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Malnutrition and Inflammatory Markers among Anemic Hemodialysis Patients

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Abstract: End-stage renal disease (ESRD) is associated with a complex interplay of malnutrition, inflammation, and anemia, significantly affecting patient outcomes. This review discusses the impact of malnutrition-inflammation syndrome on anemia among hemodialysis patients. ESRD patients experience systemic inflammation, marked by elevated levels of pro-inflammatory markers such as C-reactive protein (CRP) and cytokines (IL-6, TNF-α), contributing to immune deficiency, cardiovascular complications, and anemia. Malnutrition in chronic kidney disease (CKD) is characterized by protein-energy wasting (PEW) and micronutrient deficiencies, resulting from metabolic disturbances, poor nutrient absorption, and dialysis-related factors. These nutritional deficits exacerbate anemia, primarily due to decreased erythropoietin production and impaired red blood cell synthesis. Inflammation further suppresses erythropoiesis and accelerates protein catabolism, leading to muscle wasting and increased mortality risk. Additionally, CKD patients exhibit altered gut microbiota and gastrointestinal dysfunction, such as delayed gastric emptying, which worsens their nutritional status. The dialysis procedure itself induces inflammatory responses, aggravating malnutrition and anemia. Managing these interrelated issues requires a multidisciplinary approach that addresses both nutritional support and inflammation control. This review highlights the critical need for early identification and intervention strategies to mitigate malnutrition and inflammation, thereby improving anemia management in hemodialysis patients. Comprehensive care, including tailored nutritional plans and anti-inflammatory therapies, can enhance patient outcomes and quality of life.

Keywords: *ESRD; CRP; Hemodialysis Patients.*

Introduction.

End-stage renal disease (ESRD) is associated with immune activation (marked by systemic inflammation) and immune deficiency **(1,2)**.

Whereas systemic inflammation contributes to atherosclerosis, cardiovascular disease, cachexia, and anemia, the acquired immunodeficiency results in increased risk for infection and malignancy **(3)**.

Infectious diseases and bacterial infections are important causes of morbidity and mortality among dialysis patients. Most isolates are gram-positive bacteria, among which Staphylococcus has a predominant role **(4)**.

This review will illustrate the role of malnutrition-inflammation syndrome on anemia of hemodialysis patients.

CHRONIC KIDNEY DISEASE

Overview: Chronic kidney disease (CKD) or chronic renal failure (CRF), as it was historically termed, is a term that encompasses all degrees of decreased kidney function, from damaged–at risk through mild, moderate, and severe chronic kidney failure. CKD is a worldwide public health problem. In the world there is a rising incidence and prevalence of kidney failure, with poor outcomes and high cost **(5)**.

Epidemiology

In the United States, more than 1 in 7 adults—15% of the adult population, or 37 million people—are estimated to have chronic kidney disease **(6).** Kidney disease is the ninth leading cause of death in the United States**(7).** According to the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), the overall prevalence of CKD in the US has remained relatively stable since 2004. The largest increase occurred in people with stage 3 CKD, from 4.5% to 6.0% **(8)**.

International statistics

In 2017, 697.5 million cases of CKD (all stages) were recorded worldwide, for a global prevalence of 9.1%. From 1990 to 2017, the global all-age prevalence of CKD increased 29.3%, whereas the age-standardized prevalence remained stable. Globally, 1.2 million people died from CKD in 2017. The global all-age mortality rate from CKD increased 41.5% from 1990 to 2017. Diabetic nephropathy accounted for almost a third of disability-adjusted life years (DALYs) from CKD. Most of the burden of CKD was concentrated in the three lowest quintiles of the Socio- demographic index (SDI) **(9)**.

Race/ethnic-related demographics

In non-Hispanic white and non-Hispanic Black persons, the prevalence of stage 3 and 4 CKD has remained stable since 2004. In Mexican Americans, the prevalence of CKD in Mexican Americans had been lower than in other racial/ethnic groups, but nearly doubled between 2003-2004 and 2015-2016, from 1.6% to 3.5% **(10)**.

Sex-related demographics

In NHANES, the distribution of estimated GFRs for the stages of CKD was similar in both sexes. The United States Renal Data System (USRDS) 2020 Annual Data Report, however, notes that for all races, the lifetime cumulative incidence of ESRD from birth is 4.02% in males and 2.89% in females **(11)**.

Pathophysiology

A normal kidney contains approximately 1 million nephrons, each of which contributes to the total glomerular filtration rate (GFR). In the face of renal injury (regardless of the etiology), the kidney has an innate ability to maintain GFR, despite progressive destruction of nephrons, as the remaining healthy nephrons manifest hyperfiltration and compensatory hypertrophy. This nephron adaptability allows for continued normal clearance of plasma solutes. Plasma levels of substances such as urea and creatinine start to show measurable increases only after total GFR has decreased 50% **(12).** Thaker et al**. (13)** found a strong association between episodes of acute kidney injury (AKI) and cumulative risk for the development of advanced CKD in patients with diabetes mellitus who experienced AKI in multiple hospitalizations. Any AKI versus no AKI was a risk factor for stage 4 CKD, and each additional AKI episode doubled that risk.

Childhood kidney function and CKD in children

In children, the GFR increases with age and is calculated with specific equations that are different than those for adults. Adjusted for body surface area, the GFR reaches adult levels by age 2-3 years **(14)**.

Aging and kidney function

The biologic process of aging initiates various structural and functional changes within the kidney **(15)**. Renal mass progressively declines with advancing age, and glomerulosclerosis leads to a decrease in renal weight. Histologic examination is notable for a decrease in glomerular number of as much as 30-50% by age 70 years. The GFR peaks during the third decade of life at approximately 120 mL/min/1.73 m^2; it then undergoes an annual mean decline of approximately 1 mL/min/y/1.73 m^2, reaching a mean value of 70 mL/min/1.73 m^2 at age 70 years **(16,15).**

Genetics

Most cases of CKD are acquired rather than inherited, although CKD in a child is more likely to have a genetic or inherited cause. Well-described genetic syndromes associated with CKD include autosomal dominant polycystic kidney disease (ADPKD) and Alport syndrome. Other examples of specific single-gene or few-gene mutations associated with CKD include Dent disease, nephronophthisis, and atypical hemolytic uremic syndrome (HUS) **(17)**.

APOL1 gene

More recently, researchers have begun to identify genetic contributions to increased risk for development or progression of CKD. Friedman et al found that more than 3 million black persons with genetic variants in both copies of apolipoprotein L1 (APOL1) are at higher risk for hypertension-attributable ESRD and FSGS. In contrast, black individuals without the risk genotype and European Americans appear to have similar risk for developing nondiabetic CKD **(18)**.

FGF-23 gene

Circulating levels of the phosphate-regulating hormone fibroblast growth factor 23 (FGF-23) are affected by variants in the *FGF23* gene. Isakova et al reported that elevated FGF-23 levels are an independent risk factor for ESRD in patients who have fairly well-preserved kidney function (stages 2-4) and for mortality across the scope of CKD **(19)**.

Single-nucleotide polymorphisms

A review of 16 single-nucleotide polymorphisms (SNPs) that had been associated with variation in GFR found that development of albuminuria was associated mostly with an SNP in the *SHROOM3* gene. Even accounting for this variant, however, there is evidence that some unknown genetic variant influences the development of albuminuria in CKD. This study also suggests a separate genetic influence on development of albuminuria versus reduction in GFR **(20)**.

Immune-system and RAS genes

A number of genes have been associated with the development of ESRD. Many of these genes involve aspects of the immune system (e.g., *CCR3*, *IL1RN*, *IL4*) **(21).**

Hyperkalemia

The ability to maintain potassium excretion at near-normal levels is generally maintained in CKD, as long as aldosterone secretion and distal flow are maintained. Another defense against potassium retention in patients with CKD is increased potassium excretion in the gastrointestinal tract, which also is under control of aldosterone **(22).**

Hypokalemia

Hypokalemia is uncommon but can develop in patients with very poor intake of potassium, gastrointestinal or urinary loss of potassium, or diarrhea or in patients who use diuretics **(23)**.

Metabolic acidosis

Metabolic acidosis often is a mixture of normal anion gap and increased anion gap; the latter is observed generally with stage 5 CKD but with the anion gap generally not higher than 20 mEq/L. In CKD, the kidneys are unable to produce enough ammonia in the proximal tubules to excrete the endogenous acid into the urine in the form of ammonium. In stage 5 CKD, accumulation of phosphates, sulfates, and other organic anions are the cause of the increase in anion gap **(24)**.

Metabolic acidosis also leads to an increase in fibrosis and rapid progression of kidney disease, by causing an increase in ammonia-genesis to enhance hydrogen excretion. In addition, metabolic acidosis is a factor in the development of renal osteodystrophy, because bone acts as a buffer for excess acid, with resultant loss of mineral. Acidosis may interfere with vitamin D metabolism, and patients who are persistently more acidotic are more likely to have osteomalacia or low-turnover bone disease **(25).**

Salt- and water-handling abnormalities

Salt and water handling by the kidney is altered in CKD. Extracellular volume expansion and total-body volume overload results from failure of sodium and free-water excretion. This generally becomes clinically manifested when the GFR falls to less than 10-15 mL/min/1.73 m^2, when compensatory mechanisms have become exhausted **(26).**

Anemia

Normochromic normocytic anemia principally develops from decreased renal synthesis of erythropoietin; the hormone responsible for bone marrow stimulation for red blood cell (RBC) production. The anemia starts early in the course of the disease and becomes more severe as viable renal mass shrinks and the GFR progressively decreases **(27)**.

Bone disease

Renal bone disease is a common complication of CKD. It results in skeletal complications (e.g., abnormality of bone turnover, mineralization, linear growth) and extra-skeletal complications (e.g., vascular or soft-tissue calcification) **(28).**

Bone disease in children is similar but occurs during growth. Therefore, children with CKD are at risk for short stature, bone curvature, and poor mineralization ("renal rickets" is the equivalent term for adult osteomalacia) **(1).**

Secondary hyperparathyroidism develops in CKD because of the following factors (29): Hyperphosphatemia, Hypocalcemia, Decreased renal synthesis of 1,25-dihydroxycholecalciferol (1,25-dihydroxy vitamin D, or calcitriol) **(30).** Intrinsic alteration in the parathyroid glands, which gives rise to increased PTH secretion and increased parathyroid growth, skeletal resistance to PTH.

Hyperphosphatemia and hypocalcemia

Phosphate retention begins in early CKD; when the GFR falls, less phosphate is filtered and excreted, but because of increased PTH secretion, which increases renal excretion, serum levels do not rise initially. As the GFR falls toward CKD stages 4-5, hyperphosphatemia develops from the inability of the kidneys to excrete the excess dietary intake **(31)**.

Increased PTH secretion

Low serum calcitriol levels, hypocalcemia, and hyperphosphatemia have all been demonstrated to independently trigger PTH synthesis and secretion. As these stimuli persist in CKD, particularly in the more advanced stages, PTH secretion becomes maladaptive, and the parathyroid glands, which initially hypertrophy, become hyperplastic. The persistently elevated PTH levels exacerbate hyperphosphatemia from bone resorption of phosphate **(32)**.

Skeletal manifestations

If serum levels of PTH remain elevated, a high–bone turnover lesion, known as osteitis fibrosa, develops. This is one of several bone lesions, which as a group are commonly known as renal osteodystrophy and which develop in patients with severe CKD. Osteitis fibrosa is common in patients with ESRD **(33)**. The prevalence of adynamic bone disease in the United States has increased, and its onset before the initiation of dialysis has been reported in some cases. The pathogenesis of adynamic bone disease is not well defined, but possible contributing factors include the following **(34).**

Staging

By itself, measurement of GFR may not be sufficient for identifying stage 1 and stage 2 CKD, because in those patients the GFR may in fact be normal or borderline normal. In such cases, the presence of one or more of the following markers of kidney damage can establish the diagnosis **(35)**

Etiology

Causes of chronic kidney disease (CKD) include the following **(36):** Diabetic kidney disease, hypertension, vascular disease, glomerular disease (primary or secondary), cystic kidney diseases, tubulointerstitia3l disease, urinary tract obstruction or dysfunction, recurrent kidney stone disease, congenital (birth) defects of the kidney or bladder and Unrecovered acute kidney injury.

Vascular diseases that can cause CKD include the following (**37**): Renal artery stenosis, cytoplasmic pattern antineutrophil cytoplasmic antibody (C-ANCA)– positive and perinuclear pattern antineutrophil cytoplasmic antibody (P-ANCA)–positive vasculitides, ANCA-negative vasculitides Atheroemboli, hypertensive nephrosclerosis and renal vein thrombosis.

Primary glomerular diseases include the following (**36**): Membranous nephropathy, Alport syndrome, Immunoglobulin A (IgA) nephropathy, Focal and segmental glomerulosclerosis (FSGS), Minimal change disease, Membranoproliferative glomerulonephritis (MPGN), complement-related diseases (e.g., atypical hemolytic-uremic syndrome [HUS], dense deposit disease) and rapidly progressive (crescentic) glomerulonephritis.

Secondary causes of glomerular disease include the following (36): Diabetes mellitus ,Systemic lupus erythematosus ,Rheumatoid arthritis ,Mixed connective tissue disease ,Scleroderma ,Granulomatosis with polyangiitis (formerly known as Wegener granulomatosis) ,Mixed cryoglobulinemia, Endocarditis ,Hepatitis B and C ,Syphilis ,Human immunodeficiency virus (HIV) infection ,Parasitic infection ,Heroin use ,Gold ,Penicillamine ,Amyloidosis ,Light-chain deposition disease ,Neoplasia ,Thrombotic thrombocytopenic purpura (TTP) ,Shiga-toxin or Streptococcus pneumoniae – related HUS ,Henoch-Schoenlein purpura and Reflux nephropathy.

Causes of tubulointerstitial disease include the following (37): Drugs (e.g., sulfonamides, allopurinol**),** Infection (viral, bacterial, parasitic)**,** sjögren syndrome**,** tubulointerstitial nephritis and uveitis (TINU) syndrome**,** chronic hypokalemia**,** chronic hypercalcemia**,** Sarcoidosis**,** multiple myeloma cast nephropathy**,** heavy metals**,** radiation nephritis, polycystic kidneys and cystinosis and other inherited diseases

Urinary tract obstruction may result from any of the following (37): Benign prostatic hypertrophy, urolithiasis (kidney stones, urethral stricture, tumors, neurogenic bladder, congenital (birth) defects of the kidney or bladder and retroperitoneal fibrosis.

DIAGNOSIS

Clinical Presentation:

Patients with CKD stages 1-3 (GFR > 30 mL/min/1.73 m^2) are frequently asymptomatic; in terms of possible "negative" symptoms related simply to the reduction in GFR, they do not experience clinically evident disturbances in water or electrolyte balance or endocrine/metabolic derangements **(38)**.

Physical Examination

A careful physical examination is imperative. It may reveal findings characteristic of the condition that is underlying CKD (e.g., lupus, severe arteriosclerosis, hypertension) or its complications (e.g., anemia, bleeding diathesis, pericarditis). However, the lack of findings on physical examination does not exclude kidney disease. In fact, CKD is frequently clinically silent, so screening of patients without signs or symptoms at routine health visits is important **(39)**.

Signs and Symptoms

Patients with CKD stages 1-3 are generally asymptomatic. Typically, it is not until stages 4-5 (GFR < 30 mL/min/1.73 m^2) that endocrine/metabolic derangements or disturbances in water or electrolyte balance become clinically manifest **(40)**.

Laboratory studies

Approach Considerations

Testing in patients with chronic kidney disease (CKD) typically includes a complete blood count (CBC), basic metabolic panel, and urinalysis, with calculation of renal function. Normochromic normocytic anemia is commonly seen in CKD. Other underlying causes of anemia should be ruled out (**27).**

In certain cases, the following tests may be ordered as part of the evaluation of patients with CKD (41): Serum and urine protein electrophoresis can screen for multiple myeloma, antinuclear antibodies, serum complement levels, cytoplasmic and perinuclear pattern antineutrophil cytoplasmic antibodies, anti-GBM antibodies, Hepatitis B and C, HIV, and VDRL serology. Imaging studies and bladder function studies evaluate for obstruction and other urologic abnormalities, and may be depressed with some glomerulonephritis's.

Laboratory studies used in the diagnosis of CKD can include the following (40): Patients with CKD have an increased risk of cardiovascular disease, potentially due to factors like malnutrition, urinary protein loss, or chronic inflammation.

Evidence of renal bone disease can be derived from the following tests (19): Serum calcium and phosphate ,25-hydroxyvitamin D, Alkaline phosphatase and Intact parathyroid hormone (PTH) levels.

In certain cases, the following tests may also be ordered as part of the evaluation of patients with CKD (42): Screening for multiple myeloma, systemic lupus erythematosus, serum complement levels, cytoplasmic and perinuclear pattern antineutrophil cytoplasmic antibodies, anti-GBM antibodies, and Hepatitis B and C serology can help diagnose glomerulonephritis's**.**

Urinalysis

In adult patients who are not at elevated risk for CKD, screening with total protein can be done with a standard urine dipstick, according to guidelines from the National Kidney Foundation's Kidney Disease Outcomes Quality Initiative (KDOQI). If the dipstick test is positive (1+ or greater), patients should undergo testing for confirmation of proteinuria **(43).**

Renal Function Formulas

The Cockcroft-Gault formula for estimating creatinine clearance (CrCl) should be used routinely as a simple means to provide a reliable approximation of residual renal function in all patients with CKD. The formulas are as follows **(44)**

Renal function calculation in pediatric patients: GFR in children is calculated using the Schwartz formula. Because this formula may currently overestimate GFR, likely due to a change in methods used to measure creatinine, Schwartz et al have proposed an updated equation that includes cystatin C. However, the majority of dosing guidelines for medication adjustments due to reduced GFR use the original Schwartz equations **(45).**

Renal function calculation in elderly patients

Age is an important consideration with respect to estimated GFR. In a 70-kg man aged 25 years, a serum creatinine value of 1.2 mg/dL represents an estimated GFR of 74 mL/min/1.73m2, but in a 70-kg man aged 80 years, that same value represents an estimated GFR of 58 mL/min/1.73m2. Thus, in a 70-kg, 80-year-old man, a serum creatinine of 2 mg/dL actually represents severe renal impairment, with an estimated GFR of 32 mL/min/1.73 m2 as measured by the MDRD equation **(46).**

Imaging studies

Renal ultrasonography:

Renal ultrasonography is useful to screen for hydronephrosis, which may not be observed in early obstruction, or involvement of the retroperitoneum with fibrosis, tumor, or diffuse adenopathy. Small, echogenic kidneys are observed in advanced renal failure **(40)**.

Retrograde pyelography:

A retrograde pyelogram may be indicated if a high index of clinical suspicion for obstruction exists despite a negative finding on renal ultrasonography. Intravenous pyelography is not commonly performed, because of the potential for renal toxicity from the intravenous contrast; however, this procedure is often used to diagnose renal stones **(47)**.

Computed tomography (CT) scanning:

Computed tomography (CT) scanning can better define renal masses and cysts usually noted on ultrasonography. Also, CT scanning is the most sensitive test for identifying renal stones. Intravenous (IV) contrast– enhanced CT scans should be avoided in patients with renal impairment to avoid acute kidney injury; this risk significantly increases in patients with moderate to severe CKD. Dehydration also markedly increases this risk **(48).**

Magnetic resonance imaging (MRI):

MRI is very useful in patients who would otherwise undergo a CT scan but who cannot receive IV contrast. This imaging modality is reliable in the diagnosis of renal vein thrombosis, as are CT scanning and renal venography **(49)**.

Renal radionuclide scanning: A renal radionuclide scan can be used to screen for renal artery stenosis when performed with captopril administration; it also quantitates differential renal contribution to total glomerular filtration rate (GFR). However, radionuclide scans are unreliable in patients with a GFR of less than 30 mL/min/1.73 m^2 **(50).**

Renal Biopsy

Percutaneous renal biopsy is performed most often with ultrasonographic guidance and the use of a spring-loaded or other semi- automated needle. This procedure is generally indicated when renal impairment and/or proteinuria approaching the nephrotic range are present and the diagnosis is unclear after an appropriate workup **(40).**

Screening

Evidence-based recommendations from the American College of Physicians (ACP) regarding the screening, monitoring, and treatment of adults with stage 1-3 CKD recommend against CKD screening for asymptomatic adults with no risk factors for kidney disease. The ACP's position, however, has been disputed by the American Society of Nephrology (ASN) **(51).**

ANEMIA in CKD

Anemia may arise as a complication of several chronic diseases, and chronic kidney disease (CKD) in particular. By definition, anemia refers to an absolute reduction of the total number of circulating red blood cells (RBCs). For practical purposes, anemia is considered when one or more of the following are decreased: hemoglobin concentration, hematocrit, or RBC count. This condition is a laboratory finding that signifies the presence of illness or disease; anemia itself should not be considered a diagnosis **(52)**.

Prevalence of Anemia in CKD

In general, anemia is more common in women, in particular, those in their childbearing years. In the latter decades of life, anemia tends to occur without any particular sex predilection. However, in patients with chronic kidney disease (CKD), the risk of developing anemia is 30% higher in males than in females. Although males have higher hemoglobin values, they also have higher rates of advanced CKD. The prevalence of anemia is lower in current smokers, which has been attributed to secondary erythrocytosis **(52)**.

Mechanism of Anemia of Chronic Disease

Anemia of chronic illness traditionally encompassed any inflammatory, infectious, or malignant disease of a long-standing nature. The modern definition includes rheumatoid arthritis, severe trauma, heart disease, diabetes mellitus, and inflammatory bowel disease. Anemia of chronic disease is characterized primarily by the following **(53).**

Evaluation of Anemia and CKD

Symptoms and physical findings

Although the diseases that lead to anemia, such as malignancy or chronic kidney disease (CKD), may cause obvious symptoms, the anemia itself tends to cause quite nonspecific symptoms. Clinicians must be wary of the tendency to dismiss these symptoms as insignificant—for example, as being due to old age—when in fact they should serve as alarming signals of disease or pathology **(54).**

Complications of Anemia in CKD

Hypoxia

Hypoxia is the most potent stimulus to the production of erythropoietin by the kidneys. In the healthy individual, erythropoietin exerts its effects in the bone marrow to help in the production of RBCs, thereby improving oxygen concentration in the blood, relieving the hypoxia **(55).**

Cardiorenal anemia syndrome

Silverberg et al. (2002) described the "cardiorenal syndrome," which refers to a vicious cycle whereby decreased kidney function, as seen in chronic kidney disease, leads to decreased erythropoietin production and, thence, anemia. Severe anemia leads to a compensatory left ventricular hypertrophy (LVH). Such compensatory LVH eventually precipitates chronic heart failure (CHF), which causes a decline in blood perfusion to the kidneys, resulting in further kidney damage **(56).**

Cardiovascular disease

The risk of death from cardiovascular disease also increases with advancing age, and the impact of anemia on cardiovascular disease and chronic kidney disease (CKD) in this elderly population cannot be understated. Cardiovascular disease remains the most common cause of mortality in these patients, much higher than in the general population. Anemia has been shown to be an independent risk factor for increased cardiovascular morbidity and mortality **(57).**

Association of inflammation with anemia in patients with CKD and Role of CRP:

Acute and chronic inflammatory processes are common in individuals with CKD and especially ESKD. This is due to many underlying factors, including the uremic milieu, elevated levels of circulating proinflammatory cytokines, oxidative stress, carbonyl stress, protein-energy wasting (PEW), enhanced incidence of infections (especially dialysis access related), and others. Although the definition of inflammation is unclear in this setting, CKD-associated chronic inflammation, as assessed by increased C-reactive protein (CRP) levels above 5 mg/L over at least three months, has been reported in 30 to 60 percent of North American and European dialysis patients, with dialysis patients in Asian countries possibly having a lower prevalence (**58).**

Malnutrition in CKD

Definition:

The American Society for Parenteral and Enteral Nutrition defines malnutrition as “an imbalance between nutrient requirement and intake resulting in cumulative deficits of energy, protein or micronutrients that may negatively affect growth, development and other relevant outcomes” (1). This definition assumes a state of undernutrition, which constitutes protein energy wasting and micronutrient deficiency. For the purposes of this review, the term malnutrition refers to nutrient deficiency and undernutrition **(59).**

Protein energy wasting in CKD:

The International Society of Renal Nutrition and Metabolism (ISRNM) defines protein energy wasting as a “the state of decreased body stores of protein and energy fuels (that is, body protein and fat masses)”. This term was proposed by ISRNM in 2008 to specifically refer to a state of decreased body stores of protein and fat (wasting). This is to be distinguished from protein energy malnutrition, a form of protein energy wasting characterized purely by inadequate dietary intake. Moreover, unlike protein energy malnutrition, protein energy wasting cannot be corrected solely by increasing energy intake **(60).**

Micronutrient deficiency in CKD

CKD predisposes patients to vitamin and mineral deficiencies, which may contribute to comorbidities such as anemia, cardiovascular disease, and metabolic imbalances. The overall decrease in nutritional intake, dietary restrictions, poor intestinal absorption, inflammatory state, metabolic acidosis, and dialysate losses all put the CKD patient at risk for micronutrient deficiencies **(3).**

Pathophysiologic mechanisms of protein energy wasting in CKD: Multiple risk factors underlie the pathogenesis of malnutrition in patients with CKD. The following is an overview of the various mechanisms involved **(59).**

Metabolic dysfunction in chronic kidney disease

The metabolic milieu in CKD is significantly altered due to the progressive accumulation of metabolic by-products that are naturally cleared by the kidneys. Metabolic derangements such as metabolic acidosis, hyperparathyroidism, insulin resistance, upregulation of the renin angiotensin aldosterone system and dyslipidemia are common in CKD **(61).**

Hormonal imbalance and appetite regulation in CKD:

The kidneys play a major role in the synthesis and regulation of a wide variety of hormones in the body. As kidney function declines, hormonal imbalance becomes a characteristic feature and this has been implicated in the suppression of appetite, muscle wasting and growth impairment in CKD. Insulin resistance occurs early in CKD **(59).**

Inflammation and protein energy wasting in CKD:

Chronic systemic inflammation is highly prevalent in patients with CKD and is associated with increased disease burden. Markers of inflammation including pro-inflammatory cytokines IL-6, IL-1β, IL-18, IL- 6, TNFα, IL-8 and C - reactive protein (CRP) levels are elevated in patients with CKD and have been linked to increased mortality rates in these patients. Hypoalbuminemia and elevated ferritin levels are other markers of inflammation, with hypoalbuminemia being a strong predictor of mortality in these patients **(62).**

Altered bowel flora in CKD:

The intestinal microbial flora is significantly altered in patients with CKD and this has been thought to play a pathogenic role in the chronicinflammatory state seen in CKD. Quantitative studies have shown a reduction in the total number and composition of bacteria in patients with end stage kidney disease **(63).**

Effect of gastroparesis on nutritional status in CKD:

Delayed gastric emptying (gastroparesis) is common in patients with CKD, as demonstrated in multiple gastric emptying studies. The elevated levels of gastrointestinal hormones including gastrin, cholecystokinin and gastric inhibitory polypeptide may alter gastric motor function in CKD patients **(64)**.

Effect of dialysis procedure and dialysis dose on nutrition in CKD:

While malnutrition is common in dialysis patients in general, the dialysis technique itself might contribute to nutritional deficits in unique ways. For instance, hemodialysis patients have higher levels of CRP, inflammation, oxidative stress and increased protein muscle breakdown when compared to other CKD patients. This has been attributed to the induction of a cascade of inflammatory pathways when blood comes in contact with the dialyzer membrane **(65).**

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