significant role in the pathogenesis of various renal diseases. [33]
Padalkar *et al*. [34] reported the increased level of serum MDA in kidney disease patients, which clearly shows that they were exposed to an increased oxidative stress via lipid peroxidation.Lipid peroxidation is assayed indirectly by production of secondary products like water soluble three carbon; low molecular weight reactive aldehydeMalondialdehyde. [33]

1.5.5 Serum Electrolytes and Kidney Function

Electrolytes are positively and negatively charged ions that are found within cells and extracellular fluids, including intestinal fluid, blood, and plasma. A test for electrolytes includes the measurement of sodium, potassium, chloride, and bicarbonate. These ions are measured to assess kidney, endocrine (glandular) and acid-base functions. [35] Electrolytes are the key to homeostasis; furthermore, their regulation is dependent upon renal function. Kidney disease is associated with aberrations in the metabolism of electrolytes such as calcium, phosphates, sodium and potassium. [36]

The role of electrolytes is extensive, particularly that of the cations (sodium and potassium) which exist in the body fluids largely as free ions. As well as maintaining cellular tonicity and fluid balance between the various cellular components, they are involved in most metabolic processes, maintenance of pH, and regulation of neural and muscular function. Abnormal levels can be either the cause or result of a wide range of disorders. [37]

1.5.5.1 Serum Sodium

Sodiumis the main extracellular cation. The plasma sodium level is a major factor in the control of water homeostasis and extracellular fluid volume. An increase in plasma sodium normally results in three compensatory mechanisms coming into play, thirst prompts oral fluid intake, anti-diuretic hormone (ADH) secretion from the pituitary is increased, leading to renal water retention; there is a shift of water from intracellular to extracellular space. As the total intake of sodium chloride is almost completely absorbed from the gastrointestinal tract with no active control, regulation of the retained body sodium is maintained by the kidneys, with the excess excreted in the urine and fine control carried out by tubular reabsorption. After initial glomerular filtration some 60% of the filtered sodium is recovered in the proximal tubules together with bicarbonate. 25% is reabsorbed in the Loop of Henle of the renal tubule with chloride; the remainder is reabsorbed in the distal tubules where, with aldosterone governing its reabsorption, it competes with potassium and hydrogen ions. [37]

Sodium is primarily responsible for maintaining osmotic pressure. Increased serum sodium is present in states of dehydration as a result of diarrhea or vomiting. Low sodium levels usually are as a result of too much water in the body. [35] In order for the kidney to excrete excess water by producing a large volume of dilute urine, there must be an adequate glomerular filtration rate. Generally, less renal impairment result through hyponatraemia due to intake of large amounts of water. In contrast,hypernatraemia may result from renal water loss**.** The hallmark of marked renal water loss is polyuria, defined as a urinevolume greater than 3L/24 hours. The common defect in all cases of renal water loss is an inability of the kidney to conserve water appropriately. [38]

1.5.5.2 Serum Potassium

Potassium is the principal intracellular cation, 98% of which is maintained within the cells by the ATP dependent mechanism known as the sodium pump. Any sodium which diffuses into cells is actively excreted in exchange for potassium. Insulin also accelerates the cellular uptake of potassium and elevated levels of plasma potassium encourage secretion of insulin. In addition to its role in intracellular osmolality, potassium is essential for many enzymatic reactions, the regulation of heart muscle, and for the transmission of nerve impulses. An important factor in the control of potassium cellular transport is the acid/base status. In acidosis the flow of hydrogen ions into cells causes the outflow of an equivalent number of potassium ions. Dietary potassium intake is normally in excess of requirement and the surplus is excreted via the kidneys. Following potassium ingestion, aldosterone secretion is increased to enhance renal clearance and insulin levels rise to increase cellular absorption.[37]Serum potassium is the most convincing electrolyte marker of renal failure. The combination of decreased filtration and decreased secretion of potassium in distal tubule during renal failure cause increased plasma potassium. Hyperkalaemia is the most significant and life-threatening complication of renal failure.[3]Potassium is a major component in cardiac function; too much potassium in the blood is usually caused by poor kidney function and can cause abnormal and sometimes fatal cardiac arrhythmia. Low potassium levels are usually the result of potassium loss from intake of K^+ lowering drugs, excessive urination or from vomiting. [35]

Many of the disorders causing renal potassium loss are also associated with acid-base disorders. Therefore, numerous causes of renal potassium loss was classified according to whether they typically occur together with metabolic acidosis, metabolic alkalosis or hypokalaemia with no specific acid-base disorder .On the other hand, when GFR is reduced to <20% of normal, hyperkalemia (high serum potassium) may develop rapidly from exogenous potassium in patients with renal failure . [38]

1.5.5.3 Serum Chloride

Critically ill patients receive large amount of intravenous fluid administration during their ICU stay. Many commercially available crystalloid fluids are rich in chloride, such as the most widely used saline 0.9% that has 40% higher chloride than human plasma. Some animal studies suggest that administration of chloride-liberal fluid induces renal vasoconstriction and a decline in glomerular filtration rate. [12]

Zhang*et al*. [12]shows that higherchloride are associated with the development of AKI, indicating that chloride overload during ICU treatment may increase the risk of AKI and also indicated that restricting chloride infusion is no longer beneficial in patients with hypochloraemia.

1.5.5.4 Serum Bicarbonate

Decreasing kidney function causes progressively increased retention of acids, resulting in numerous deleterious consequences, such as protein catabolism and protein-energy wasting, worsening uremic bone disease and an association with decreased functional capacity and with increased mortality in patients with ESRD.Metabolic acidosis has also been linked directly to kidney damage and to increased progression of CKD, possibly through mechanisms associated with adaptive responses meant to enhance acid excretion in the face of progressive loss of kidney function.[39] The association between elevated serum bicarbonate concentrations in patients with kidney disease is positive and should be taking to consideration in every patient with the disease. [40]Sankar*et al.* [41]reported that, low serum bicarbonate levels are associated with death among stage 3 CKD, while high serum bicarbonate levels are associated with death among both stage 3 and stage 4 CKD patients.

1.5.5.5 Serum Calcium

The adult human body contains approximately 1,300g of calcium with 99% in skeleton, 0.6% in soft tissues, and 0.1% in extracellular fluid.[42] Normal values for serum total calcium concentration vary among clinical laboratories, depending on the methods of measurement, with a normal range being 2.15 to 2.57mmol/L for adults. [9, 43]

Maintenance of normal calcium balance and serum calcium levels depend on integrated regulation of calcium absorption and secretion by the intestinal tract, the excretion of calcium by the kidney, and calcium release from and calcium deposition into bone. Parathyroid hormone stimulates bone resorption, kidney distal tubular calcium reabsorption, and activating renal hydroxylation of 25(OH) D_3 to 1, 25$(OH)_2D_3$ and thereby increasing serum calcium levels. Depression in serum levels of calcium by itself stimulates, through the calcium-sensing receptor (CaR) in the parathyroid gland, the secretion of preformed parathyroid hormone(PTH) from parathyroid gland within seconds. Subsequently, PTH biosynthesis by parathyroid gland increases over 24 to 48 hours and, if persistent, is followed by parathyroid gland hypertrophy and hyperplasia. Vitamin D metabolites and serum phosphorus levels also regulate PTH levels in blood. These homeostatic mechanisms are distorted in early stages of Kidney disease and continue to deteriorate as loss of kidney function progresses. [42] Evidence reports that hypocalcaemia is a risk for bone disease and for development of secondary hyperparathyroidism and/or increased risk of mortality. Thus, the detection of true hypocalcaemia and its appropriate treatment is important for management of patients with kidney disease.[44]Hypercalcaemia poses a risk for kidney patients as it would increase the Ca-P product index in blood. [42]

1.5.5.6 Serum Phosphate

Human phosphate homeostasis is regulated at the level of intestinal absorption of phosphate from the diet, release of phosphate through bone resorption, and renal phosphate excretion, and involves the actions of parathyroid hormone, 1, 25-dihydroxy-vitamin D, and fibroblast growth factor 23 to maintain circulating phosphate levels within a narrow normal range, which is essential for numerous cellular functions, for the growth of tissues and for bone mineralization. [45] Elevated serum phosphateshave clinically been associated with vascular stiffness and cardiovascular mortality. [46]

Hyperphosphataemia is one of the most important risk factors associated with cardiovascular disease in CKD patients. The exact mechanism underlying this association remainsunclear. It is believed to be related to hyperparathyroidism and vascular calcification, which results from high phosphorus levels. [9] As kidney disease progresses there is diminished filtration and excretion of phosphate resulting in hyperphosphataemia. [36]
Mechanistic studies over the past decade regarding local effects of phosphate on the vessel wall have provided insight into various pathways that culminate in vascular calcification. Smooth muscle cell phenotype change and apoptosis play prominent roles. The sodium-phosphate cotransporter PiT-1 is required for the osteochondrogenic differentiation of smooth muscle cells in vitro. Less is known about phosphate-driven valve interstitial cell calcification and elastin degradation. [46] Serum phosphorus levels should be maintained between 2.7 and 4.6 mg/dL in patients with stages 3 and 4 CKD, and between 3.5 and 5.5 mg/dL in individuals with stage 5 CKD. [8]

1.5.6 Serum Vitamin D

Vitamin D is derived from either 7-dehydrocholesterol or ergosterol by the action of ultraviolet radiation. [47] It has been appreciated that vitamin D insufficiency may lead to osteoporotic fractures, overt deficiency states such as rickets and osteomalacia and it may also have important extraskeletal roles in the prevention of cancer, autoimmune disease, diabetes, and other disorders. [48] African Americans are particularly susceptible to vitamin D insufficiency because the darker colour of their skin limits the amount of ultraviolet light that penetrates, thereby reducing the cutaneous synthesis of vitamin D. [48]

The prevalence of vitamin D deficiency in the CKD population has been described to range between 70 and 80%. [49] Serum 1, 25-dihydroxyvitamin D (1, 25 OH_2 D_3) deficiency is known to occur during the progression of CKD because the final hydroxylation step of 25-hydroxyvitamin D (25(OH) D3) to 1, 25 OH_2 D_3 (Calcitriol) is mediated by kidney 1-α hydroxylase. [50] Because Patients with kidney disease have reduced activity of the enzyme 1-α hydroxylase (CYP27B1) in their kidneys, which converts 25-hydroxyvitamin D (25(OH)D) to its more active form, 1,25-dihydroxyvitamin D ($1,25(OH)_2D$). As kidney function worsens, low circulating 1, 25-dihyrdoxyvitamin D levels is experienced. [51]
A 25(OH) vitamin D (calcidiol) level 75 nmol/L (30 ng/ml) has been identified as a cause of falls which may lead to fracture that responds to treatment with a reduction in falls. 25 (OH) Vitamin D deficiencies are very common in renal failure patients. [52]

1.6 Renal Dysfunction and Glomerular Filtration Rate (GFR)

As Glomerular filtration rate (GFR) declines, a wide range of disorders develops, including fluid and electrolyte imbalance such as hyperkalemia, metabolic acidosis, volume over load and hypophosphataemia .[4]Renal function can be evaluated by measuring the GFR. Renal damage or alterations in glomerular function affect the kidneys' ability to remove metabolic substances from the blood into the urine.[7]Glomerular filtration rate (GFR) is the rate (volume per unit of time) at which ultra filtrate is formed by the glomerulus. Approximately 120 mL are formed per minute. The GFR is a direct measure of renal function. It is reduced before the onset of symptoms of renal failure and is related to the severity of the structural abnormalities in chronic renal disease. The GFR can predict the signs and symptoms of ureamia, especially when it falls to below 10-15 mL/min. Unfortunately it is not an ideal index, being difficult to measure directly, and is sometimes insensitive for detecting renal disease. Directly, the serum creatinine concentration is often used to assess renal function. GFR can be calculated from the serum creatinine or more exactly from the results of a 24-hour urine collection. Isotopic methods can be used if a very accurate measurement of the GFR is required.[7]Although creatinine clearances can be calculated from urine creatinine concentration measured in a 24 hour urine collection and a concomitant serum Creatinine concentration, a more practical approach in the office is to estimate GFR (estimated GFR or eGFR) from the serum creatinine concentration.[8]

1.7 Fracture and Kidney Disease

A fracture is a slight crack or break of a bone. It may be a complete break in the continuity of a bone or incomplete break or crack. Increased bone remodeling, leading to micro architectural deterioration and increased fragility, may accompany declining kidney function. Patients with kidney disease have higher rates of fracture than the general population.[53]

After renal transplantation, there is a rapid decrease in bone mineral density over the first year which is associated with increased risk of fractures. The causes of this increased loss of bone include renal osteodystrophy, Glucocorticoids, immunotherapy, vitamin D deficiency, hypophosphataemia, hypogonadism, and osteoporosis. Bisphosphonates (oral and intravenous), vitamin D, and calcitonin have all been shown to slow the rate of bone loss. [52]

Overall studies suggest that the fall rate is much greater in dialysis patients than in the general population. In the general population over 75 years of age, 30% of persons fall each year, with one in five having an injury. Hip fractures in persons on dialysis occur three to four times more commonly than in the general population. Falls and associated fragility fractures are a major cause of morbidity and mortality in older persons with kidney disease. [52]

1.8 Burns and Kidney Function

Extensive burn is not only a skin injury but also a serious systemic illness often accompanied by various complications. Acute renal failure (ARF) is one of the major complications of burns, carrying an extremely high mortality rate. Although ARF is not commonly encountered in burned patients, this complication merits a special attention depending on the severity and adequacy management of the burn injury.[54] The reported incidence and mortality rate of ARF among burned patients varies depending on the severity of the burn injury.ARF occurs either immediately after burn or at a later stage, most often in the third week or later. It is still a life-threatening complication; particularly in patients with extensive third degree burns.[55] Renal pathologies in burns are characterized by the development of extensive inflammation inducing an intensive acute phase response in the kidney. Urinary Malondialdehyde (MDA) is a gross indicator of renal lipid peroxidation and has been shown to increase after burns.[54]

1.9 Rheumatoid Arthritis and Kidney Function

Rheumatoid arthritis (RA) is a chronic, progressive, inflammatory autoimmune disease associated with articular, extra-articular and systemic effects. Although some patients have mild self-limited disease, many

experience joint destruction, severe physical disability and multiple co-morbidities. It has been reported that RA affects 0.51% of the adult population of developed regions.[56]RA is characterized as a chronic, inflammatory disease in which the immune system destroys synovial joints and accessory structures. As it progresses, this autoimmune condition can cause extra-articular complications within several organ systems, it is the most common autoimmune disease, and the second most common form of arthritis compared to osteoarthritis.[57]Hickson *et al.* [58] reported that, patients with RA were more likely to develop reduced kidney function over time.

1.10Gouty Arthritis and Kidney Function

Gouty arthritis is an inflammatory arthritis caused by the deposition of monosodium urate crystals into joints cavity, which is therefore considered to represent a metabolic joint disease.[29] Gout is the most common inflammatory joint disease in men. Overall, the range of prevalence was from 0.03% for Nigerian men to 15.2% for Taiwanese aboriginal men.[59]Based on recent estimates, between 47% and 54% of patients with gouty arthritis are affected with kidney disease.[60]

1.11Osteoarthritis and Kidney Function

Osteoarthritis (OA) is a debilitating condition characterized by pain, joint inflammation and joint stiffness, and results in a substantial degree of physical disability. It is the most common form of arthritis. World Health Organization (WHO) estimates that globally 25% of adults aged over 65 years suffer from pain and disability associated with this disease but almost every age group is affected. The prevalence increases dramatically after age 50 years in men and 40 years in women. The direct cause of OA is unknown, but it is thought that it results from intrinsic alterations of the articular tissue, or as a response to cumulative mechanical stress, it is also caused primarily by the degradation of the collagen and proteoglycans in cartilage, leading to fibrillation, erosion and cracking in the superficial cartilage layer. Over time, this process spreads to the deeper layers of cartilage, and eventually large, clinically observable erosions are formed. The second and third most commonly involved joints are those of the knee and hip respectively.[61]Zayed*et al.* [62] reported middle-aged obese Egyptian patients with knee OA represent a high risk group for renal dysfunction.

1.12Osteomyelitis and Kidney Function

Osteomyelitis is localized bone infection.[63] It has traditionally been classified into three categories. The first category, hematogenous osteomyelitis, is bone infection that has been seeded through the bloodstream. The second, osteomyelitis due to spread from a contiguous focus of infection without vascular insufficiency, is seen most often after trauma or surgery, and is caused by bacteria which gain access to bone by direct inoculation or extension to bone from adjacent contaminated soft tissue. The third category, osteomyelitis due to contiguous infection with vascular insufficiency, is seen almost exclusively in the lower extremities, most commonly as a diabetic foot infection. Each of these three categories of osteomyelitis can present in the acute or chronic phase. [64] Griffin reported the association between Glomerulonephritis and acute renal failure with Osteomyelitis.[65]

1.13Spinal Injury and Kidney Disease

Spinal cord injury (SCI) is defined as any injury resulting from an insult to spinal cord that disrupts its major functions, either completely or partially.[66] The presence of either proteinuria with protein of 500 mg/dl or greater or Creatinine Clearance less than 60 mL/min is associated independently with increased mortality in the chronic spinal cord injury population. The presence of both conditions further increases the risk of kidney disease.[67]

1.14Spinal Tuberculosis and Kidney Function

Spinal tuberculosis is one of the oldest diseases known to mankind and has been found in Egyptian mummies dating back to 3400 BC. The disease is popularly known as Pott's spine. Spinal tuberculosis is a destructive form of tuberculosis. It accounts for approximately half of all cases of musculoskeletal tuberculosis. Spinal tuberculosis is more common in children and young adults. Currently, the term 'Pott's disease/Pott's spine' describes tuberculous infection of the spine and the term 'Pott's paraplegia' describes paraplegia resulting from tuberculosis of the spine. [68]

Tuberculosis is caused by a bacillus of the *Mycobacterium tuberculosis* complex. Vertebral infection by the bacillus results from hematogenous dissemination from a primary focus. Infection in the vertebral marrow is followed by a chronic inflammatory response characterized by epithelioid cells, Langhans giant cells, lymphocytes, and inflammatory exudates, which together constitute the typical histopathological lesion called the tubercle. With progressive destruction, caseous necrosis occurs to form the cold abscess.[69]Pott's disease should be suspected in end-stage renal disease patients with back pain and/or neuromuscular complaints.[70]

1.15 Sickle Cell Disease and Kidney Function

Sickle cell disease (SCD) is caused when the glutamic acid in the 6th position of beta chain of Haemoglobin A (HbA) is changed to Valine in Haemoglobin S (HbS).The single amino acid substitution leads to polymerization of Haemoglobin molecules inside red blood cells which causes a distortion of cells into sickle shape.[47]

The presence of renal failure in sickle cell disease (SCD) ranges from 5 to 18% of the total population of SCD patients.[71]Young people with SCD usually have normal renal function. Grossly, the kidneys tend to be hypertrophied, with a characteristic smooth, capsular surface. As people with SCD grow older, the kidneys progress to end-stage renal disease (ESRD). The kidneys eventually shrink, and the capsular surface becomes grossly distorted and scarred.[72]

SCD is associated with both proximal and distal tubular abnormalities. The high GFR in association with the increased loss of salt and water leads to a reactive increase in sodium and water reabsorption by the proximal tubule driving the reabsorption of other solutes such as phosphate and β2 microglobulin; hence, many patients have hyperphosphataemia. Other solutes such as creatinine and uric acid have a marked increase in proximal tubular secretion. Up to 30% of the total creatinine excretion can arise from tubular secretion, resulting in an overestimation of GFR when creatinine-base formulas are used. Distal tubule function is often impaired, leading to reduced potassium and hydrogen ion excretion.[73]

II. Conclusion

The incidence of kidney dysfunction in orthopaedic cases has been reported to be increasing in an alarming rate. It is therefore recommended that post treatment and post operative monitoring of kidney biomarkers should be conducted with immediate effect.

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