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The Impact of HAART on Kidney Function in HIVAIDS Patients

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Abstract
Highly Active Antiretroviral Therapy (HAART) has brought improvement in the management of HIV/AIDS, significantly reducing morbidity and mortality. However, emerging evidence indicates that HAART may have complex effects on kidney function in HIV-positive individuals. We reviewed the impact of HAART on renal function, examining both its protective and potentially nephrotoxic effects. HIV-associated nephropathy (HIVAN) is a known complication of uncontrolled HIV infection, and HAART has been shown to delay its progression by suppressing viral replication. Conversely, some antiretroviral drugs, particularly tenofovir disoproxil fumarate (TDF), indinavir, and certain protease inhibitors have been linked to nephrotoxicity, manifesting as proximal tubular dysfunction, reduced glomerular filtration rate (GFR), and, in some cases, acute kidney injury (AKI). The role of comorbid conditions such as hypertension, diabetes, and co-infection with hepatitis B or C have been reported in the literatures. Findings suggest that while HAART contributes to overall renal preservation by controlling HIV replication, the risk of kidney impairment persists, particularly with prolonged exposure to nephrotoxic agents and in individuals with pre-existing renal conditions. Tailored antiretroviral regimens and regular renal monitoring are essential to mitigate these risks. Understanding the dual role of HAART in kidney health can help optimize treatment protocols and improve long-term outcomes for people living with HIV/AIDS.

Keywords: Highly Active Antiretroviral Therapy, HIV-associated Nephropathy, Nephrotoxicity, Kidney Function, Acute Kidney Injury

Introduction

Human immunodeficiency virus (HIV), is a virus that attack the immune cells of the human body which is the white blood cells, it contains the (clusters of differentiation 4) CD4 T cells also known as helper cells or the T cells which are the immune cells and they plays vital roles in responding to infection in the body, these virus decreases the function of CD4 T cells thereby

impairing the immune function of the body making the individual become opportunistic, prone to several infection or other health problem, if not properly managed HIV can lead to Acquired immunodeficiency syndrome (AIDS) or even death [1].

AIDS is a life threatening disease which causes a shift in the immune function of the body, just as its name goes, it is an acquired disease and not a genetic disease and cannot be transferred from parent to offspring through genetic control, it also affects the immunity of an infected individual and this viral infection causes some signs and symptoms to the individual [1] AIDS has no cure but can be managed with the appropriate medication which helps to enhance a healthier and a prolonged life.

It has been estimated by World Health Organization (WHO) that about 47million cases have been identified, close to about 26million lives have been lost to death while about 32million people are living with HIV as at 2020 with over two third of the fraction from Africa [2].

In 1981, a sudden spot of cases of lung infections due to Pneumocytstis carini pneumonia and a peculiar type of cancer called Kaposi sarcoma were observed in many young homosexual men. Observing them more, a deficiency in helper T cells and also CD4 cells were observed [3]. In June 1981, the US Centers for Disease Control and Prevention (CDC) first described the symptoms of this unknown disease in one of their publications. Soon, healthcare providers from around the country began reporting similar cases. The number of people with disease increased. Sadly, so did the number of people dying from the unidentified diseases. In September 1982, the CDC uses the term Acquired Immune Deficiency Syndrome (AIDS) for the first time when describing the mystery disease [4].

In Nigeria, the first two cases of HIV were identified in Lagos 1985 and were reported at an international AIDS conference in 1986 [5], in 1987 the Nigerian health sector established the National Expert Advisory Committee on AIDS (NEACA). At first the Nigerian government was slow to respond to the increasing rates of HIV transmission and it was only in 1991 that the federal ministry of health made their first attempt to assess Nigeria's AIDS situation. The results showed that around 1.8% of the Nigerian population were infected with HIV. Subsequent surveillance reports revealed that during the 1990s HIV prevalence rose from 3.8% in 1993 to 4.5% in 1998 [6].

Pathophysiology of HIV

Once an individual gets infected with the virus, it replicates inside the host T helper cells which is required for adaptive immune response of an individual, there is usually an initial stage of influenza like illness in the form of; fever, chills, malaise, dry cough, loss of appetite, nausea, and then a latent asymptomatic stage. When the CD4 count of the host fall below 200cells/ml of blood, then it is said to have progressed to AIDS which is characterized by deficiency in cell mediated immunity thereby resulting to an increase to susceptibility to opportunistic infection and then some cancer [7]. CD4 cells also known as T cells are white blood cells the fight infections and plays important roles in the immune system, CD4 count is done on patients' blood to check the amount of CD4 cells present in the body, its normal reference is 500 to 1600 cells per cubic millimeter of blood (cells/mm3) whereas once the CD4 count becomes lower than 200cells/mm3 the person will be diagnosed on AIDS. Once HIV infects an individual, it makes copies of itself by their replication mechanism thereby killing the CD4 cells, once this is done it reduces the number of the patient CD4 cell which now makes them prone to infection and other diseases, the more the virus in the patient the lesser their CD4 count the more immunocompromised the patient become [8].

Signs and symptoms

HIV signs and symptoms depend on the stages of the viral infection, in most cases people with the infection do not know until about 2-6 weeks of the unset of the symptoms when the body immune system begins to fight, It is called the Acute Retroviral Syndrome or Primary HIV infection, this is first stage of the infection, the symptomsare usually like that of every other viral infection and they include fever, flu, fatigue, malaise, muscle ache, swollen lymph nodes, pharyngitis, red rash that doesn't itch [9]. The second stage which is called the Asymptomatic Period or the Chronic HIV Infection, at this stage the CD4 T cells becomes weaken thereby impairing immune functions, the number of the CD4 cell decreases which now makes the individual susceptible to any kind of infection, at this stage the individual do not present any visible symptoms.

At the third stage HIV has advanced to AIDS, the CD4 cells count has gone below 200per micro liter of blood, the immune system at this stage has become so damaged that the individual will become prone to whatever infection that comes its way, the individual even become at a risk of cancer and other life threatening diseases, some of the symptoms at this stage include tiredness, weight loss, shortness of breath, loss of vision, swollen lymph on the neck or groin, yeast infection in the mouth, throat or vagina and also some neurologic symptoms like memory loss, confusion, depression. This signs and symptoms begins to manifest between 2-4 weeks of getting infected [10].

Transmission

HIV is basically transmitted in three ways which are as follow: Sexual intercourse; Vertical transmission (mother to child transmission); Blood transfusion and other body fluid. In developed countries like the united states of America (USA), Europe, 90% of cases are seen in homosexual and individual using intravenous drugs resulting to more male been infected than the females. HIV is seen in seminal fluid, vagina or cervical fluids during sexual intercourse, the viral particles penetrate tiny ulceration within the vagina, rectal, penal or erectile mucosa into the circulation [1].

In developed countries, proper screening of blood is done before transfusion and this has reduced the risk of HIV transmission by blood transfusion rather by intravenous drug users who share needles whereas in developing countries, blood screening is often neglected before transfusion and this has a major source of transmitting the virus [11]. About 42% of this viral infection occurs in mother to child during childbirth or breastfeeding due to unknown HIV positive mothers. HIV can be transmitted at a high concentration through blood (including menstrual blood), semen, vaginal secretion, and breast milk, while at a low concentration can be found in pus, saliva, tears, urine, vomiting, feces, and nasal mucus [1].

Structure and life cycle of HIV

HIV is a spherical virus, the outer shell of the virus is called the Envelop and it is covered in spikes of glycoproteins (gp), this glycoproteins are the gp120 and gp 41; gp120 has a molecular weight of 120, it is essential for the entry of virus into the cells and plays a role in the attachment of virus to specific cell surface receptor while gp41 function to replicate the host cell through the process of reverse transcriptase, it targets the host cell [1]. Inside the envelope is a layer called the Matrix, the nucleus of the virus is held in the capsid which is a cone shapes structure in the Centre of the virion, the capsid consist of two essential enzymes which assist in HIV replication, the enzymes are; Reverse Transcriptase and Integrase Molecule which enables the genetic materials of the virus to be integrated into the Deoxyribonucleic Acid (DNA) of infected cells [11].

HIV Ribonucleic Acid (RNA) is made up of nine genes which contains all the instructions for making a new virus, the genes are gag, pol, env, tat, rev, nef,vif,vpr, and vpu; the genes gag, pol and env provides information to make protein that will form new virus particle, env provides code for making the protein that forms the envelop, pop makes the enzymes that are essential for making new virus while gag makes the structural protein such as the matrix and capsid whereas the remaining six genes "tat, rev, nef, vif, vpr and vpu" provides code to make proteins that controls the ability of HIV to infect cells, produce new copies of virus or release viruses from infected cells [12].

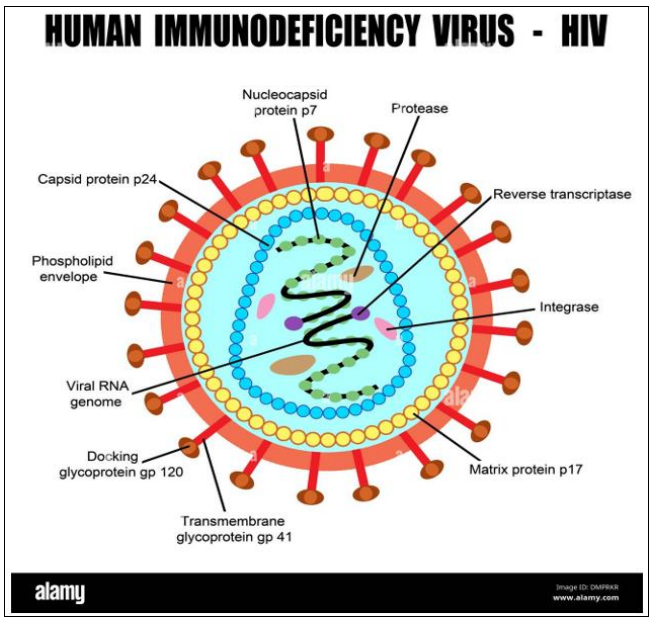

Fig 1: Structure of HIV

The life cycle of HIV

The life cycle of HIV involves 5 stages namely the Attachment and Entry Stage, Reverse Transcription, Integration, Transcription and Translation stage and final the Assembly and Budding Stage.

Attachment and Entry stage: HIV enters into the human body to make new copies of itself, on entry into the cell the virus glycoprotein (gp120) on the cell surface attaches to the CD4 cell receptor, the gp41 protein fuses the HIV envelop with the cell wall, this process of fusion allows the HIV capsid to enter the CD4 cell, affecting more cells and therefore weaken the immune system [13].

Reverse Transcription: This stage involves the conversion of viral RNA to DNA by the action of the enzyme reverse transcriptase after which the DNA is transported to cell nucleus where insertion of DNA is done by the enzyme Integrase [13].

Integration: DNA of HIV enters into the CD4 cell nucleus and then make use of the enzyme integrase to insert itself into the host cell DNA making the HIV DNA strand to insert in the host DNA, at this stage the virus is kill dormant within the host [1].

Transcription and Translation: The HIV DNA uses the host CD4 cells enzymes to make messenger RNA (mRNA) which provides instruction for the making of a new viral protein in a long chain [11].

Assembly and Budding: The enzyme protease cut long chain of HIV protein into smaller chains, the chains begins to assembly into new virus at the cell wall, after the new virus is formed, it leaves the CD4 cell to become infectious, the virus takes lipid from the cell wall to make its surface glycoprotein [1].

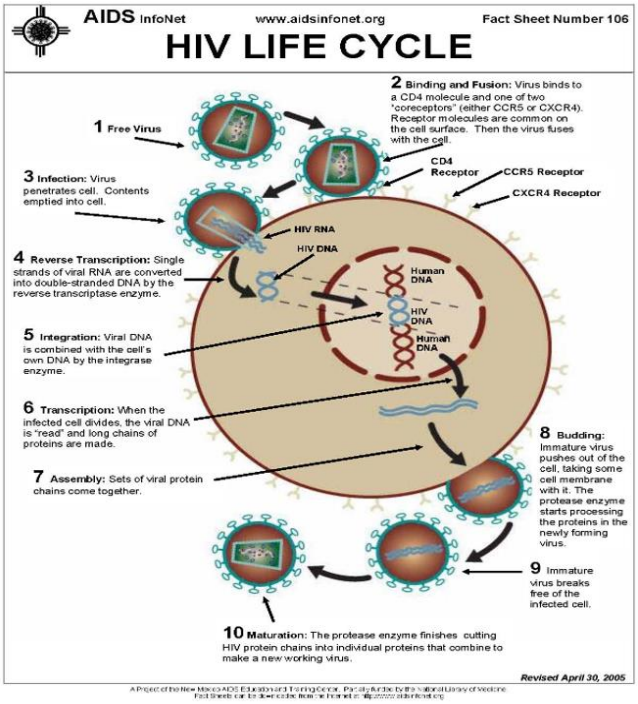

Fig 2: Life cycle of HIV

HIV strands and types

There are two different types of HIV and they are HIV-1 and HIV-2, they are of distinct type genetically.

HIV-1 is the most predominant type of virus accounting for about 95% of people living with HIV in the world, this virus is further classified into four subgroups which are group M, group N, group O and group P. Group M is the major case of HIV worldwide while the other three types are less common [14].

HIV-2 is mostly found in Western Africa, it accounts for about 55% of those living with HIV, it progresses slowly compared to its counterpart HIV-1 thereby leading to fewer death but if not properly treated or managed can lead to AIDS or even death, it is resistant to some types of retroviral drugs like Non-nucleoside reverse transcriptase inhibitors, and it is further subdivided into nine different group; group A, group B, group C, group D, group E, group F, group G,

group H and group I. group A and group D are the only groups currently circulating in the human [15].

HIV risk factors

This factors put individuals at the risk of been infected with the virus and they include: Unprotected sex is one of the leading cause of HIV infection, abstinence is key but if sex must happen between two people that are not partner or properly screened then a protection (condom) should be used. Transfusing unscreened blood or transplanting tissue and organ from an infected person to a healthy person. Using contaminated needles, syringes and other sharp objects used in skin piercing and making tattoos. Giving birth in clinics or maternity home that does not have good facility to prevent mother to child transfusion during delivery in an accident scene [16].

Laboratory features

The following laboratory investigation are done in the diagnosis and management of HIV/AIDS; HIV antibody testing(Enzyme Linked Immunosorbant Assay-ELISA) and counselling. Antigen testing use for assaying HIV infections in infants below 18months of age, to monitor viral load in patients receiving HAART and to detect treatment failure. Hematological testing which involves the measurement of packed cell volume (PCV), hemoglobin, platelet counts, total and differential white blood cells count. Microbial tests to diagnose HIV associated infections like Tuberculosis, abscesses and unhealing wounds, fungal infections, cerebral toxoplasmosis, syphilis, other sexually transmitted diseases etc. CD4+ T cells counting, Tests to monitor patients on HAART.

Prevention and control

Efforts directed towards the control and prevention of this virus is directed to; Prevention of the virus through awareness, educating people on how to avoid the spread of the virus. Development of vaccine. Proper screening of blood before transfusion. Avoidance of sex between people that have not properly screened themselves of the virus but if sex must occur either vagina, anal or oral, protection should be used. Avoidance of the use of same sharp objects like needles, blade, pins, tattooing tools, clippers, shaving sticks that have been use by HIV positive patients. Education on stigmatization is very important to help protect the mental health of the patient [1].

Highly active antiretroviral therapy (HAART)

Highly active antiretroviral therapy HAART) is a medication used in the management of AIDS and treatment of HIV usually HIV-1 depending on the viral load of the individual. This therapy has helped in the reduction of mortality, reduction of viral load of an individual, improving the quality of life of an infected individual, improve immunity and also helps in preventing the transmission to other which is the primary goal especially mother to child transmission during childbirth and breastfeeding [17]. The drugs had been in use since 1996, it is a combination of three or more drugs depending on the patients' viral load, the drug functions to inhibit the replication of the virus by several mechanisms which reduces the risk of transmitting the virus to sexual partners and also between mothers to child [18].

Mechanism of action

This explains how HAART function in curtailing the transmission of the virus to others, it involves various stages which are targeted at the different lifecycle of the virus to inhibit its replication and this mechanism include;

Nucleotide Reverse Transcriptase Inhibitors (NRTIs)

Intracellular phosphorylation from host enzyme is required to inhibit viral replication. These agents are nucleotide analogs with an absent hydroxyl at 3' end that are incorporated into the growing viral DNA strand. They competitively bind to reverse transcriptase and causes premature DNA chains terminating as the inhibit 3' to 5' phosphodiester bond formation. Examples include; Lamivudine, Abacavir, Didanosine, tenofovir, stavudine and zidovudine [19].

Non-nucleoside Reverse Transcriptase Inhibitors (NNRTIs)

It binds to the HIV reverse transcriptase, it causes a stereochemical change within reverse transcriptase thereby inhibiting nucleoside binding and DNA polymerase. Examples are Delavirdine, Efevirenz, Nevirapine and Rilpivirine [20].

Protease inhibitore (PLs)

It inhibits the proteolytic cleavage of the gag/pol polyprotein in an HIV infected cell which results in immature noninfectious virions. PLs is used for patients that failed their initial HAART regimen and should be administered with boosting agents such as Ritonavir or Cobicistat [20]. Examples include; Atarzanavir, Darunavir, Indinavir.

Integrase Strand Transfer Inhibitors (INSTIs)

INSTIs prevents viral DNA from being incorporated into the host cell chromosome by binding to the viral integrase. Examples include; Elvitegravir, Raltegravir, Dolutegravir [21].

Fusion Inhibitors (FIs)

It inhibits viral fusion to the CD4 T-cells by binding to the enveloped glycoprotein gp41. Example; Enfuvirtide [21].

Chemokine Receptor Antagonists (CCR5 Antagonists)

It blocks the entry of the virus into the CD4 T-cells by preventing the interaction between CD4 cell and the gp120 subunit of the viral envelop glycoprotein. Example; Maraviroc.

Route of administration

HAART is administered to a patient on confirmation of the virus, the therapy starts immediately to reduce severe cases or the underlining illnesses. A detailed patient history is necessary before a combination therapy will be given. It is often given orally and in some patients who finds it difficult to swallow, the drug can come in a liquid preparation or crushable tablet. The recommended dosage by the Food and Drug Administration for this drug is a single tablet once a day but some are administered in two or three tablet, the dosage of this drug is regulated due to some factors like; renal or hepatic disorders, childbearing potential and some comorbid conditions like; hepatitis, cardiovascular disorders, tuberculosis [22].

Adverse side effect

The adverse effects of HAART is stimulated by the various mechanism of action of the drugsbut some of its general side effects include; Gastrointestinal complication (like pancreatitis, hepatotoxicity), hypersensitivity reaction (rashes, fever, headaches, dizziness).Some patients may experience sleep disturbance, psychosis-like behavior, delusion.

Contraindication

There is no general contraindication of HAART on a patient except one with an underlying illness or comorbidity causing a contraindication to a specific antiretroviral drug, it is left for the healthcare provider to find a different HAART combination for the patient. The therapy should be administered immediately to a positive patient irrespective of their CD4 counts [23].

The kidney

The human kidney is a beans shaped organ, it is located on both sides of the spine, just below the rib. This organ helps in the filtration of waste substances from the blood, it controls the body fluid balance and keeps the body electrolyte at a stable level [24]. The basic function of the kidney is homeostasis and production of hormones. The kidney comprises the nephron which is the functional unit of the kidney, there are approximately one million nephron in each kidney. Each nephron consist of a Glomerulus, proximal convoluted tubule, descendingloop of Henle, ascending loop of Henle, distal tubule and collection duct which functions to filter small solute from the blood, reabsorb ions, remove toxins and adjust filter pH, allows water to pass from the filter into the interstitial fluid, reabsorbs sodium and chloride from the interstitial fluid, selectively secretes and absorbs different ions to maintain blood pH, electrolyte balance and reabsorbs solute and water from the filter respectively [25].

Biological function of the kidney

Controlling of Water Balance: It controls water balance by regulating the volume of urine produced by the body, the kidney adapts to ones hydrated state thereby producing more urine and the opposite occurs during dehydration.

Acid-Base Balance: The kidney excrete excess acid and base or retains them when needed by the body.

Maintanance of Electroyte: The kidney filters electrolyte out of the blood and them returns a part of it to the circulation and excess of it is excreted through the urine. The level of electrolyte in the body depends on the health of the kidney.

Removal of Toxins and Waste from the Body: The kidney filters all waste and toxins from the body through the urine, once there is a dysfunction or impairment of the kidney function, it leads to the pile up of toxins and waste in the body.

Control of Blood Pressure: The kidney produced the enzyme Renin which convert angiotensinogen produced in the liver into angiotensin I, it is later converted to angiotensin II. Angiotensin II constricts the blood vessels and increase blood pressure but when ones blood pressure is too high, the kidney produces more urine to reduce the volume of liquid circulating in the body and the compensating the blood pressure [25].

Production of Hormones: The kidney produces the hormone erythropoietin which helps the body in creating more red cells that are essential for the transport of oxygen throughout the tissues and organs.

Activation of Vitamin D: The kidney coverts vitamin from supplements or the sun to calcitriol which is the active form of vitamin D (also known as 1,25-dihydroxycholecalciferol). It circulates in the blood and function to regulate calcium and phosphate balance in the body which is important for bone growth, healing and immune system function.

Urine is formed in the nephron by a combination of simple filtration and selective reabsorption. The HIV destroys the nephron of the kidney which affects the ability of the kidney to filter waste and toxins as it ought to, it also infect the kidney cells and this has caused a remarkable change in the creatinine and urea level of an HIV patient because the kidney cannot freely filter the toxins and waste out of the kidney or the kidney excrete excess of this analyte from the body. Once the kidney is unable to carry out its biological functions as stated above, there are various test that should be done to check out the kidney, this test can be done using blood or urine some of the test include; serum creatinine and urea, Glomerular Filtration Rate(GFR). Interest of this study is using urea and creatinine for the analysis of kidney function.

Serum urea

Urea is an organic compound with its chemical formula as $CO(NH_2)_2$. Urea was first isolated from man by Rouelle in 1773 and first used as a clinical diagnostic test for kidney function in 1903.It is the main nitrogenous end product of protein breakdown, it is synthesized from ammonia by the liver enzymes of the urea cycle and then excreted by the kidney. It account for about 75% of the Non-Protein Nitrogenous Compounds excreted, more than 90% of urea is excreted through the kidney and the remaining percentage been excreted by the Gastrointestinal tract and skin [26].

Urea is neither actively reabsorbed or secreted by the tubule rather it is freely filtered by the glomeruli, normally 40-70% of urea is highly diffused passively out of the renal tubule and into the interstitium ultimately to re-enter the plasma [27].

Metabolism of urea

The urea cycle consist of four reaction, the first reaction occurs in the mitochondria while the second, third and fourth occurs in the cytosol.

Reaction one: It is catalyzed by ornithine transcarbamoylase that transfers a carbamoyl group from carbamoyl phosphate to ornithine to form citrulline.

Reaction two: It is catalyze by the enzyme argininosuccinatesynthetase which use ATP to activate cirtrulline by forming a citrullyl-ATP intermediate, the intermediate is attacked by the amino group of an aspartate residue to form argininosuccinate.

Reaction three: This reaction is catalyzed by argininosuccinatelyase that cleaves argininosuccinate into fumarate and arginine.

Reaction four: The last step is catalyzed by arginase that cleaves arginine to produce urea and ornithine completing the urea cycle.

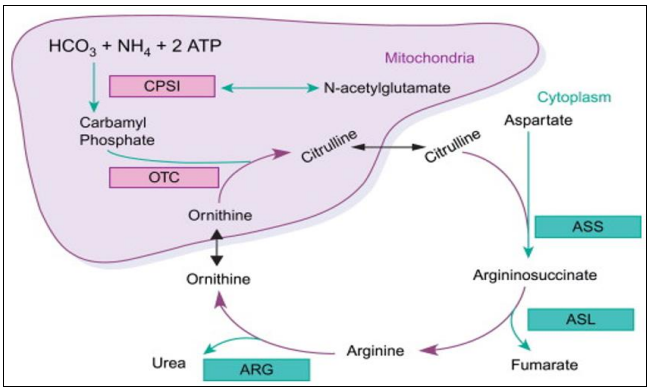

Fig 3: Metabolism of urea

Importance of urea as a kidney function test

The blood urea nitrogen provides information about the amount of protein metabolized in the body, urea makes up about 80-90% of the non-protein nitrogenous substances excreted in the body, the body's dependency on the renal system to excrete urea makes it a useful analyte to evaluate renal function, the increase in blood urea nitrogen could be as a result of increased protein diet or a decreased renal excretion, urea have a normal reference range of 2.1-7.1mmol/l in a healthy adult [28].

Limitation of urea in kidney function test

Serum or plasma urea concentration has regarded as a test for kidney function but it possesses some characteristic that limits it as an ideal test for kidney function and this limitation include;

Increased urea concentration when a high protein diet is taken and decreases at a very low protein diet intake

Increased protein catabolism and muscle wasting. Reabsorption of blood protein after gastrointestinal hemorrhage.

Serum creatinine

Creatinine is the byproduct of muscle metabolism, it is produced from the breakdown of creatine and phosphocreatine and can serve as a marker for renal function. Creatine is synthesized from arginine, glycine and methionine in the kidney and liver by two enzymatic reaction. The first reaction is the transamidation of arginine and glycine to form guanidinoacetic acid and the second reaction is the methylation of guanidinoacetic acid occurring with S-adenosyl methionine as the methyl donor.

Creatine is transported from the liver to tissues such as skeletal muscles and brain where it undergoes phosphorylation and serves as a short term energy store.

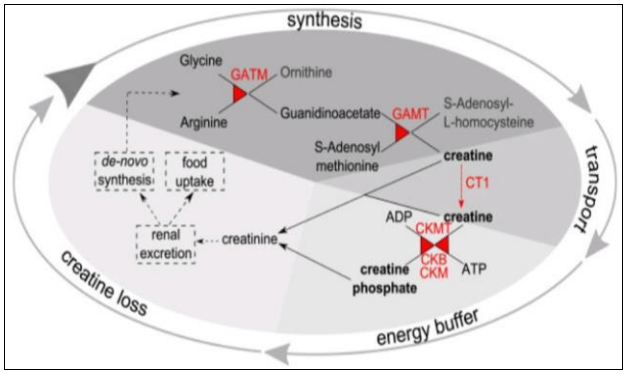

Fig 4: Metabolism of creatinine

Importance of creatinine as a kidney function

Creatinine is released into the circulation at a relatively constant level, it is present in all body fluid and secretion and is freely filtered by the glomeruli but neither metabolized nor actively reabsorbed within the tubules rather it is secreted and these makes it a major maker for kidney function test [27].

When there is an abnormally high increase in serum creatinine level of an individual, it indicates a kidney disease or a dysfunction of the kidney, the normal reference range of creatinine in an adult male is 0.6-1.2mg/dl while in an adult female it is 0.5-1.1mg/dl.

Limitations of creatinine as a marker for kidney function test

There are various factors that can hinder creatinine from being a marker for kidney function, this factors either causes a decrease or an increase in the value of creatinine when it is estimated and this factors have to be considered before a conclusion can be made on the result, this factors include:

Increased dietary meat intake causes an increase in the creatinine value of an individual to compare with vegetarians.

Muscle mass influences creatinine level, individual with high muscle mass usually have a high creatinine value to compare with those with a lower muscle mass (children, aged) owing to the fact that creatinine is the end product of muscle metabolism. Male usually have a higher creatinine level than females. Race, blacks usually have a higher creatinine level than the white race, making the reference range different for each race,

Exercise leads to a reduction in renal flow of blood which in turn causes a slight decrease in creatinine concentration [27].

Serum creatinine and urea in HIV/AIDS patients

Owing to the fact that HIV infection destroys the kidney cells (nephron) thereby impairing the functionality of the kidney it causes a remarkable change in the creatinine and urea level of an HIV patient because the kidney cannot freely filter the toxins and waste out of the kidney or the kidney excrete excess of this analyte from the body [26]. Studies has shown the HAART causes renal toxicity to the patient thereby they should be monitored by carrying our laboratory tests such as urinalysis, serum creatinine and urea to prevent further damage on the kidney. Researches carried out on related topic has shown that serum creatinine level is higher in naïve patients to compare patients on HAART, urea level is also higher in naïve patients than that of the patients on HAART [29], antiretroviral drug has a way of reducing the effect of the viral infection on the kidney but the drugs on its own causes renal toxicity on the patients kidney.

Conclusion

The impact of HAART on kidney function in HIV/AIDS patients is complex. While HAART effectively reduces HIV-associated nephropathy by suppressing viral replication, certain antiretroviral agents pose a risk of nephrotoxicity, potentially leading to chronic kidney disease. The balance between therapeutic benefit and renal safety requires careful consideration, especially in patients with pre-existing kidney conditions or other risk factors. Regular monitoring of renal function and the use of less nephrotoxic drug alternatives are crucial in managing these

patients. Optimizing HAART regimens can enhance both viral suppression and renal outcomes, improving the overall quality of life for individuals living with HIV/AIDS.

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