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REVIEW ARTICLE

MALNUTRITION- INFLAMMATION- ATHEROSCLEROSIS SYNDROME IN CHRONIC KIDNEY DISEASE

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ABSTRACT

Chronic kidney disease is becoming a major health problem globally and in India an alarming number of about 8 million people are suffering from this disease. Patients undergoing hemodialysis have a high prevalence of protein-energy malnutrition and inflammation. As these two conditions often occur concomitantly in hemodialysis patients, they have been referred together as 'malnutrition-inflammation-atherosclerosis syndrome' to emphasize the important association with atherosclerotic cardiovascular disease. The three factors related to the pathophysiology in these patients are dialysis related nutrient loss, increased protein catabolism and hypoalbuminemia. Inflammation in Chronic Kidney disease is the most important factor in the genesis of several complications in renal disease. Pro-inflammatory cytokines like IL-1 and TNF –alpha play a major role in the onset of metabolic alterations in Chronic Kidney disease patients. Atherosclerosis is a very frequent complication in uremia due to the coexistence of hypertension, hyperhomocysteinemia, inflammation, malnutrition and increased oxidative stress, generation of advanced glycation end products, advanced oxidation protein products, hyperlipidemia and altered structural and functional ability of HDL. LDL-cholesterol, apolipoprotein (A), apolipoprotein (B), and Lp(a) are also associated with atherosclerosis. Studies have now provided enormous data to enable the evaluation of the severity of malnutrition-inflammation-atherosclerosis syndrome as well as effective monitoring of these patients.

KEY WORDS

Chronic Kidney Disease, Hemodialysis, Malnutrition, Inflammation, Atherosclerosis, Syndrome.

INTRODUCTION

Chronic Kidney Disease (CKD) is kidney damage defined as reduction of renal function and glomerular filtration rate (GFR) of less than 80ml/min/1.73m^2 for more than three months (1). As kidney failure progresses, it moves into 'uremia' characterized by a variety of signs and symptoms constituting the uremic syndrome (2). Globally CKD is becoming a major health problem causing enormous economic strain on the health care system. It is estimated that in India 100,000 new patients of end stage renal disease enter renal replacement programmes annually and an alarming number of about 8 million people are suffering from CKD (3).

Patients undergoing maintenance hemodialysis (HD) have a high prevalence of protein-energy malnutrition and inflammation. As these two conditions often occur concomitantly in HD patients, they have been referred together as 'malnutrition-inflammation -atherosclerosis' (MIA) syndrome to emphasize its important association with atherosclerotic cardiovascular disease.

Possible causes of MIA syndrome include comorbid illnesses, oxidative and carbonyl stress, nutrient loss through dialysis, anorexia and low nutrient intake, uremic toxins, decreased clearance of inflammatory cytokines, volume overload, and dialysis-related factors. MIA syndrome is believed to be the

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main cause of erythropoietin hyporesponsiveness, high rate of cardiovascular atherosclerotic disease, decreased quality of life, and increased mortality and hospitalization in dialysis patients.

The different biochemical mechanisms and features of MIA syndrome will be discussed in this article. This would throw light on the understanding of the anomalous biochemical presentations often observed in patients with MIA syndrome.

I MALNUTRITION IN PATIENTS WITH MIA SYNDROME

The cellular metabolism is down regulated in uremic state, with tendencies for reduced protein synthesis but increased degradation. In addition, CKD patients have an adaptive low thyroid state, and correction often accelerates negative balance and protein degradation (4). These patients also have impaired peripheral conversion of T_4 to T_3 and decreased binding of T_4 to thyroid binding protein, but TSH level is within normal limits (4). Protein energy malnutrition is strongly associated with high morbidity and mortality rate in dialysis patients (5). There are two major causes of malnutrition in dialysis patients, one associated with or due to the uremic syndrome and the other with comorbid conditions and inflammation (6).

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Early CKD brings a loss of lean body mass but a preservation of fat mass (7), probably due to interplay of metabolic processes with lipogenic influences from growth hormone/ insulin like growth factor-1 (GH/IGF-1) (8,9). The loss of skeletal muscle mass might result from uremia, per se or from micro inflammation, metabolic acidosis, nutritional insufficiency (10, 11) and possibly hyperleptinemia (12). However, at the later stage of CKD, these adaptive responses can be overwhelmed by hyper catabolic factors like infection, oxidative stress, cytokines and dialysis with a consequent loss of lean and fat body mass (13). Uremia may increase protein degradation by activating the ubiquitin proteasome pathway, including branched-chain ketoacid dehydrogenase, increasing insulin resistance (14) and reducing functions of GH/IGF-1 (10,11).

Table1: Common causes of malnutrition in MIA syndrome

1	*Accumulation of anorectic factors*
2	*Elevated serum leptin*
3	*Inflammation and / or infection*
	• ↑concentrations or actions of inflammatory and catabolic cytokines (IL-6, TNF-α) and other acute phase proteins
4	*Gastropathy / enteropathy*
	• blood loss due to GI bleeding
5	*Loss of metabolic processes*
	• ↓ synthesis of amino acids, glucose, fatty acids
6	*Physiological factors:*
	• medication, depression, poverty
	• Alcohol/drug abuse
7	*Hemodialysis related factors:*
	• Inadequate Kt/V
	• Post dialysis fatigue
	• Cardiovascular instability
	• Nausea, vomiting

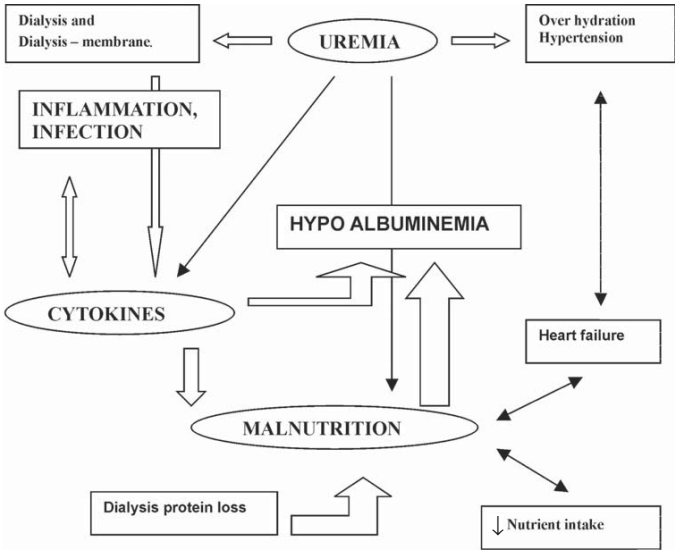
***Causes of Malnutrition*:**

There are many possible causes (Table 1) for protein malnutrition in patients receiving maintenance hemodialysis (15).

***Pathophysiology of Malnutrition*:**

The various aspects of the pathophysiology are schematically presented in Figure 1.

Figure 1: Pathophysiology of malnutrition in patients with MIA syndrome.



(i) ***Dialysis Related Nutrient Loss :*** There is a loss of free amino acids, peptides during dialysis (16). In glucose free dialysate, blood glucose is lost to dialysate.

(ii) ***Increased Protein Catabolism :*** It has been postulated that protein catabolism should increase in uremia as a consequence of metabolic acidosis and hemodialysis, exposure of blood to hemodialysis membrane with consequent activation of complement and monocytes and release of pro-inflammatory cytokines (17).

(iii) ***Hypoalbuminemia :*** Patients with CKD develop hypoalbuminemia due to a complex setting of conditions (Figure 1), with systemic inflammatory response as a

major cause,not withstanding other factors such as malnutrition and over hydration which can also play a relevant role (18). Albumin has been considered as the most important negative acute phase protein (19). Animal experiments in vivo and in vitro, which imitate inflammatory pathological conditions, have been shown to significantly decrease hepatocyte synthesis of albumin m-RNA in response to cytokines, such as interleukin-1 (20).

Biochemical Monitoring of Malnutrition in MIA syndrome:

Serum albumin, serum pre-albumin and serum transferrin levels are used to measure visceral protein. Serum albumin level even when only slightly less than 4.0 g/dl, is one of the most important markers of malnutrition in patients with CKD. Albumin level will also be affected by its rate of synthesis and catabolism (half life 20 days), which is altered negatively in the presence of inflammation (21). The distribution of albumin between extra cellular and intravascular spaces may be visible depending on the etiology of kidney disease, magnitude of proteinuria, and the state of extra cellular fluid volume. It was reported that synthesis of albumin increased according to its loss through dialysis (22), so hepatic disorders may not be causing hypoalbuminemia in dialysis patients. However, there is significant decrease in albumin synthesis, secondary to systemic inflammatory process, as a leading mechanism of hypoalbuminemia in dialysis patients.

Serum pre-albumin (half life 2 days), and serum transferrin (half life 8 days) are useful markers of early malnutrition (23). Due to rapid turnover rate, short half-life, high tryptophan content, and small pool size, pre-albumin is a highly sensitive marker of nutritional status (24). Chertow et al (25) confirmed that prealbumin provides prognostic value in hemodialysis patients, independent of albumin and other established predictors of mortality. The circulating levels of IL-6 and TNF-alpha predict the presence and intensity of hypoalbuminemia and malnutrition in hemodialysis patients (26).

In undernourished, non-dialysis patients with CKD, significant elevated C-reactive protein (CRP) and lipoprotein (a) [Lp(a)] serum levels were observed, compared to patients with adequate nutritional status (27).

In our study on MIA syndrome associated with anemia of CKD, the correlation analysis of nutrition markers with pro-inflammatory cytokines and iron indices revealed that, in IV iron receiving dialyzed patient group, prealbumin significantly negatively correlated with serum ferritin (r= -0.156, p<0.044) and with interleukin-6 (r= -0.222, p<0.005). Serum transferrin also in dialyzed CKD patients receiving IV iron was strongly, negatively associated with serum ferritin (r= -0.411, p<0.0001), tissue iron (r= -0.466, p<0.0001) and moderately negatively correlated with transferrin saturation (r= -0.170, p<0.046) and interleukin-1β (r= -0.190, p<0.029).

In patients not on dialysis receiving oral iron therapy, prealbumin and transferrin were strongly negatively correlated with interleukin-6 (r= -0.371, p<0.028 and r= -0.448, p<0.008 respectively). Serum transferrin was also positively correlated with TIBC (r=0.417, p<0.011), total protein (r=0.418, p<0.011), and albumin (r=0.421, p<0.01) indicating that less of tissue iron overload occurs, as mobilization of tissue iron is possible in non-dialyzed patients. Serum total protein and serum albumin levels were strongly negatively correlated with interleukin-6 (r= -0.451, p<0.005 and r= -0.394, p<0.016 respectively).

II INFLAMMATION IN PATIENTS WITH MIA SYNDROME

Inflammation in CKD is the most important factor in the genesis of several complications in renal disease. The potential causes of inflammation in uremia are listed in Table 2. The kidney is the major site of elimination of many cytokines, as evidenced in studies of IL-1 and Tumor Necrosis Factor (TNF) clearance in nephrectomized rats. (28). Decamps–Latscha demonstrated that plasma levels of IL-1 receptor antagonist were significantly increased from the earliest stage of kidney disease. Plasma levels of TNF-α and soluble TNF- receptors rise with the severity of renal failure and correlate with GFR (29). Both pro and anti-inflammatory cytokines and mediators accumulate in renal failure and it has been observed that spontaneous and lipoprotein saccharide induced production of IL-1 and IL-6 in whole blood from hemodialyzed patients is almost doubled compared to normal subjects (30). Thus, the net effect of mediators appears to promote inflammation. Among the numerous other products that accumulate in renal failure possibly contributing to inflammation are advanced glycation end products (AGEs) and advanced oxidation protein products (AOPPs) (31). Stenvenkel summarized the prevalence of elevated C-reactive protein levels from several studies and

Table 2 : The potential causes of inflammation in uremia

Potential causes of inflammation
Cytokines (33)
Acidosis (34)
Oxidative Stress (35)
Blood Compatibility of dialysis Membranes (36)
Dialysate Contamination
Access Infection (37)

concluded that 35% of patients with renal failure not yet on dialysis showed elevated levels of CRP but more than 50% of hemodialysis patients had elevated CRP levels (32).

Cytokines:

Inflammation results from an imbalance between effects of pro-inflammatory and anti-inflammatory cytokines synthesized and secreted by circulating monocytes, tissue macrophages, Kupffer cells and endothelial cells (38). TNF–alpha, interleukin-1 represent major pro- inflammatory cytokines, whereas interleukin (IL) -6 appears to be the major mediator of acute phase reactant synthesis (39).TNF-alpha and other pro inflammatory cytokines may play an important direct role in the onset of the metabolic alterations in CKD patients, including increased skeletal muscle protein degradation rate, reduced synthesis of skeletal muscle protein (39), albumin (40) and insulin resistance (41).Direct contact between blood cells and dialysis membrane and lipopolysaccharides on the dialysate side of the membrane or chronic sub clinical inflammation at the vascular access site represents potential mechanisms leading to inflammatory states in dialysis patients.

(i) Interleukin -1 β :

Interleukin-1 (IL-1) is the prototypic multifunctional cytokine. It exists in two forms IL-1α and IL-1β, which have indistinguishable effects in terms of biologic activity. In spite of upregulation of host defenses and being an immunoadjuvant, IL-1 is a highly inflammatory cytokine. IL-1β is synthesized as a precursor form with molecular mass of 31 KD. The specific cellular proteases convert the precursor IL-1β to mature IL-1β, with molecular mass of 17 KD (42). Disassociation between transcription and translation is characteristic of IL-1β (43). In hemodialysis patients with complement-activating membranes, most of the IL-1β m RNA is degraded without translation (44). Bacterial endotoxin, lipopolysaccharide stabilizes the AU-rich 3^1-untranslated regions on m-RNA, and these AU-rich sequences suppress normal hemoglobin synthesis (45).

(ii) *Interleukin -6:*

Interleukin-6 is a pleiotropic cytokine that plays an important role in regulating the immune response. IL-6 plays a prominent role in the coordinated systemic host defense response to injury by regulating inflammatory responses and hepatic acute phase protein synthesis (46). IL-6 mRNA is constitutively expressed at low levels in numerous cell types, including peripheral blood leukocytes, spleen, liver, kidney, and intestine of healthy individuals. During infection, trauma or immunologic challenge, nearly every human tissue and cell type synthesizes IL-6 protein (47). The different cell types and stimuli causing synthesis of IL-6 and its role in inflammation (48) are shown in Table 3.

Table 3: Sources and roles of interleukin-6 during inflammation

Cell sources	Monocytes, macrophages, amnion, B-cells, astrocytes, bone marrow stromal cells, chondrocytes, endothelial cells, epithelial cells, fibroblasts, glial cells, mast cells, eosinophils, neutrophils, osteoblasts, osteoclasts, hepatoma cells, keratino cells, kupfer cells, T-cells.
Stimuli Factors	IL-1, TNF, bacterial endotoxin, c-AMP, diacyl glycerol, GM-CSF, IFN, leukotriens, platelet activating factor, platelet derived growth factor, reactive oxygen metabolites, TGF-β, viruses.
Biologic roles:	
Immune response	B-cell maturation/differentiation, T-cell/thymocyte activation
Acute response	Stimulates acute phase protein synthesis
Hematopoiesis	Hemopoietic stem cell growth, GM-CSF induction.
Nervous system	Induces fever through PGE_2-dependent mechanism, Alters release of pituitary hormone (corticotrophin).

GM-CSF, granulocyte-macrophage colony stimulating factor; IFN, interferon; IL,interleukin; LPS, Lipopolysaccharide; PGE_2, Prostaglandin E_2; TGF, Transforming growth factor; TNF, Tumor necrosis factor.

The multifunctional cytokine IL-6 is involved in the induction of acute phase protein synthesis in hepatocytes, stimulation of hemopoietic progenitors, and activation of T cells and thymocytes. IL-1 and TNF stimulate the generation of only a limited subset of acute phase proteins (49), where as IL-6 induces a broad spectrum of acute phase proteins in hepatoma cells and hepatocytes (50). The metabolic role of IL-6 in MIA syndrome is given in Table 4.

(iii) *Tumor necrosis factor:*

Tumor necrosis factor (TNF), which is produced by activated macrophage-monocytes, plays an important role in the pathogenesis of inflammation, septic shock, and tissue injury (51). The various metabolic effects of cytokines TNF-alpha and IL-1 in MIA syndrome are depicted in Table 5. The principal source of serum TNF during endotoxemia is the liver (52).

Exogenous and endogenous factors produced by bacteria, viruses, parasites and tumors are capable of inducing cells to produce TNF. Under normal conditions, the synthesis of TNF

Table 4: Schematic representation of the major metabolic effects of pro-inflammatory cytokine IL-6 in MIA syndrome (38)

INTERLEUKIN-6 (IL-6)

Acute Phase Response

Positive phase proteins	Negative phase proteins
• Fibrinogen	• Albumin
• Plasminogen	• Transferrin
• Fibronectin	• Leptin
• Complement	• α -fetoprotein
• CRP	• Thyroid binding Globulin.
• Ceruloplasmin	• IGF-1
• Haptoglobin	• Factor XII
• Angiotensinogen	
• Serum amyloid	

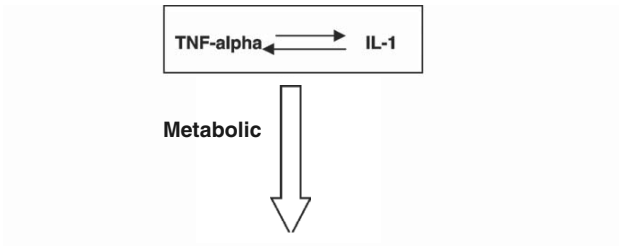
is tightly controlled to ensure the production of vanishingly small amounts of TNF in quiescent cells. Regulation of TNF synthesis is controlled at transcriptional and translational level.

In our study ,we observed significant high levels of IL-1β, IL-6, and TNF-α in erythropoietin -resistant CKD patients supporting the finding that all erythropoietin -resistant patients who had hemoglobin <11 g/dl, also had inflammation.

III ATHEROSCLEROSIS IN PATIENTS WITH MIA SYNDROME

Atherosclerosis is a very frequent complication in uremia due to the coexistence of hypertension, hyperhomocysteinemia, inflammation, malnutrition and increased oxidative stress, generation of AGEs, AOPPs, hyperlipidemia and altered structural and functional ability of HDL. LDL cholesterol, apolipoprotein (A), apolipoprotein (B), and Lp (a) are also associated with atherosclerosis.

Table 5: Schematic representations of major metabolic effects of pro-inflammatory cytokines TNF-alpha and IL-1 in



• Anorexia	• ↓ Skeletal muscle protein synthesis
• Fever	• ↓ Lipoprotein lipase
• Insulin resistance	• ↑ O_2 utilization
• ↑ Gluconeogenesis	• ↑ Basal metabolic rate
• ↑ Skeletal muscle proteolysis	• ↑ Free radical production

Serum Lipids in patients with MIA syndrome:

The importance of plasma lipids and lipoprotein abnormalities in CKD is recognized for several different reasons. Ischemic heart disease is associated with hyperlipoproteinemias and is the major cause of death in HD patients (53). The incidence of cardiovascular complications is also abnormally elevated in predialysis patients with CKD (54). Abnormalities in lipid and lipoprotein metabolism may be involved, not just in initial injury to kidney, but also in the ongoing process that eventually leads to end-stage renal disease (55). A series of self-perpetuating secondary events follows an initial glomerular injury. Increased glomerular basement membrane permeability leads to loss of lipoprotein lipase activators, resulting in hyperlipidemia.

Circulating LDL binds with glycosaminoglycans in glomerular basement membrane and increases its permeability. Filtered lipoprotein accumulates in mesangial cells and stimulates them to proliferate and produce excess basement membrane material. The proximal tubular cells metabolize some of the filtered lipo-protein and the remainder is altered during its passage down to the nephron. Luminal apolipoprotein precipitates, initiating or aggravating the tubulo-interstitial disease (56). Coronary artery thrombosis is generally a result of atherosclerosis, which develops primarily as a result of endothelial damage. Elevated triglycerides, intermediate-density and low-density lipoproteins as well as lipoprotein (a), and lowered high-density lipoproteins increase the risk of atherosclerosis in CKD (57). The inflammatory cytokines, interleukin-1, and TNF-alpha, present within the atherosclerotic plaque mediate platelet activation and aggregation (58).

Very Low Density and Intermediate Density Lipoproteins (VLDL and IDL) :

Very low-density lipoprotein (VLDL) and intermediate-density lipoprotein (IDL) were increased due to a defect in degradation rather than formation of triglyceride-rich lipoproteins (59). Impaired degradation of triglyceride-rich lipoproteins in patients with CKD may be due to a deficient lipolytic system (59, 60). Arnadottir et al, have observed that VLDL particles from patients on hemodialysis were lipolyzed to a lesser extent than VLDL particles from healthy controls, and suggested that

increased relative contents of cholesterol, phospholipids and in particular, increased levels of apolipoprotein C-III, bound to apoB- containing lipoproteins may represent the main compositional abnormalities interfering with the lipolytic degradation of uremic triglyceride rich lipoproteins (61, 62).

Low Density Lipoprotein (LDL) :

The patients with CKD appear to have the lipoprotein phenotype with hypertriglyceridemia, low HDL levels, and LDL-III. However, the increase in LDL-III levels was confined to patients undergoing peritoneal dialysis, and there is a marked variability in the LDL-III levels in HD and pre-dialysis cases. Triglyceride rich, cholesterol depleted LDL is the characteristic finding when LDL-III is prominent (63).

High Density Lipoprotein (HDL) :

In CKD patients with inflammation, HDL levels decreased (64) and apolipoprotein A-1 that normally composes about half of the protein in HDL is replaced by serum amyloid-A protein (64, 65). This form of HDL is chemo attractive and has a reduced capability to reduce oxidized LDL.

Lipoprotein (a) [Lp (a)] :

Various cell types in the kidney express the LDL receptor-related protein, believed to have a role in the catabolism of Lp (a) (66). Lp (a) may be involved in the pathogenesis of kidney disease. Fragments of apolipoprotein (a) are present in human atheroma and their potential bioactivity has been suggested by in vitro and cell culture studies (67). It was observed that in CKD, elevation in Lp (a) was dependent on apo (a) phenotype. Only renal patients with high molecular weight apo (a) phenotypes expressed higher median Lp (a) concentrations (68). Studies considering the apo (a) size polymorphism concluded that the apo (a) gene locus determines the risk for cardiovascular disease through its allelic control of Lp (a) concentrations (69). Dialysis patients with low molecular weight apo (a) phenotypes have a two–to–three fold higher prevalence as well as incidence of major cardiovascular events than those with high molecular weight apo (a) types (70).

Fibrinogen :

Fibrinogen is a positive acute phase protein and plasma fibrinogen levels were associated with elevated CRP and with the presence of abnormalities of cardiovascular system including left ventricular hypertrophy, arterial stiffness or systolic myocardial dysfunction (71). Fibrinogen levels were consistently elevated in patients with CKD and in dialysis patients (72).

Advanced Glycation End Products in Atherosclerosis :

Advanced glycation end products (AGEs) represent another stimulus for vascular disease in the CKD patients. AGEs accumulate in the plasma and vasculature of non-diabetic uremic patients (73) leading to several vascular complications.

Endothelial Cell Dysfunction :

Endothelial cell dysfunction can promote transduction of atherogenic risk factors, thus playing an important role in the initiation and progression of atherosclerosis. Oxidatively modified low-density lipoproteins, cholesterol and diabetes may initiate atherosclerosis through endothelial activation (74). Endothelial cell activation designates one specific type of endothelial dysfunction, characterized by increased cytokine – induced interactions with blood leukocytes. Endothelial dysfunction may play a role in the development of CRF by increasing intra glomerular pressure and glomerular basement permeability. Inflammatory cytokines are also likely to be involved as uremia can be considered a state of chronic low-grade inflammation.

***Hyperhomocysteinemia-atherosclerosis* :**

Increased homocysteine levels in patients on dialysis therapy may contribute to the excess vascular morbidity (75). Hyperhomocysteinemia is an independent risk factor for vascular disease in both healthy population and dialysis patients (76). Elevated homocysteine and Lp (a) levels in CKD patients might be particularly atherogenic because of the potential biochemical interactions between these two risk factors. It is postulated that Lp(a) may compete with plasminogen for binding to fibrin and homocysteine may enhance the binding of Lp(a) to fibrin, thereby potentiating the atherogenecity of Lp(a) (77).

IV METABOLIC ACIDOSIS IN PATIENTS WITH MIA SYNDROME

Metabolic acidosis, a common condition in patients with renal failure, may be linked to the MIA syndrome. In patients with CKD, a significant number of endocrine, musculoskeletal and metabolic abnormalities are believed to result from acidemia. Metabolic acidosis may be related to MIA due to an increased protein catabolism, decreased protein synthesis, endocrine abnormalities including insulin resistance, decreased serum

leptin level and inflammation among individuals with renal failure. Evidence suggests that the catabolic effects of metabolic acidosis may result from an increased activity of the adenosine triphosphate (ATP)-dependent ubiquitin-proteasome and branched-chain keto acid dehydrogenase. In addition, metabolic acidosis is a potent inhibitor of hepatic synthesis of albumin (78).

CONCLUSION

Chronic kidney disease patients on maintenance hemodialysis have been shown to have a strong association between malnutrition, inflammation and arthrosclerosis – MIA syndrome. The available biochemical mechanisms of MIA syndrome have paved the way for the laboratory provision of specialized biochemical markers towards the evaluation of the severity of MIA syndrome as well as effective monitoring of these patients.

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