

## Review

# Nutritional Impact on Cardiovascular Risk in Chronic Hemodialysed Patients - A Systematic Review

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## REZUMAT

### *Impactul nutrițional pe risc cardiovascular la pacienții hemodializați cronic - o revizuire sistematică*

Stadiile avansate de boală cronică de rinichi (BCR) și hemodializa cronică sunt două entități clinice care prezintă susceptibilitate crescută pentru diverși factori de risc cardiovasculari, implicând mortalitate ridicată. Această relație de cauzalitate este accentuată de modificările bioumorale specifice progresiei afecțiunii renale, dar și hemodializei per se. BCR poate favoriza malnutriția, dar și importante tulburări mineralo-osoase, astfel, parțial explicându-se apariția riscului cardiovascular la pacienții hemodializați cronic.

**Cuvinte cheie:** boala cronică de rinichi, malnutriția, riscul cardiovascular, hemodializa

## ABSTRACT

Advanced stage chronic kidney disease (CKD) and chronic hemodialysis are two clinical entities associated with increased cardiovascular risk and thus with elevated mortality. This causal relationship is largely due to biohumoral changes occurring in the disease evolution. CKD leads to protein-energy malnutrition, mineral and bone related disorders. These features are partially determining cardiovascular risk in chronic hemodialysis patients.

**Key words:** chronic kidney disease, malnutrition, cardiovascular risk, hemodialysis

## INTRODUCTION

Protein-energy malnutrition is a frequent clinical condition in chronic hemodialysis patients (1). The causes of protein-energy malnutrition are: interac-

tion between blood and dialyzer with subsequent activation of the complement, amino acids and peptides losses when undergoing hemodialysis, metabolic acidosis, chronic inflammation and anorexia (2). There are two types of protein-energy

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malnutrition. Type 1 protein-energy malnutrition is characterized by patients' poor food intake. This occurs along with slow decrease of serum albumin and loss of muscle mass, the presence of normal levels of C-reactive protein and response to nutritional interventions. The second type of protein-energy malnutrition is characterized by an increased serum level of C-reactive protein and lower serum albumin level than in type 1, even with an optimal food intake. This type of protein-caloric malnutrition is strongly associated with chronic inflammation and does not respond to nutritional intervention (3).

Therefore, in the last decade, a keen interest has been noticed in better understanding the nutritional impact on cardiovascular risk in chronic kidney disease patients, especially the hemodialysis population. There are several studies that concluded the beneficial effect of a dietary fiber related to cardiovascular risks in this group of individuals, with marked consequence even in the improvement of oxidative and inflammation state (4-8).

#### **The correlation between nutrition state and inflammatory / cardiovascular markers**

In patients with chronic kidney disease, serum level IL-1, TNF-alpha values are increased. They are known as proinflammatory markers and are responsible for stimulating hepatic synthesis of C-reactive protein. Adipose tissue, in addition to energy storage capacity, is responsible for the secretion of various cytokines such as leptin, adiponectin, IL-6, TNF-alpha, with an important role in increasing systemic inflammation in chronic hemodialysis patients (9). Some researchers believe that adiponectins, cytokines with anti-inflammatory action, do not lead to the development of fatal cardiovascular events (10). There are recent studies that correlate protein-energy malnutrition with inflammation markers (CRP, TNF-alpha), providing a link to the inflammatory cytokines secreted by visceral fat (11). Other studies present an existing association between nutrition and inflammatory cytokines secreted by adipocytes. For instance, we can mention the presence of high level serum leptin and an adequate nutritional status in normal weight patients (12). Therefore, the presence of chronic inflammation and oxidative state in patients on chronic hemodialysis is associated with a low nutritional status, and also with increased cardiovascular risk and high risk of mortality (13). These data are in concordance with other studies that emphasized the importance

of adequately correcting the oxidative and inflammation status with a clear beneficial impact on increasing the patients' appetite and consequently their daily food intake, improving, in this manner, the over-all outcome (14).

B-type natriuretic peptide (BNP) - secreted from ventricular myocytes - is a marker of cardiovascular disease (15). In patients undergoing chronic hemodialysis, fluid loading between hemodialysis sessions is correlated with increased serum values of BNP (16). In recent studies, this brain natriuretic peptide is also associated with protein-energy malnutrition. In malnourished patients with low serum albumin level there is a tendency to hyperhydration. Due to hyperhydration, preload increases, causing various degrees of heart failure with high level of serum BNP. This correlation suggests an association in chronic hemodialyzed patients between protein-caloric malnutrition, BNP and increased cardiovascular risk (17).

#### **The optimal nutritional status in hemodialysis patients. Recommendations**

Given that protein-caloric malnutrition is associated with increased cardiovascular risk, early diagnosis can be essential for the further evolution of the patient. To diagnose protein-caloric malnutrition in chronic hemodialysis patients, a careful assessment of food intake, body composition and bioumoral markers, albumin and pre-albumin is required (18,19). Currently different assessment scores are used to determine the nutritional status of the hemodialyzed patient. Subjective Global Assessment (SGA), combined with the specific bioumoral markers for nutritional status, are the basic tools for the clinician to detect malnourished patients (19). Recent studies show that in obese patients, nutritional status assessment using the SGA score does not provide conclusive evidence and no definite diagnosis due to its association with low serum albumin levels (20).

Nutritional approach to improve protein-caloric malnutrition is extremely important. A satisfactory nutritional status is also associated with decreased cardiovascular risk. The dietitian needs to focus on the evolution of patients to avoid protein-caloric malnutrition and in those cases in which it is present, prompt nutritional intervention is required. There are numerous studies describing a favorable evolution of patients with protein-caloric malnutrition (21). In these cases we can observe besides the

reduction of cardiovascular risk, an improved quality of life (22). Nutrition in chronic hemodialysis patients should be closely monitored. It must provide the necessary micro and macronutrients (23). Recent studies show a correlation between insufficient intake of micronutrients and protein-calorie malnutrition. The micronutrients we are referring to here are selenium, copper and manganese (24).

To ensure an optimal protein intake, red meat snacks are recommended during dialysis (25). Another way to improve the nutritional status of chronic hemodialysis patients is oral administration of amino acids supplements. It is described that these supplements can improve serum albumin and inflammatory markers (26). Although there are studies that failed to notice the advantages of longer dialysis time, recent evidence highlighted that increasing the frequency of hemodialysis sessions is beneficial to ensure a good nutritional status in chronic hemodialysis patients by improving metabolic acidosis and decreasing serum levels of C-reactive protein (27-29). Chronic inflammation and acidosis reduction contribute to improving patient nutritional status and helps decrease cardiovascular risk (30).

Another clinical condition commonly seen in chronic hemodialysis patients and associated with increased cardiovascular risk, is minerals and bone disorder, that presents various nutritional implications, similar to protein-caloric malnutrition (31,32).

Minerals and bone disorders associated with chronic kidney disease (CKD-MBD) appear in early stage of the disease at a GFR < 45 mL/min/1.73 m<sup>2</sup>, and in chronic dialysis patients we noted an increase in these imbalances (33,34). CKD-MBD is associated with increased cardiovascular risk of the patient (35). Recent studies have shown that hyperphosphatemia is the CKD-MBD component that favors the most the increasing of cardiovascular risk (36). There are many hypotheses that hyperphosphatemia increases cardiovascular risk in patients with chronic kidney disease undergoing hemodialysis. Among these, we should mention that hyperphosphatemia induces vascular endothelial cell transformation in osteoblast-like cells (vascular calcifications emergence with consequent increase in vascular stiffness) (37). Hyperphosphatemia is also incriminated in inducing cell proliferation. Inorganic phosphate stimulates osteoblastic differentiation of smooth muscle cell via a co-dependent phosphate transporter Na. More than

this, hyperphosphatemia is also incriminated in the onset of cellular apoptosis (38,39). These processes contribute to vascular calcifications development. The increases in chronic inflammation and the presence of elevated levels of TNF-alpha leads to increased expression of bone morphogenetic protein-2 (BMP-2). BMP-2 is an osteogenic bone protein, which is an indispensable formation that occurs in the process of vascular calcification (40).

The serologic response to the occurrence of hyperphosphatemia, has been an increase in serum levels of FGF-23 (fibroblast growth factor-23). FGF-23 is a hormone involved in the metabolism of calcium and phosphorus and the connection to the specific receptor occurs in the presence of co-receptor Klotho. Among his actions we can mention lowering serum phosphate, 1,25-dihydroxy-vitamin D synthesis inhibition and decreased parathyroid hormone (41). The level of serum FGF-23 is associated with patients' nutritional status (42). The influence of FGF-23 on nutritional status is achieved independently of Klotho co-receptor (43). A high level of serum FGF-23 is attributed to the occurrence of left ventricular hypertrophy, also contributing to increased cardiovascular risk in chronic hemodialysis patients (44,45).

Rigorously conducted CKD-MBD management is crucial for future development of patients. In chronic hemodialysis patients, CKD-MBD management includes correction of hyperphosphatemia (using diet and intestinal phosphorus chelators), also trying to maintain an optimal level of calcium, correction of acidosis, patient monitoring and ensuring adequate dialysis. Along with CKD-MBD specific medication, nutritional management of patients is the key to a positive development. Hyperphosphatemia being the component that is mostly associated with increased cardiovascular risk, CKD-MBD management has to be focused on the correction of this component. As the largest share of serum phosphate comes from food, nutritional management of these patients should include lowering dietary phosphate. Choosing the right food can be beneficial in increasing the life expectancy of patients by improving cardiovascular risk (46-48).

It is important to note that phosphate is found in association with proteins (49,50). In patients with advanced kidney chronic disease, hypoproteic diets are used to slow down disease progression. They provide a low dietary intake of phosphorus (51). Instead, in patients undergoing chronic hemodialy-

sis, protein restriction is not recommended; in these cases, the presence of protein-caloric malnutrition prevents the dietitian from using this type of diet. The class of foods containing high biological value proteins are: eggs, meat, dairy products. For each of them the quantity recommended should be adjusted and those with low phosphorus foods but that can provide a sufficient amount of protein should be identified. Egg white is a food rich in proteins of high biological value and can be used in chronic hemodialysis patients' diet because of the low phosphate content. This combination of nutrients is favorable both for the avoidance of protein-caloric malnutrition and to obtain an optimal serum phosphate level (52). Meat is also considered to increase serum levels of phosphorus. Meat consumption should not be limited to patients undergoing chronic hemodialysis, because it is rich in protein, but it is recommended to consider the type of meat used and the method of preparation. There are studies showing as a way of preserving chicken meat, addition of preservatives and phosphorus food additives. These products would considerably increase serum levels of phosphorus and their consumption should be avoided (53). There are also studies that suggest various methods for the preparation of meat in order to obtain the lowest possible phosphorous level. For example, keeping it in water for several minutes, boiling in water or oil suppression. These methods reduce the amount of phosphorus and simultaneously allow preservation of proteins (54).

### CONCLUSIONS

To ensure a balanced diet and to prevent protein-caloric malnutrition and hyperphosphatemia, food should not be forbidden, but the amounts adjusted. Avoiding these clinical conditions improves patients' outcome by reducing cardiovascular risk. The tools used to achieve adequate nutritional management of chronic hemodialysis patients are food surveys, identifying errors in patient nutrition, nutritional advice, providing adequate nutritional intake (macro- and micro-nutrients) and making arrangements tailored to the patients' preferences and their culinary program.

### Conflict of interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

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