A review on vitamin D and Insulin resistance in HIV infection

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Abstract

Human Immunodeficiency Virus is a member of the genus Lentivirus, part of the family of retroviridae. HIV is different in structure from other Lentiviruses. It is roughly spherical with a diameter of about 120nm, around 60 times smaller than a red blood cell, yet large for a virus. HIV seeks out and destroys CCR5 expressing CD4+ T-cells during acute infection. A vigorous immune response eventually controls the infection and initiates the clinically latent phase. The HIV Virus is commonly transmitted via unprotected sexual activity, blood transfusions, hypodermic needle, and from mother to child. Upon acquisition of the virus, the virus replicates inside and kills T-helper cells, which are required for almost all adaptive immune responses; there is an initial period of influenza-like illness, and then a latent, asymptomatic phase. Vitamin D refers to a group of fat-soluble secosteroids responsible for enhancing intestinal absorption of calcium, iron, magnesium, phosphate and zinc. In humans, the most important compounds in this group are vitamin D3. Higher vitamin D levels were associated with a slower progression of HIV to AIDS. Insulin resistance, a risk factor for cardiovascular disease, is increasingly seen in persons infected with HIV.

Keywords: vitamin D, insulin resistance, HIV infection

Introduction

Human Immunodeficiency Virus (HIV)

Human Immunodeficiency Virus is a member of the genus Lentivirus, part of the family of retroviridae (Kumar and Viny, 2012; Obeagu et al., 2018)

Many species are infected by Lentiviruses, which are characteristically responsible for long-duration illness with a long incubation period (International Committee on Taxonomy of Viruses, 2002).

History of HIV

According to centers for Disease Control (CDC), both HIV-1 and HIV-2 are believed to have originated in non-human primates in West Africa and were transferred to humans (a process known as zoonosis) in the early 20th century. HIV-1 appear to have originated in Southern Cameroon through the evolution of SIV[CPZ], a simian immunodeficiency virus (SIV) that infects wild chimpanzee (HIV-1) discs from the SIVCPZ endermic in the chimpanzee subspecies Pan Troglodytes] (Altman, 1982).
The closet relative of HIV-2 is SIV [SMM], a virus of the sooty mangabey, and a old wild monkey living in the littoral west Africa (From Southern Senegal to Western Cote d’ Idoire (Smith and Daniel, 2006). There is evidence that humans who participate in bush meat activities, either as hunter or as bush meat vendors, commonly acquire SIV. It is thought that several transmission of the virus from individual in quick succession is necessary to allow it enough time to mutate into HIV (Barre –Sinoussi et al., 1983).

The HIV Structure

HIV is different in structure from other Lentiviruses. It is roughly spherical with a diameter of about 120nm, around 60 times smaller than a red blood cell, yet large for a virus (Reevers, Doms, 2002). It is composed of two copies of positive single –stranded RNA that codes for the virus nine genes enclosed by a conical capsid composed of 2,000 copies of the viral protein P24 (McGovern et al., 2002). The single stranded RNA is tightly bound to nucelocapsid proteins p7, and enzymes needed for the development of the virion such as reverse transcriptase, potease, ribonuclease and integrase. A matrix composes of the viron protein p17surround the capside ensuring the integrity of the virion particles (McGovern et al., 2002).

This is in turn, surrounded by the viral envelope that is composed of two layers of fatty molecules called phospholipids taken from the membrane of human cell when a newly formed viruses particules buds from the cell. Embedded in the viral envelope are proteins from the host and about 70 virus particles (McGoern et al., 2002) This proteins, known as ENV, consist of a cap made of three molecules called glycoprotein (gp) 120, and a stem consisting of three gp41 molecule that anchore the structure into the viral envelop (Fisher and Black, 2007). Both these surface proteins, especially gp120, have been considered as targets of future treatments or vaccines against HIV (Weiss, 1993).

During the chronic phase, the consequences of generalized immune activation coupled with the gradual loss of the ability of the immune system to generate new T. cells appears to count for the slow decline in CD4+ T cell numbers.

Although the symptoms of immunodeficiency characteristic of AIDS do not appears for years after a person is infected, the bulk of CD4+ T-cells lose occurs during the first week of infection, especially in the intestinal mucosa, which harbours the majority of the lymphocyte found in the body (Douek et al., 2009). The reasons for the preferential lose of mucosal CD4+ T-cells is that a majority of mucosa CD4+ T-cells express the CCR5 coreptore, whereas a small Fraction of CD4+ T-cells in the blood stream do so (Cunnigham et al., 2010).

HIV seeks out and destroys CCR5 expressing CD4+ T-cells during acute infection. A vigorous immune response eventually controls the infection and initiates the clinically latent phase.

However, CD4+ T-cells in mucosa tissue remains diameted throughout the infection, although enough remain to initially ward off life threatening infections.

Mode of transmission of HIV

The HIV Virus is commonly transmitted via unprotected sexual activity, blood transfusions, hypodermic needle, and from mother to child (International Committee on Taxonomy of Viruses, 2002).

Upon acquisition of the virus, the virus replicates inside and kills T-helper cells, which are required for almost all adaptive immune responses; there is an initial period of influenza-like illness, and then a latent, asymptomatic phase.

When the CD4 lymphocyte count falls below 200 cells/ml of blood, the HIV host has progressed to AIDS, a condition characterized by deficiency in cell-mediated immunity and the resulting increased susceptibility to opportunistic infections and certain forms of cancer (Levy, 1993).

Signs and symptoms of HIV

Center for Disease control (1982) illustrated that many people do not have any symptoms when they first become infected with HIV.

Some have a flu-like illness, called HIV seroconversion syndrome, a month or two weeks after exposure to the virus.

This illness may cause a variety of symptoms including: Diarrhea, enlarged liver or spleen, Fever, enlarged or swollen lymph nodes, headache, muscle pain, nausea and vomiting, neurologic symptoms, rash
on the abdomen, arms and legs, face, sore throat, thrush, a common fungi infection of the mouth caused by Candida. The symptoms usually disappear in a week to a month and may be mistaken for other viral infections. During this period, people are very infectious and HIV is present in large quantities in genitian fluids (Center for Disease Control, 1982). An infected person may not experience severe symptoms for eight to ten years or more. This period called asymptomatic period varies in length for each person. Some people may have symptoms within a few months and other may be symptoms free for years (Dudgeion et al., 2006). Children born with HIV usually have symptoms within two years of birth. Children may grow slowly or become siac free gently.

As the immune system weakens, other complications may occur. For many people, the first signs of infection are large lymph node or swollen glands that may be enlarged for more than three months. Other symptoms before the onset of AIDs including fever and sweats, herpes infections that cause severe mouth, genital or anal sores, lack of energy, pelvic inflammatory disease in women that does not respond to treatment persistent skin rashes or flaky skin, shingles, a painful nerve disease often accompanied by rash or blisters, short term memory lose, weight loss (Rivera et al., 1998).

Prevention of HIV

HIV infection can be prevented by adhering to the following strategies
1) Pharmaceutical: some commonly considered pharmaceutical interventions for the prevention of HIV includes the use of the following;
   a) Microbicides for sexual transmitted disease
   b) Antiretroviral drugs can be used also to prevent the rate of viral load
2) Abstinence from sex
3) HIV infection can be prevented by the use of condom
4) Advertisement and campaign against HIV/AIDS
5) Total avoidance of fluids contaminated with HIV virus.

Diagnosis of HIV

(ELISA) or enzyme immunoassay (EIA) was the first screening test commonly employed for HIV. It has a high sensitivity.

In an ELISA test, a person serum is diluted 400-fold and applied to a plate to which HIV antigen have been attached. If antibodies to HIV are present in the serum, they may bind to these HIV antigens. The plate is then washed to remove all other components of the serum. A specially prepared “secondary antibody” an antibody that binds to human antibodies is then applied to the mate, followed by another wash. This secondary antibody is chemically linked in advanced to an enzyme. Thus the plate will contain enzyme in proportion to the amount of secondary antibody bound to the plate. A substrate for the enzyme is applied, and catalysis by the enzyme leads to a change in color or fluorescence.

ELISA results are reported as a number, the most controversial aspect of this test is determining the cutoff point between a positive and negative result.

Other diagnostic methods for HIV are:
1) Use of determine strip
2) Use of unigold
3) And use of stat pack.

Procedure for using determine strip
- Place a 50ul of the patient serum on a test band
- Allow it to stand for 10-15 minute and observe the strip for the presence and absence of line.

Result

Single line indicate negative. Double line indicates positive result. No line indicates invalid result. When using determine strip, any positive result or case is further confirmed by using unigold and when using unigold, if it is still positive, it is then proceed to the final stage which is the stat pak.

Vitamin D

Vitamin D refers to a group of fat-soluble secosteriods responsible for enhancing intestinal absorption of calcium, iron, magnesium, phosphate and zinc. In humans, the most important compounds in this group are vitamin D3 (also known as cholecalciferol) Alagarasu et al. (2009).

Cholecalciferol and ergocalciferol can be ingested from the diet and from suppliments (Annaporna et al. 2004). Very few foods contains vitamin D, synthesis of vitamin D (specifically cholecalciferol) in the skin
is the major natural sources of thee vitamin. Dermal synthesis of vitamine D from cholesterol is dependent on sun exposure (specifically ultra violet Beta Radiation (UVB) vitamine D from the diet or dermal synthesis from sunlight is biologically in active, activation requires enzymatic conversion (hydroxylation) in the liver and kidney. Evidence indicates the synthesis of vitamin D from sun exposure is regulated by a negative feedback loop that prevents toxicity, but because of uncertainty about the cancer risk from sunlight, no recommendation are issued by institute of medicine (US), for the amount of sum exposure required to meet vitamin D requirements. Accordingly, the Dietary Reference Intake for Vitamin D assumes no synthesis occurs and all of a person’s vitamin D is from food intake, although that will rarely occur in practices. As vitamin D is synthesized in adequate amounts by most mammals exposed to sun light, it is not strictly a vitamin e and may be considered a hormone as its synthesis and activities occur in different locations. Vitamin D has significant roles in calcium homeostasis and metabolism. Its discovery was due to effort to find the dietary substance lacking in rickets (Arpadi et al., 2009; Obeagu, 2018).

Functions of vitamin D

Vitamin D promotes absorptions and use of calcium and phosphate for healthy bones and teeth.

Vitamin D deficiency

A diet deficient in vitamin D in conjunction with inadequate sun exposure causes osteomalacia or (rickets) when it occurs in children, which is a softening of the bones. In the developed world, this is a rare disease. However, vitamin D deficiency has become a worldwide issue in the elderly and remains common in children and adult (Erikson and Glemp, 2002) low blood calcidial (25-hydroxyl-vitamin D) can result from avoiding the sun. Deficiency results in impaired bone mineralization and bone damage which leads to bone softening diseases (Brown, 2008) which includes;

1) Ricket

Rickets, Is a childhood disease, is characterized by impeded growth and soft, weak, deformed long bones that bend and bow under their weight as children start to walk. This condition is characterized by bow legs (Brown,2008) which can be caused by calcium or phosphorus deficiency, as well as lack of vitamin D; today, it is largely found in low-income countries in Africa, Asia or the middle East (Lerch and Melshner ,2007) and in those with genetic disorders such as pseudovitamin D deficiency rickets (Zargar et al., 2000). Rickets was first described in 1650 by Francis Glison, who said it had first appeared about 30 years previously in the countries of Dorset and Somerest; In 1857, John Snow suggested rickets, then widespread in Britain was being caused by the adulteration of bakers bread with alum (Dunnigan, 2003).

2) Osteomalacia

Osteomalacia is a disease in adults that results from vitamin D deficiency characteristics of this disease are softening of the bones, leading to bending of the spine, bowing of the legs, proximan muscle weakness, bone fragility. Oestiomalacia is usually present when 25-hydroxylvitamin D levels are less than about 10ng/ml (Holick, 2007). The effects of osteomalacia are thought to contribute to chronic musculoskeletal pain.

Forms of vitamin D

Several forms of vitamin D exist, the two major forms are vitamin D2 or ergocalciferol, and vitamin D3 or cholecalciferol. Vitamin D without a subscript refers to either D2 or D3 or both. These are known collectively as calciferol (Cozzolino et al., (2003). In 1935, the chemical structure of vitamin D3 was established and proven to result from the ultraviolet irradiation of 7-dehydrocholesterol (Dela Torre et al., 2008). Chemically the various forms of vitamin D are secosteriod, i.e., steroids in which one of the bonds in the steroids ring is broken. The structural difference between vitamin D2 and vitamin D3 is the side chain of D2 contains a double bond between carbons 22 and 23, and a methyl group on carbon 24.

Dietary sources of vitamin D

Vitamin D is found in few dietary sources (Holick, 2007). Vitamin D is found in milk (Fortified) cheese, whole eggs, liver, salmon, and fortified margarine. The skin can synthesize vitamin D if exposed to enough sunlight or a regular basis.
3) Influence of Skin Pigmentation

Some research shows dark-skinned people living in temperate climate have lower vitamin D level (Ford et al., 2006) dark skinned people may be less efficient at making vitamin D because melanine in the skin hinders vitamin D synthesis, however a recent study has found novel evidence that low vitamin D levels among a … may be due to other reasons.

Vitamin D level and HIV

In Tanzania, pregnant women with HIV were studied for about five years, findings includes

- Higher vitamin D levels were associated with a slower progression of HIV to AIDS (International Committee on Taxonomy of Virus, 2002)
- Women with vitamin D levels above 32ng/ml (80nmol/L) had a 25% lower risk of disease progression.
- Women with higher vitamin D levels had a lower risk of dying from any cause during the study.
- Vitamin D reduces the risk of bone mineral lose and osteosporosis.
- Vitamin D reduces inflammation by shifting protein production away from inflammation.

Insulin Resistance and HIV

Insulin resistance, a risk factor for cardiovascular disease, is increasingly seen in persons infected with HIV. In those affected, it is unclear whether insulin resistance is a direct result of HIV infection alone (Mayfield, 1998). However, the development of insulin resistance has been established as a complication of antiretroviral therapies (Lovejoy and Girolalamo, 1992).

Some protease inhibitors (PI) have a significant difference in the impact of different protease inhibitors on glucose metabolism with current evidence suggesting that atazanavir does not cause insulin resistance.

The paucity of standardized laboratory test makes early diagnosis of insulin resistance relatively exclusive.

Still there are some clinically useful methods for assessing its presence for prevention and or treatment, exercise and optimal diet are useful.

Metformin and rosiglitagon have been reported and shown to improve insulin resistance.

Changing an effective antiretroviral regimen to counter insulin resistance must be approached (Kraegen et al., 1991).

Insulin

Insulin is a hormone made by the pancreas that allows your body to use sugar (glucose) from carbohydrates in the food that you eat for energy or to store glucose for future use. Insulin help keeps your blood sugar level from getting too high (hyperglycemia) or too low (hypoglycemia).

Insulin resistance

Insulin resistance (IR) is a physiological condition in which cells fails to respond to normal actions of the hormone insulin. The body produces insulin, but the cells in the body becomes resistance to insulin and are unable to use it as effectively, leading to hyperglycemia. Beta a cells in the pancreas subsequently increase their production of insulin, further contributing to hyperinsulinemia.

This often remains undetected and can contribute to a diagnosis of Type 2 Diabetes or latent autoimmune diabetes of adult (Mayfield, 1998).

Signs and symptoms of insulin resistance

These depend on poorly understood variations in individual biology and consequently may not be found with all people diagnosed with insulin resistance (Lovejoy and Girolalamo, 1992).

1) Brain fogginess and inability to focus
2) High blood sugar
3) Intestinal bloating—most intestinal gas is produced from carbohydrates in the diet, mostly those that humans cannot digest and absorb
4) Sleepiness, especially after meals
5) Weight gain, fat storage, difficulty losing weight – for most people, excess weight is from high fat storage the fat in IR is generally stored in and around abdominal organs in both males and females; it currently is suspected that hormones produced in that fat are a precipitating cause of insulin resistance.
6) Increased blood pressure, many people with hypertension are either diabetic or pre-diabetic and have elevated insulin levels due to insulin resistance;
7) one of insulin’s effects is to control arterial wall tension throughout the body.
8) Increased blood triglyceride levels

Risk Factor of Insulin Resistance

Several associated risk factors include the following:
- Genetic factors (inherited component)
- Family history with type 2 diabetes
- Insulin receptor mutations (Donoluve syndrome)
- LMNA mutation (familial partial L1 Podystrophy)

Causes of insulin resistance

Diet

It is well known that insulin resistance commonly coexist with obesity.

However, causal links between insulin resistance, obesity, and dietary factors are complex and controversial. It is possible that one of them arises first, and tends to cause the other, or that insulin resistance and excess body weight might arise independently as a consequence of a third factor, but end up reinforcing each other.

Some population groups might be genetically predisposed to one or the other.

Dietary fat has long been implicated as a driver of insulin resistance.

Studies on animals have observed significant insulin resistance in rats after just 3 weeks on a high fat diet (59% fat, 20% carbon). Large quantity of saturated, monounsaturated and polyunsaturated (Omega-6) fats all appear to be harmful to rats to some degree, compared to large amount of starch, but saturated fat appears to be harmful to rat to some degree, compared to large amount of starch, but saturated fat appears to be the most effective at producing insulin resistance (IR). This is partly caused by direct effects of high-fat diet on blood markers but, more significantly, ad libitum high-fat diet has the tendency to result in caloric intake that is far in excess of animal energy needs, resulting in rapid weight gain. In humans, statistically evidence is more equivocal. Being insensitive to insulin is still positively correlated with fat intakes and negatively correlated with dietary fiber intake, but both these factors are also correlated with excess body weight.

Disease

Recent research and experimentation has uncovered a non-obesity related connection to insulin resistance and type 2 diabetes. It has long been observed that patients who have had some kinds of bariatric surgery have increased insulin sensitivity and even remission of type 2 diabetes. It was discovered that diabetic/insulin resistance non-obese rat whose duodenum has been removed surgically, also experienced increased insulin sensitivity and remission of type 2 diabetes.

Pathophysiology in Insulin Resistance

Any food or drink containing glucose or the digestible carbohydrate that contains it, such as sucrose, starch, etc) causes blood glucose to increase. In normal metabolism, the elevated blood glucose instructs beta (β) cells in the islet of langerhans, located in the pancreas to release insulin into the blood.

The insulin in turn, makes insulin-sensitive tissues in the body (primarily skeletal muscle cells adipose tissue, and liver) absorb glucose and thereby lower the blood glucose level. The beta cell cells reduced insulin output as the blood glucose level falls, allowing blood glucose to settle at a constant of approximately 5mmol/L (90mg/dl).

In an insulin-resistant person, normal levels of insulin do have the same effect in controlling blood glucose levels. During the compensated phase on insulin resistance, insulin levels are higher, and blood glucose levels are still maintained. If compensatory insulin secretion fails, then either fasting (impaired fasting glucose tolerance) glucose concentration increased.

Diagnosis of insulin level

Fasting Insulin Levels

A fasting serum insulin level greater than 25mlu/L or 174pmol/L are considered insulin resistance. Some levels apply for levels after 3 hours of last meal.

Glucose Tolerance Testing (GTT)

During a glucose tolerance test, which may be used to diagnose diabetes mellitus, a fasting patient takes a 75
gram oral dose of glucose. Then blood glucose levels are measured over the following two hours. Interpretation is based on WHO guidelines. After two hours a glycaemia less than 7.8mmol/L (140mg/dl) is considered normal, a glycaemia of between 7.8 to 11.0mmol/L (140 to 197mg/dl is considered as impaired glucose tolerance (IGT) and a glycaemia of greater than or equal to 11.0mmol/L (200mg/dl is considered diabetes mellitus.

**Oral Glucose Tolerance Test**

An oral glucose tolerance test (OGTT) may be normal or mildly abnormal in simple insulin resistance.

Often, there are raised glucose levels in the early measurement, reflecting the loss of a post prandial peak (after the meal) in insulin production. Extension of the testing (for several more hours) may reveal hypoglycaemic “dip” that is a result of an overshoot in insulin production after the failure of the physiologic postprandial insulin response.

**Measuring insulin resistance**

**Hyperinsulinemia Euglycemic Clamp**

The gold standard for investigating and quantifying insulin resistance is the hyperinsulinemic euglycemic clamp, “so-called because it measures the amount of glucose necessary to compensate for an increased insulin level without causing hypoglycemia. It is a type of glucose clamp technique.

The test rarely is performed in clinical care, but is used in medical research, for example, to access the effects of different medications. The rate of glucose infusion commonly is referred to in diabetes litera.

**Hypervitaminosis D (excess of vitamin D)**

Vitamin D toxicity is rare (Holick, 2007), it is caused by supplementing with high doses of vitamin D rather than sunlight. The threshold for vitamin D toxicity has not been established; however, the tolerable upper intake level (ul) according to some research is 4,000iu/day for ages 9-7 while another research concludes that in healthy adults, sustained intake of more than 1250ug/day (50,000iu) can produce overt toxicity after several month and can increase serum 25-hydroxyvitamin D level to 150ng/ml and greater.

**Conclusion**

Human Immunodeficiency Virus is a member of the genus Lentivirus, part of the family of retroviridae. HIV seeks out and destroys CCR5 expressing CD4+ T-cells during acute infection. A vigorous immune response eventually controls the infection and initiates the clinically latent phase. Vitamin D refers to a group of fat-soluble secosteroids responsible for enhancing intestinal absorption of calcium, iron, magnesium, phosphate and zinc. In humans, the most important compounds in this group are vitamin D3. Higher vitamin D levels were associated with a slower progression of HIV to AIDS. Insulin resistance, a risk factor for cardiovascular disease, is increasingly seen in persons infected with HIV.

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