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Role of Creatine in the Body and Its Creatinine Clearance in Humans and Animals

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ABSTRACT
Creatinine is a nitrogenous waste chemical formed from the metabolism of creatine, it is utilized as an energy source in skeletal muscle for the production of ATP by the use or adding of phosphorous to ADP. Creatine is synthesized in the liver, kidney, and pancreas from the aminoacids arginine, glycine, and methionine. Creatine is used by skeletal muscle, when it is used it releases the creatinine as a waste chemical there is no useinskeletal muscle it releases into the bloodstream, it easily crosses the plasma membrane andcirculates in the blood, and reaches the kidney where it leaves the body and is filtered in glomerular nephritis, there is no reabsorption in the tubule. The difference between creatine and BUN [blood urea nitrogen] is that BUN is reabsorbed in the tubule, whereas creatinine is not reabsorbed in the tubule. Creatinine levels are an indicator of the functioning of the kidneys, and pancreas in diabetes mellitus patients. The normal levels of creatinine found in a healthy person:are 0.9 to 1.3 mg/dl in men and 0.6 to 1.1 mg/dl in women, these levels are high in unhealthy people with kidney failure, and diabetes mellitus patients. Creatinine levels are high in urine it indicating that your kidney is not working properly, and low serum creatinine levels in blood serum indicate that the pancreas not working properly for the production of insulin.New biomarkers are available for acute kidney infection like nystatin cand neutrophil gelatinase-associated lipocalin [NGAL] for the early detection of kidney infection. Creatinine elimination in veterinary animals is based on a meat diet and casein diet, the metabolism of creatinine in animals differs in carnivores due to a higher concentration of creatine and lesser creatinine in meat.

KEYWORDS: creatine, creatinine, arginine, glycine, methionine, glomerular nephritis, BUN, diabetes mellitus, acute kidney infection, nystatin c, NGAL

I. INTRODUCTION

Creatinine is an amino acid compound derived from crea-tine when creatine is metabolized in skeletal muscle and releases creatinine into the bloodstream, it is freely filtered by the nephron tubule and output through the urine. The level of creatinine is increased in acute kidney failure, and reduced in diabetes mellitus. Creatinine is an indicator also of heart failure. creatinine levels are high or low based on the body mass of people, body mass can decrease by muscle dystrophy. Body mass increased in athletic people because they can use creatine as a supplement. So, they can get early diabetes and kidney infections compare to normal people (1). Creatinine metabolism is seen in vertebrates and dogs, for the detection of GFR function (2).The new biomarkers used are cystatin C and NGAL for acute kidney injury in a kidney patient. In a recent view of kidney function by the RIFLE method, this method prospective and retrospective study was conducted in a hospital toestimate kidney function (3). The biosynthesis of creatinine from creatine in the liver, kidney, and pancreas was determined, the produced creatinine was easily cross the plasma membrane and circulates into the blood and filtered through the kidney, and excreted through the urine (4). creatinine clearance by Cockcroft gault formula for estimating and creatinine ratio by measuring microalbuminuria and differentiate metabolism in vertebrates and dogs (5). The new biomarkers introduced are cystatin C, and NGAL these two are biomarkers bio estimating glomerulus filtration capacity or rate (6). The creatinine levels are increased or decreased depending on the skeletal muscle it uses as an energy reservoir for the production of ATP and gives energy to the body. In pregnancy, the creatinine levels are decreased due to preeclampsia, and the creatinine clearance value decreases because the kidneys are filtering less creatinine out of the blood (7). The amount of kidney damage can be estimated by the decrease in the creatinine clearance value (8). In a healthy person, the creatinine ranges from 95 ml per minute for females and about 120 ml for males. Creatinine clearance also depends on age, size, and the condition of the kidneys. Consuming lemon water

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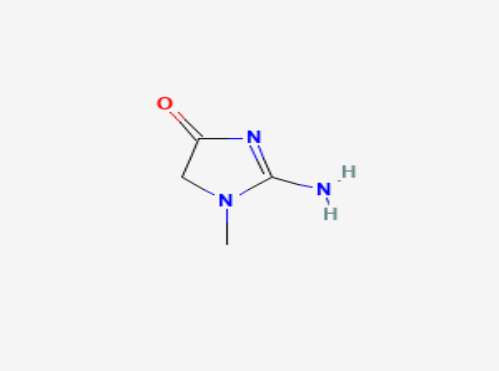
or juice cannot increase or decrease creatinine levels (9).

STRUCTURE OF CREATININE



2-amino -1- methyl-4,5- dihydro -1-imidazole-4-one
The molecular weight of creatinine: 113 Daltons
The molecular formula of creatinine: $C_4H_7N_3O$ (10)

BIOSYNTHESIS OF CREATINE AND CREATININE

Biosynthesis of creatine takes place in the kidney, where transamination from arginine to glycine produces guanidinoacetate in the presence of a mitochondrial enzyme arginine glycine amidino transferase (AGAT) it exists in the liver of some mammals, guanidinoacetate underdoes N-methylation catalyzed by the enzyme guanidinoacetate methyltransferase (GAMT), leading to the production of creatine which has no function in hepatocytes. Creatineis penetrated through the Na+/Cl- channel and distributedthrough the blood and rest of the body and itpenetrates the brain and muscle where it is used as energy and converts the creatine phosphateinto creatine kinase. Skeletal muscles contain about 90% of total body creatine. Plasma creatinine filtered through the glomeruli undergoes tubular reabsorption, so the urine creatinine elimination is weak. (11) (12) (13).
Creatinine is the product, formed by spontaneous, irreversible, and non-enzymatic reactions, creatine undergoes dehydration and dephosphorylation of creatine phosphate(14)

$$\text{Glycine} + \text{L} - \text{arginine} \xrightarrow{\text{AGAT}} \text{L} - \text{omithine} + \text{guanidinoacetate}$$

$$\text{guanidinoacetate} + \text{S} - \text{adenosylmethionine} \xrightarrow{\text{GAMT}} \text{Creatine} + \text{S} - \text{adenosylhomocysteine}$$

$$\text{creatine} + \text{ATP} \overset{\text{CK}}{\Leftrightarrow} \text{creatine phosphate} + \text{ADP}$$

$$\text{creatine} \xrightarrow{\text{nonenzymatic}} \text{creatinine} + \text{H2O}$$

In the course ofthe evaluation, both AGAT and GAMT have been evaluated by the appearance of the lampreys (15). These enzymes are not actively detected in invertebrates, whereas they are found most but not all in vertebrates examined. Some invertebrates (e.g., annelids, echinoderms, hemichordates, and urochordates) contain significant amounts of creatinine, P- creatinine, and creatinine kinase (CK), present particularly in spermatozoa (16). So, these species can take CR from the environment and or from the feed, or the enzymes for biosynthesis in these animals' detection so far.

Many of the lower vertebrates have both AGAT, and GAMT in their livers and alsokidneys, they are fish, frogs, and birds (17) (18) (19). In mammals, the pancreas contains high levels of both enzymes, whereas kidneys express a fairly high amount of AGAT but lower levels of GAMT. Livers of all mammalian species tested contain a high amount of GAMT and low levels of CR and a complete lack of CK activity. Although livers of cows, pigs, monkeys, and humans also contain a high amount of AGAT, livers of common laboratory animals like rats, mice, cats, dogs, and rabbits are reported to lack AGAT activity. CR biosynthesis is reduced in nephrectomized animals (20) (21) (22).

In pyridoxine-deficient rats, despite a 65% decrease in kidney AGAT actively relative to controls, displayed increased liver and skeletal muscle concentration of creatinine (23). In another study extrarenal synthesis was recommended to account for 40 – 60%of total Creatine (24).A comparison of the hepatic and renal venous levels with the arterial levels of Arg, GAA, and CR, suggested that in humans, the liver is the most important organ for the biosynthesis of both GAA and Cr, whereas the kidney plays a secondary role (25). Furthermore, AGAT activity is detected by the heart, spleen, muscle, brain, lung, testis, and thymus these are estimated for the total amount of AGAT in their tissues and it was found in the kidney and pancreas (26) (27). Although AGAT is absent in the human placenta, the decidua of the pregnant females shows the highest specific AGAT activity of all rat tissues examined (28). The transport of creatinine through the maternofetal is demonstrated in the rat (29). GAMT, mRNA, and protein levels are higher than in the male liver these are detected in mouse testis, caput epididymis, and ovary (30).

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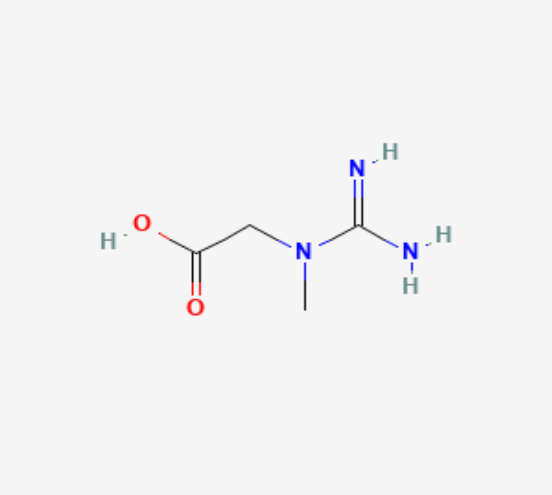
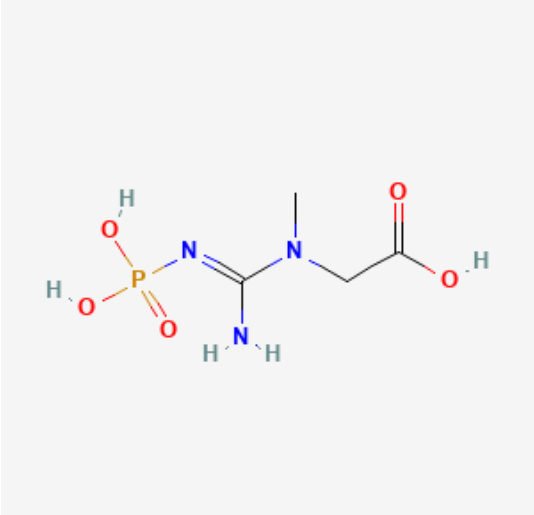
STRUCTURE OF CREATINE AND PHOSPHOCREATINE



2-[carbamimidoyl(methyl)amino]acetic acid
Creatine Molecular formula: $C_4H_9N_3O_2$
Molecular weight: 131-13



N-Methyl-N-(phosphonocarbamimidoyl)glycine
Phosphocreatine molecular formula: $C_4H_{10}N_3O_5P$
Molecular weight: 211-11 (31)

PRINCIPLE

The principle of the Jaffe reaction is that creatinine reacts with the picrate ion, and it produces a red-orange color in an alkaline medium. The produced color from the sample is compared with the calorimeter at the wavelength of 505 nm with that known amount of creatinine at the same condition. TheJaffe reaction is not specific to the measurement of creatinine in plasma. Many compounds like protein, glucose, ascorbic acid, acetone, and keto acids can also form the overestimation of creatinine in plasma. Deproteinization is an important step in the creatinine determination of plasma. The urine is required for the measurement of creatinine concentration in the spot urine samples. In spot urine samples there is no take total collection of urine. measurement of daily creatinine urine, and serum creatinine for estimation of glomerular filtration rate. Creatinine is neither to be reabsorbed nor to be secreted in the tubule from the primary urine of some animals like sheep, dogs, cattle, and cats. It May be used as an endogenous/internal estimation of GFR in these animals (32).

NEW BIOMARKERS OF KIDNEYS AND OTHER DISEASES

Creatinine does not detect acute kidney infection, because of is a marker for renal function, recent research uses renal biomarkers for renal function among those NGAL, cystatin C is most frequently used. NGAL is a 25-kDa protein covalently bound to gelatinases from neutrophils which forms a barrel-shaped tertiary structure with a hydrophobic calyx that binds with small lipophilic molecules (33). other diseases like troponins for acute myocardial infarction (AMI), and procalcitonin for infection (34).

RECENT VIEW OF CREATININE

Creatinine is important in AKI patients, all the variables are clinically measured and these are related to renal function they creatinine, urea, pH, bicarbonate, potassium, and urine output. The acute dialysis quality initiative decided to create a consensus definition using creatinine in AKI this is called RIFLE (Risk, Injury, Failure, Loss, and End-stage kidney disease) (35). Validation of this study for RIFLE criteria uniformly found in higher stages of the criteria is associated with higher mortality. The author and the colleagues of their review conduct retrospective studies for all hospitals on adult patients (36). They found that 9.1% of all patients are in the risk category, 5.2% are in the injury category, and 3.7% are in the failure category. They found a linear increase in mortality rate in hospitals from normal to failure. Another study's multivariate logistic regression analysis showed that all RIFLE criteria are significant predictive factors for hospital mortality, with an almost linear increase in odds ratios from risk to failure. A systematic review of 13 validation studies for the RIFLE criteria including over 71000 patients found that with non-AKI there is a stepwise increase of relative risk for death going from Risk to Injury (37). The authors simply concluded that RIFLE is a classification is very

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easy to classify AKI in different populations. Some changes in serum creatinine it is more sensitive than the Risk category of the RIFLE criteria and are found to have an impact on the outcome. Lassnigg et al (38). conducted a prospective cohort study on 4118 patients who have cardiac and thoracic aorta surgery, changes were observed in serum creatinine within 48hrs postoperatively on day-30 mortality. They found that increased mortality rate of up to 6% in patients whose creatinine remained unchanged or increased up to o.5mg/dl compared to patients whose creatinine levels decreased (39).

Even short duration of study creatinine increase has been found, to higher hospital mortality compared to patients with no AKI. The authors of this review and colleagues using the same database looked at the impact of transient azotemia on hospital mortality. These all are new findings that suggest that not all ideal markers for renal function, creatinine is highly related to outcome in patients who have AKI (40).

CLINICAL SIGNIFICANCE

Measurement of creatinine concentration in plasma and urine samples for detecting the filtering capacity of glomerular filtration rate. Creatinine is an endogenously produced product and is easily filteredby the glomerulus. Creatinine is a useful endogenous marker for creatinine clearance. In renal disease, the GFR rate is decreased when the creatinine clearance is compromised in the renal system. When the GFR is reduced the plasma creatinine concentration is increased. Plasma creatinine levels may not affect until the renal damage has occurred. Plasma creatinine level that is within normal ranges that are not equal to the renal system (41).

Not only creatinine but BUN is also an indicator of the renal system, BUN is not a preferred marker for clearance because it is influenced by a high protein diet, variables in protein synthesis, and protein hydration. BUN is not an ideal marker for GFR, combined with plasma creatinine as a creatinine/BUN ratio, BUN is also useful as an analyte for a pre-or post-renal increase of plasma NPNs (nonprotein nitrogenous) (42).

SPECIMEN REQUIREMENT

The creatinine is measured by serum, plasma, and urine specimens. In this process additives such as fluoride and ammonium heparin should not be used because they react with the method of measurement. Measuring the creatinine clearance requires the collection of 24hr urine and plasma sample collecting within the period of 24hr urine collection period.

Serum or plasma may be tested for BUN, additives such as fluoride and citrate should not be used because they interact with the method of measurement (43).

HIGH CREATININE

There are many possible causes of high creatinine like dehydration, the large amount of protein intake, drug toxicity, and creatine supplement.Some drugs can cause damage to the kidney and high levels of creatinine Examplesinclude antibiotics (aminoglycosides, rifampicin, and vancomycin). Cardiovascular drugs such as ACE inhibitors, and statins. Diuretics, chemotherapy drugs, lithium, and proton pump inhibitors. However other causes of high creatinine kidney infection, glomerulonephritis, diabetes, high blood pressure, and heart diseases such as congestive heart failure, atherosclerosis, and kidney failure both acute and chronic. If high creatinine levels, we have to avoid high-protein foods: like red meat, dairy products, and eggs. high creatinine levels are increased by serious kidney damage or chronic kidney disease. Life-threatening infection, shock, and cancer can be damaged the kidney and the supply of blood to the kidney is low.

KIDNEY INFECTION

It is also called pyelonephritis, the kidney is a major organ in the body, it is the only filtering system in the body, in your body, two bean-shaped kidneys are present on either side of the left and right side of retroperitoneal space, they receive both blood and water along with some chemicals, minerals, ions, and protein they filter all and reabsorb the water and protein remaining all waste product are eliminated through the kidney in the form of urine. when your kidney is infected, these all are not filtered properly in the kidney,and also reabsorption does not occur, the creatinine is present in the urine, so the levels of creatinine in urine are high.

GLOMERULONEPHRITIS

Your kidney has filtering nephrons, they filter all substances which is entered the glomerular when it is inflamed the parts of your kidney are damaged, and also by autoimmune diseases, lupus, and good pasture syndrome.

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HIGH BLOOD PRESSURE

High blood pressure occurs due to the pressure pushing on the walls of arteries being too high. This can damage kidney function and high creatinine. Heart diseases such as atherosclerosis and congestive heart failure and blood vessels cause aneffect on kidney functioning, then an increase in creatinine levels in urine.

CREATININE IN HYPERTENSION

The serum elevated creatinine is associated with increased mortality in hypertensive persons, the elderly, and patients with myocardial infarction or stroke in whom the cardiovascular disease is the major cause of death. The stress of a heart attack can result in hormonal changes within the body, and that can harm how well the kidneys work. When the heart function will be changed the supply of blood to the kidney is decreased (44).

URINARY TRACT BLOCKAGE

The urinary tract is blocked by a kidney stone, prostate enlarge or tumors in this condition urine can accumulate in the kidney this condition is called hydronephrosis

LOW CREATININE

The low levels of creatinine present in muscle dystrophy, in this the muscle does not use creatine for the production of energy, so the creatine is still present in muscle does not utilize by muscle. The low levels of creatinine were found in pregnant and after giving birth the creatinine levels are normal

DIABETES MELLITUS:

Muscle so creatine does not convert into creatinine. The creatinine levels are low in type 2 diabetic patients, diabetes is a metabolic disorder, in which blood sugar levels are high and caused by destroying of beta Langerhans cells in the pancreas. Diabetes is 2 types, type 1 and type 2.

Type 1 diabetes mellitus:this is an insulin-dependent diabetes mellitus, in type 1 diabetes mellitus, the body's immune system destroys the cells that release the insulin, without insulin cells cannot absorb sugar(glucose), which is required for the production of energy, so in type 1 diabetes mellitus the creatinine levels are very low because of there is no insulin production in muscle, so in this type of DM the creatine is not converted into creatinine in skeletal muscle so no energy production takes place in this type of DM. This is the only hypothesis there is no scientific evidence.

Type 2 diabetes mellitus: this is noninsulin-dependent diabetes mellitus, in this type of DM your pancreas makes insulin but does not use it properly by your body, your body gets resistant to insulin, so no use of insulin by muscle, creatine is not used by muscle so does not the production of energy, in this type of DM lower serum creatinine levels in type2 DM is very dangerous to diabetic people. Both type 1 and type2 diabetes are associated with cardiovascular diseases (45).

CREATININE CLEARANCE

Creatinine input into plasma is the almost constant rate and excretion of creatinine in glomerular filtration, plasma creatinine is also equal to plasma creatinine clearance. The mean true creatinine clearance was higher than the mean regular creatinine clearance due to lower creatinine concentration in plasma. The mean regular creatinine clearance approximated the mean inulin clearance, whereasthe mean true creatinine clearance was higher (46).

Generally, body mass decreases with age. serum creatinine in the elderly will not increase until 50% of nephrons are no longer functional.

The Cockcroft-gault formula for estimating creatinine clearance:

- Creatinine clearance = [140-age(years) ×ideal weight (kg) ÷ ([creatinine (mg/dl)] × 72)

For women, multiply by 0.85 (47)

TECHNIQUES

1. Endogenous creatinine clearance

Determination of endogenous creatinine clearance by measuring the total amount of endogenous creatinine urine eliminated over some time and p-creatinine. Measuring endogenous creatinine clearance requires both plasma and urine creatinine concentration and the exact volume of urine eliminated over periods ranges from 20 min to 24hr, based on the method of clearance (48) (49).

2. Exogenous creatinine clearance

Creatinine clearance by exogenous it can be evaluated after administration of a known amount of creatinine by various routes of administration like bolus SC, IM, and IV infusion of creatinine. It can also be determined by repeated administration of P- creatinine measurement after IV administration (50).

Extracts used forcreatinine clearance in blood serum by using astragalus, clove, siberianginseng, cinnamon, sage, corn silk, dandelion root, etc. these extracts are useful in lowering creatinine levels in kidney failure (51).

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URINARY ELIMINATION OF CREATININE IN VETERINARY ANIMAL

Creatinine in plasma is freely filtered by glomeruli so their concentration in glomeruli filtrate and plasma is the same. Veterinary animals like dogs in this animal creatinine are secreted in the renal proximal tubule (52) (53), especially in male dogs (54), but this is negligible significance (55) (56), even in chronic renal failure dogs (57).

The input of creatinine in plasma when creatine is used by muscle releases the creatinine into plasma and depends on the muscle mass of dogs, their urinary elimination of creatinine is constant. In the dog, there is no difference in creatinine elimination according to sex (58) (59) or higher in males than in females (60). Urine creatinine concentration is not different between day and night urinary creatinine increased or decreased after meals (61). Total urinary creatinine excretion was different according to studies, with meals ranging from 170 to 425 µmol/kg/d (62) (63). This difference may be due to the consumption of meals like a meat-based diet with more protein eat dogs eliminates more creatinine than casein diet dogs (64) (65), and also differs due to urine dilution and concentration and which ranges from 4.7 to 42.0 mmol/L (66) (67).

METABOLISM OF CREATININE IN THE DOG

Creatinine is a metabolized chemical product produced from the cyclization of creatine and phosphate creatine. It is the higher water-soluble and molecular weight of 113 Daltons. Creatine and creatinine originate from amino acids like arginine, glycine, and methionine and also from the alimentary supply. Creatinine is more important in carnivores than in other animals due to the higher concentration of creatine and lesser amount of creatinine in meat (14).

PATHOLOGIC VARIATIONS IN P-CREATININE

Relationship between P-creatinine and GFR

The P-creatinine and GFR are determined independently (i.e., not by endogenous creatinine clearance), their relationship was hyperbolic (68) (69) (70), exponential (71) (72) (73) (74), or curvilinear (75). A similar relationship can also be determined from GFR it was measured by exogenous creatinine clearance (76).

Several outcomes of the dispersion values and shape of the curve. At both ends, a large variety of one variable corresponds to a very small change in the other, which means the reduction of GFR from 3.5 to 2.5 mL/min/kg has little effect on P-creatinine and that a large decrease of P-creatinine from 500 – 300 µmol/L (5.7 to 3.4 mg/dL) corresponds to only a minor increase in GFR. The variation is large in interindividual and it was the same for p-creatine concentration match to reduced GFR (14).

CREATININE RATIO

Microalbuminuria is a predictor of cardiovascular diseases and all-cause mortality in diabetic (77) and nondiabetic men and women and, it is also useful for future indicators of cardiovascular disease (78). Microalbuminuria is a tool to identify people who are at high risk of cardiovascular diseases in comparison to normal people and patientswithalbumin excretion rates (79). According to the American diabetes association (ADA), the gold standard for measuring urine albumin excretion is 24hr urine collection (80). However, a more convenient method for measuring of albumin (µg)/creatinine (mg) ratio(ACR), was measured in a random urine specimen (79). Currently, the national kidney foundation states that the use of spot urine ACR obtained under standardized conditions avoids morning, midstreamspecimens, to detect microalbuminuria. The ACR is a more convenient test for the patient and it gives an error due to improper collection of urine methods and variations in 24hr protein excretion compared with a random urine specimen (79).

The ADA and national kidney foundation define microalbuminuria as an ACR between 30 to 300 µg/ml in both men and women (79) (80). These guidelines are not taken into account sex differences in creatinine excretion, and several kinds of research had explained the sex-specific cut-points of the ACR to detect microalbuminuria (81) (82).

The current definitions of microalbuminuria as measured by the ACR in a random urine specimen also do not take account into racial differences in creatinine excretion. Previous studies have reported urine creatinine excretion rates to be 5 to 30% higher in black people compared to white people (83) (84). Distribution of urine albumin and creatinine concentration and ACR measured in spot urine specimens in a nationally representative sample of men and women and non-Hispanic whites and non-Hispanic blacks and Mexican Americans (85).

BLOOD CREATININE TEST

In the serum creatinine test in this test, blood is collected from a vein and sent to a lab for further

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analysis. According to the mayo clinic, the normal blood creatinine rangesare

- U.S units: 0.84 to 1.21 mg/dl
- European units: 74.3 to 107 µmol/L

Creatinine levels above the normal rangeindicate high creatinine levels in the blood

URINE CREATININE TEST

Urine creatinine test in this test the urine is collected 24hr sample for analysis of urine. according to mayo clinic laboratories, the normal range of urine creatinine levels are

- U.S units:955 to 2,936 mg/day for men
- European units: 8.4 to 25.9 mmol/day for women (1) (14)

ASSAY OF CREATININE BY THE JAFFE REACTION

Chemistry of the reaction

Jaffe in 1888 was observing the red color formed when creatinine reacted with picric acid in the alkaline medium (86), the reaction bears his name. in 1904, Folin utilized the Jaffe reaction to measure creatinine in urine (87). Greenwald was the first to make a systematic study of the chemistry of the Jaffe reaction (88). He ascribed the red color to a salt of creatinine, picric acid, and sodium hydroxide, and noted that there were at least two places in the creatinine molecule where a shift in a hydrogen atom could produce a tautomer: a lactam-lactim rearrangement between position 3 and 4 or keto-enol change between position 4 and 5 (9).

CREATININE IN PREGNANCY

In normal pregnancy, increased blood volume and kidney function cause an increase in the amount of creatinine filtered out of the blood and passed into the urine. estimating GFR in pregnancy, the physiologic increase in GFR during pregnancy normal results in a decrease in the concentration of serum creatinine, which falls by an average of 0.4 mg/dl to a pregnancy normal range of 0.4 to 0.8 mg/dl.

In pregnancy, the flow of blood to the kidney is higher. Due to this the increase in excretion and GFRT. Due to this reason, pregnant people typically have lower levels of blood creatinine. Decreased renal function in pregnant, creatinine above 75 µmol/L, and urea above 4.5 mmol/L are an indication for further investigation. In pregnancy, the GFR is no requirement for estimation (89).

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II. CONCLUSION

I am giving a conclusion to my review article “creatinine is a metabolic product produced from creatine, which is released in the liver, kidney, and pancreas. The creatinewhich is utilized as an energy source like in skeletal muscle releases the waste chemical known as creatinine. The produced creatinine can easily cross the plasma membrane and enterthe bloodstream, it can reach to kidney and be filtered through the glomerulus nephrons excreted through the urine. I concluded this topic with that the type 2 Diabetes mellitus in this patient the serum creatinine levels are low, so it can cause type 2 diabetes mellitus. Also, cause acute kidney infection by high levelsof creatinine, in this, the kidney is infected and rising the levels of creatinine also, I wrote difference between the metabolism of creatinine in dogs and vertebrates. Biomarkers are used for detecting acute kidney infection they are nystatin C, and NGAL these two are used as biomarkers for clearance of creatinine in urine by two methods exogenous and endogenous creatinine clearance and by Cockcroft gault formula for estimating creatinine clearance and measuring of microalbuminuria for creatinine ratio and albumin.

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