

# Microalbuminuria in Human Immunodeficiency Virus Infection and Acquired Immunodeficiency Syndrome

Sharan Badiger, Prema T. Akkasaligar, Patil LS, Manish Patel, Biradar MS

**Abstract**—Human immunodeficiency virus infection and acquired immunodeficiency syndrome is a global pandemic with cases reporting from virtually every country and continues to be a common infection in developing country like India. Microalbuminuria is a manifestation of human immunodeficiency virus associated nephropathy. Therefore, microalbuminuria may be an early marker of human immunodeficiency virus associated nephropathy, and screening for its presence may be beneficial. A strikingly high prevalence of microalbuminuria among human immunodeficiency virus infected patients has been described in various studies. Risk factors for clinically significant proteinuria include African - American race, higher human immunodeficiency virus ribonucleic acid level and lower CD4 lymphocyte count. The cardiovascular risk factors of increased systolic blood pressure and increase fasting blood sugar level are strongly associated with microalbuminuria in human immunodeficiency virus patient. These results suggest that microalbuminuria may be a sign of current endothelial dysfunction and micro-vascular disease and there is substantial risk of future cardiovascular disease events. Positive contributing factors include early kidney disease such as human immunodeficiency virus associated nephropathy, a marker of end organ damage related to co morbidities of diabetes or hypertension, or more diffuse endothelial cells dysfunction. Nevertheless after adjustment for non human immunodeficiency virus factors, human immunodeficiency virus itself is a major risk factor. The presence of human immunodeficiency virus infection is independent risk to develop microalbuminuria in human immunodeficiency virus patient. Cardiovascular risk factors appeared to be stronger predictors of microalbuminuria than markers of human immunodeficiency virus severity person with human immunodeficiency virus infection and microalbuminuria therefore appear to potentially bear the burden of two separate damage related to known vascular end organ damage related to know vascular risk factors, and human immunodeficiency virus specific processes such as the direct viral infection of kidney cells. The higher prevalence of microalbuminuria among the human immunodeficiency virus infected could be harbinger of future increased risks of both kidney and cardiovascular disease. Further study defining the prognostic significance of microalbuminuria among human immunodeficiency virus infected persons will be essential. Microalbuminuria seems to be a predictor of cardiovascular disease in diabetic and non diabetic subjects, hence it can also be used for early detection of micro vascular disease in human immunodeficiency virus positive patients, thus can help to diagnose the disease at the earliest.

**Keywords**—Acquired immunodeficiency syndrome, Human immunodeficiency virus, Microalbuminuria.

## I. INTRODUCTION

**A**QUIRED immunodeficiency syndrome is a disease of human immune system caused by human immune deficiency virus [1,2,3]. This condition progressively reduces the effectiveness of the immune system and leaves individuals susceptible to opportunistic infections and tumors. Human immunodeficiency virus is transmitted through direct contact of mucous membrane or blood stream with bodily fluids containing human immunodeficiency virus such as blood, semen, vaginal fluid, seminal fluid and breast milk [4, 5]. This involves anal vaginal and oral sex and blood transfusion, and contaminated hypodermic needles, exchange between mother and baby during pregnancy, child birth, breast feeding or other exposure to one of the above bodily fluids. Acquired immunodeficiency syndrome is now a pandemic [6] as of 2009, AVERT estimated that there are 33.3 million people worldwide living with human immunodeficiency virus / acquired immunodeficiency syndrome, with 2.6 million new human immunodeficiency virus infections per year and 1.8 million annual deaths due to acquired immunodeficiency syndrome [7].

In 2007 United Nations acquired immunodeficiency syndrome estimated 33.2 million people had acquired immunodeficiency syndrome that year. Acquired immunodeficiency syndrome killed 2.1 million people in the course of that year including 3, 30,000 children and 76% of those death occurred in sub Saharan Africa [8]. According to United Nations acquired immunodeficiency syndrome 2009 reports, worldwide some 60 million people have been infected, with some 25 million deaths, and 14 million orphaned children in Southern Africa alone since the epidemic began [9].

Genetic research indicates that human immunodeficiency virus originated in west central Africa during the late 19th or early 20th century [10, 11]. Acquired immunodeficiency syndrome was first recognized by the United States centre for disease control and prevention in 1981 and its cause, human immunodeficiency virus was identified in early 1980s [12]. Although treatments for human immunodeficiency virus and acquired immunodeficiency syndrome can slow the course of disease, there is no known cure or vaccine. Anti-retroviral therapy reduces both the mortality and morbidity of human immunodeficiency virus infection, but these drugs are expensive and routine access to anti-retroviral therapy is not available in all countries [13]. Due to difficulty in treating human immunodeficiency virus infection, preventing infection is a key aim in controlling the acquired immunodeficiency syndrome pandemic, with health organization promoting safe

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sex and needle exchange programmes in attempts to slow the spread of virus. Acquired immunodeficiency syndrome was first reported June 5, 1981 when the United States centre for disease control recorded a cluster of pneumocystitis carinii pneumonia in five active homosexual men in Los Angeles [14]. In the beginning, of the centre for disease control did not have an official name for the disease .often referring to it by way of the disease that were associated with it, for example lymphadenopathy the disease after which the discoverer of human immunodeficiency virus originally named the virus [15,16]. They also used Kaposi sarcoma and opportunistic infections by the name by which a task force had been setup in 1981 [17].

In general press, the term gay related immune deficiency, which stood for gay related immune deficiency, had been coined [18]. The centre for disease control, in search of a name, and looking at the infected communities coined "the 4H disease". As it seemed to single out Haitians .homosexuals, hemophiliacs and heroin users [19]. However, after determining acquired immunodeficiency syndrome was not isolated to homosexual community, [17] the term gay related immune deficiency became misleading and acquired immunodeficiency syndrome was introduced at a meeting in July 1982 [20]. By the September 1982 the centre for disease control started using the name acquired immunodeficiency syndrome, and properly defined the illness [21]. The earliest known positive identification of human immunodeficiency virus 1 comes from the Congo in 1959 and 1960. Though genetic studies indicate it passed into human population from chimpanzees around fifty earlier [11]. A recent study states that a strain of human immunodeficiency virus 1 moved from Africa to Haiti and then entered the United States around 1969 [22].

The human immunodeficiency virus descends from the related simian immunodeficiency virus which infects apes and monkeys in Africa. There is evidence who participate in bush meat activities, either as hunters or as bush meet vendors, commonly acquire simian immunodeficiency virus [23], however .only a few of these infections were able to cause epidemics in humans and all dead so in the late 19th and early 20th century to explain why human immunodeficiency virus became epidemic only by that time, there are several theories, each invoking specific driving factors that may have promoted simian immunodeficiency virus adaptation to humans, or initial spread social changes following colonialism, [24], rapid transmission through unsafe or unsterile injections [25], colonial abuses and unsafe smallpox vaccinations or injections [26], or prostitution and the concomitant high frequency of genital ulcer diseases(such as syphilis) in nascent colonial cities.[27,28]. A more controversial theory known as the oral polio vaccine acquired immunodeficiency syndrome hypothesis suggests that the acquired immunodeficiency syndrome epidemic was inadvertently started in the late 1950s in the Belgian Congo by Hilary Koprowski's research into a poliomyelitis vaccine. [29,30].

According to scientific consensus, this scenario is not supported by the available evidence [31, 32, 33]

Human immunodeficiency virus -positive individuals have a significantly higher risk of having small quantities of a protein in their urine that indicates an increased risk of both cardiovascular and kidney disease, according to American researchers [34]. The investigators compared microalbuminuria the presence of small amounts of the protein albumin in urine, a marker for both kidney and cardiovascular disease in a cohort of human immunodeficiency virus - positive patients and age-matched human immunodeficiency virus - negative controls and found that the prevalence of elevated microalbuminuria was significantly higher in human immunodeficiency virus - positive patients. The presence of microalbuminuria in human immunodeficiency virus-positive patients was significantly associated with traditional risk factors for cardiovascular disease as well as human immunodeficiency virus -related factors, most notably a weak immune system. Kidney disease, involving symptoms such as protein in urine or elevated creatinine output, has been well described as a complication of human immunodeficiency virus infection. Studies conducted before potent anti- human immunodeficiency virus therapy became available suggested that between 19% - 34% of human immunodeficiency virus - positive individuals had elevated levels of albumin in their urine [35]. Investigators were interested in these observations because microalbuminuria has been associated with an increased risk of heart disease in the general population. As there is an increasingly robust body of evidence to show that antiretroviral therapy can increase the risk of cardiovascular disease, researchers wished to determine if microalbuminuria occurred with greater frequency in human immunodeficiency virus -positive patients compared to age-matched human immunodeficiency virus -negative controls. The researchers also wished to see if any factors predicted an increased risk of microalbuminuria in human immunodeficiency virus -positive patients [35]. The study population consisted of individuals enrolled in the cross-sectional study of 1-at Redistribution and Metabolic Change in human immunodeficiency virus infection (FRAM) cohort.

The control population consisted of a population-based sample of healthy white and African-American men and women recruited to the CARDIA study. Albumin and creatinine concentrations were measured in spot urine tests, and the investigators calculated the albumin to creatinine ratio with a creatinine of above 30mg/g defined as microalbuminuria. Data were also gathered on measures of cardiovascular risk, including blood pressure, insulin and glucose levels, family history of heart disease and smoking. For human immunodeficiency virus -positive patients, the investigators obtained information on CD4 cell count and viral load. Microalbuminuria was present in 11% of human immunodeficiency virus -positive patients and 2% of controls, a statistically significant difference ( $p < 0.001$ ). This difference remained significant even after the investigators

adjusted for traditional predictors of microalbuminuria ( $p = 0.0008$ ). Significant predictors of microalbuminuria in human immunodeficiency virus -positive patients were older age ( $p = 0.02$ ) and African American race ( $p = 0.001$ ). Several factors associated with an increased risk of cardiovascular disease were also strongly associated with microalbuminuria in patients with human immunodeficiency virus. These were higher systolic blood pressure ( $p = 0.01$ ) a family history of hypertension ( $p = 0.03$ ) and glucose in urine ( $p = 0.002$ ). Smoking was not, however, significantly associated with microalbuminuria. Human immunodeficiency virus -specific factors associated with microalbuminuria were a CD4 cell count below 200 cells/mm<sup>3</sup> ( $p = 0.05$ ). Current viral load ( $p = 0.05$ ) and treatment with an NNRTI ( $p < 0.05$ ). "This analysis demonstrated that human immunodeficiency virus infection is a strong risk factor for the presence of microalbuminuria [39], independent of the risk factors for the presence of renal disease", write the investigators.

The presence of markers for kidney or cardiovascular disease in human immunodeficiency virus positive patients with microalbuminuria may be because of the increase in cardiovascular risk due to the metabolic complications caused by some anti retro virus. The investigators conclude, "The high prevalence of microalbuminuria among the human immunodeficiency virus infected could be a harbinger of future increased risks of both kidney and cardiovascular disease. Further study defining the prognostic significance of microalbuminuria among human immunodeficiency virus infected persons will be essential" [36].

Microalbuminuria or dipstick negative albuminuria is conventionally defined as urinary albumin excretion between 30-300 mg/24 hour for timed 24 hours urine collections and between 20-200 mg/L for untimed samples [37]. High normal albuminuria is defined as morning urinary albumin concentration up to 30 mg/l. Low- normal albuminuria is morning urinary albumin concentration of less than 10 mg/l.

Normoalbuminuria =  $<30$  mcg/min.

Microalbuminuria (Incipient nephropathy) =  $30 - 300$  mcg/min.

Macroalbuminuria (Clinical nephropathy/ Overt nephropathy)  $> 300$  mcg/min.

## II. MECHANISM OF MICROALBUMINURIA

The intimate relationship between low-level albumin excretion and vascular permeability makes urinary albumin excretion highly sensitive to the presence of any inflammatory processes. Pathophysiological processes associated with microalbuminuria:

### *Local Process*

1. Increased intra-glomerular capillary pressure
2. Increased shunting of albumin through glomerular membrane pores.

### *Systemic Process*

1. Activation of inflammatory mediators
2. Increased transcapillary escape rate of albumin
3. Vascular endothelial dysfunction

The kidney is ideally placed to amplify any small changes in the systemic vascular permeability. The glomeruli receive 25% of the cardiac output. Of the 70 kg of albumin that pass through the kidneys every twenty four hours, less than 0.01% reaches the glomerular ultra filtrate (i.e. less than 7g/24 hour) and hence enters the renal tubules. Almost all the filtered albumin is absorbed by the proximal tubule via a high affinity, low capacity endocytotic mechanism, with only 10-30 mg/24 hr appearing in the urine. Assuming that 7.0 Gms of albumin is filtered every twenty four hour, 1% increase in systemic vascular permeability in response to an inflammatory stimulus would result in an additional 70 mg of albumin passing into the filtrate. Since tubular mechanisms for albumin reabsorption are near saturation, urinary albumin excretion would increase from a maximum of 30 to approximately 100 mg/24 hour [38]. Glomerular permeability to albumin is dependent on endothelial charge selectivity as well as size selectivity. The negative charge conferred on the glomerular membrane by its consistent glycoprotein plays a role in restricting the permeability of anionic proteins. Loss of glomerular charge selectivity has been found in both diabetic and non-diabetic population with microalbuminuria [39]. Other possible mechanisms of microalbuminuria include the following:

#### *A. Systemic transvascular albumin leakage:*

TERalb is defined as the fraction of the intravascular mass of albumin going through the vascular bed per unit time. The transcapillary escape rate of albumin is an overall measure of macromolecular permeability of the vascular bed in vivo. As microalbuminuria reflects systemic transvascular leakiness for albumin, which may also allow for a higher degree of lipid in sudation into the large vessel wall, this may link microalbuminuria to atherogenesis [40].

#### *B. Role of sialic acid:*

Sialic acid has been reported to affect several hematological factors, transvascular permeability and accumulation of lipid in the arterial wall. Studies showed that in subjects without diabetes mellitus, an elevated serum concentration of sialic acid is predictive of atherosclerotic vascular disease in presence of concomitant elevation of urinary albumin excretion [40].

#### *C. Impaired arterial dilatatory capacity:*

Slightly elevated urinary albumin excretion is associated with impaired conduit arterial dilatatory capacity in clinically healthy subjects, and this impairment may be explained by a reduced dilatatory response to nitric oxide of both endogenous and exogenous origin. Impaired arterial dilatatory capacity may contribute to the increased cardiovascular risk in subjects with elevated urinary albumin excretion [41].

#### *D. Elevated Von Willebrand Factor concentrations and other prothrombotic factors*

Studies showed that prothrombotic factors like fibrinogen and factor VII, C, Von Willebrand factor antigen are elevated in patients with type 1 diabetes complicated by microalbuminuria, so also in hypertensive patients. These were considered potential markers of endothelial dysfunction [42, 43].

#### *E. Hyperinsulinaemia*

In vitro insulin has been shown to cause smooth muscle cell proliferation. It stimulates low density lipoprotein binding to smooth muscle cells, fibroblasts and monocytes and stimulates cholesterol synthesis in monocytes [44]. Hyperinsulinaemia and microalbuminuria are components of metabolic syndrome and are associated with a highly abnormal cardiovascular risk factor pattern.

#### *F. Hyperhomocysteinaemia*

The enhanced risk of cardiovascular and cerebrovascular disease with microalbuminuria may also be due in part to an association with hyperhomocysteinemia, a risk factor for atherosclerosis [45].

Microalbuminuria signifies abnormal vascular permeability and its presence may be considered as kidney's notice for markedly enhanced cardiovascular risk [46]. The importance of microalbuminuria was first appreciated in the early 1980s when two landmark studies in London and Denmark independently reported that it was predictive of development of overt diabetic nephropathy and progressive renal failure [47, 48]. Since then, various studies have established the significance of microalbuminuria in several conditions.

### III. REVIEW OF LITERATURE

Several studies have shown that microalbuminuria in diabetic patients predicts diabetic nephropathy as well as increased cardiovascular and overall mortality [49]. Persistent microalbuminuria in these patients also correlates with the presence of hypertension, obesity and dyslipidemia [50]. American Diabetes Association has adopted cut off values for diagnosis of diabetic nephropathy [51]. In 1998, American Diabetic Association included positive microalbuminuria as the risk factor for coronary artery disease in diabetic subject [52].

Studies have shown that the prevalence of microalbuminuria is enhanced in hypertensive subjects, in particular in those with blood pressure characteristics that are associated with enhanced cardiovascular risk, such as salt sensitivity and an abnormal diurnal blood pressure rhythm. Microalbuminuria possibly identifies at an early stage, hypertensive patients with an enhanced risk of developing the well-known renal and cardio vascular hypertensive complications [53].

Studies have documented the relationship between the presence of microalbuminuria and other atherosclerotic risk factors such as hypertension, dyslipidemia and smoking in the

general population. Studies have revealed the significance of microalbuminuria as predictor of increased mortality in elderly persons [54]. Microalbuminuria is detected early in the course of acute myocardial infarction and is considered as an independent predictor of early mortality in this condition. Microalbuminuria has been found to be proportional to the size of the infarct. Gosling et al suggested that early rise in urinary albumin concentration is useful in distinguishing myocardial infarct from angina [55]. Spyridon K et al found that microalbuminuria is a strong independent predictor of 3 year adverse prognosis in patients who has sustained acute myocardial infarction [56]. Roine et al demonstrated that microalbuminuria distinguished bacterial meningitis from aseptic meningitis with specificity of 94% [57].

Shearman et al found that microalbuminuria peaked 36 hours after admission in patients with acute pancreatitis and that serious complications developed later, only in those with the higher values of microalbuminuria [58]. Pallister et al found that microalbuminuria levels 8 hours after admission in trauma victims predicted the development of acute respiratory distress syndrome with a positive predictive value of 85% and a negative predictive value of 95% [59]. Microalbuminuria has been found to be associated with wide variety of inflammatory conditions like rheumatoid arthritis, inflammatory bowel disorder, and surgery etc [60, 61].

Highly significant association between microalbuminuria and carotid artery intima-media thickness has been reported a finding which suggests that microalbuminuria may be a marker for early development of carotid artery atherosclerosis and points to a possible linkage between microalbuminuria and atherothrombotic stroke mechanism [62]. Microalbuminuria is unlikely to be a marker for susceptibility to the development of clinical nephropathy but it is more likely to be a sign of early disease.

### IV. MICROALBUMINURIA: A PRACTICAL PERSPECTIVE

Several pathways may link microalbuminuria and vascular disease. Several factors that cluster with microalbuminuria include insulin resistance, central obesity, low levels of high-density lipoprotein cholesterol, high triglyceride levels, systolic hypertension, and lack of nocturnal dip in blood pressure on twenty four hour monitoring, salt sensitivity, endothelial dysfunction, hypercoagulability, impaired fibrinolysis and renal dysfunction. This provides enough proof to support the role of microalbuminuria as a predictor or vascular events in high-risk population. Hence, screening for microalbuminuria on a regular basis may help to identify a subgroup of patients who are at high risk for cardiovascular disease and need more intensive therapy and closer follow-up because they could benefit from early intervention and treatment [63].

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