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Supplements and Their Role in Reducing Chronic Kidney Disease Progression

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ABSTRACT

Conservative treatment of chronic kidney disease, apart from simply treating symptoms and associated complications, consists in slowing chronic kidney disease progression, in order to improve patient and family quality of life, to postpone the need for renal replacement therapy and to reduce the treatment costs. Slowing chronic kidney disease progression involves therapeutic strategies, aiming to avoid/treat malnutrition and inflammation, correct anemia, treat mineral bone disorders of CKD and correct vitamin, mineral and microelement's deficit. This review aims to shed light to the rationale behind these strategies through evidence from clinical studies and the recent guideline recommendations for use of ketoanalogues, essential aminoacids, calcium, Vit D3, iron, Vit B12, folates and unsaturated fatty acid supplements.

KEYWORDS: CKD progression, supplements.

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KETOANALOGUES AND ESSENTIAL AMINOACIDS

Despite the fact that urea has not been considered a major uremic toxin, over the last few years, there has been evidence that high levels of urea cause changes in the gut microbiota and are associated with insulin resistance [1,2]. Thus, the presence of high serum urea levels, increase intestinal proliferation of urease-containing bacteria, and leads to disruption of the epithelial barrier, bacterial translocation and endotoxemia. Alteration of the intestinal microbiota and barrier leads to chronic inflammatory conditions, which is a major risk factor for cardiovascular disease and progression of chronic kidney disease (CKD) [2].

Ketoacids are aminoacids that lack an amino group at the alpha carbon, and can be converted to the corresponding amino acid by taking-up a circulating nitrogen, so preventing its incorporation into urea. This reaction occurs under conditions of high ketoacid and/or low aminoacid concentration; otherwise ketoacids may undergo degradation [3,4]. In uremic patients, urea nitrogen can be re-used for protein synthesis. Also, as in non-CKD subjects, in uremic patients, phenylalanine and valine can be produced from the respective ketoanalogues (KA). Ketoanalogues of lysine and threonine cannot be trans-aminated in the human body, while keto-analogues of tryptophan and histidine are not produced by the pharmaceutical industry, therefore they are available as essential amino acids (EAA) and not as their KA. Another valuable effect of ketoanalogues is that, by avoiding extra nitrogen intake (by limited protein intake in the diet), urea production is further reduced. Ketoacids in large doses can also serve as phosphorus binders, since they are formulated as calcium salts, where each tablet contains 50 mg of calcium [5]. Some authors report positive, direct effects of EAA and KA supplementation such as antioxidant effects, phosphorus binding or reduction of protein catabolism [6,7]. In an experimental study in guinea pigs under a low protein diet (LPD) regime supplemented with KA, favorable changes in muscle mass are reported, through the direct action of KA on the muscle cell [8]. KA and EAA are the most commonly used supplements in CKD patients that consume a protein-restricted diet. In the conditions of implementing a very low protein diet (VLPD) (for the beneficial effects on phosphorus, proteinuria, metabolic acidosis, CKD progression) supplementation with EAA/KA is mandatory, in order to ensure an intake of essential amino acids and to prevent malnutrition [9-11].

The recommended dose, when prescribing VLPD is 1tb/5-7 kg body weight. In a prospective comparative study in patients with creatinine > 6 mg/dl, Chen et al. found that low-dose Ketosteril treatment (1tb/10 kg body weight) after 6 months, was not inferior to the standard dose (1tb/5 kg body weight) regarding CKD progression [12]. One study, with 1483 subjects with CKD stage 4 & 5 under LPD, supplemented with Ketosteril, showed that a beneficial effect in CKD progression was present only with adequate dosing

and the daily prescription of doses > 5.5 tb was recommended. The authors' concluded that KAs provide an additional tool to delay CKD progression [13].

Recommendations for the use of KA and EAA are based on the evidence from many studies. Their use, together with the so-called "Swedish diet" was suggested by Bergstrom in the 60s [14]. This dietary regimen was well tolerated by patients and neutral nitrogen balance was achieved after long-term treatment [15]. Walser et al in 1973 reported good effects even in advanced CKD. A meta-analysis by Jiang Z. [16] confirmed that LPD and VLPD supplemented with KA prevents CKD progression and has beneficial effects on hyperparathyroidism, hypertension and hyperphosphatemia (compared to unrestricted diet) and it is not associated with malnutrition. A number of studies also confirm that this regime is not associated with an increase in long-term mortality (after the start of dialysis or renal transplant) [17,18]. Positive effects and maintaining a good nutritional status have been observed in diabetic and non- diabetic patients [13,19] as well as in patients with nephrotic proteinuria [20, 21]. In the latter, the effect may be partially related to the reduction of proteinuria (effect of the LPD and VLPD). A positive effect of EAA and KA has been observed in subjects with inadequate protein intake (either quantitatively or qualitatively). In this case, the primary goal is to correct malnutrition and restore normal nutritional status [3]. The quantity and quality of protein consumed is essential for maintaining a good nutritional status. In the conditions of not meeting the minimum energy needs, effective transamination of KA may not occur, and degradation may occur instead. The formulation called Aminotrophic, although proven effective in sarcopenia and chronic heart failure, has only been used in a pilot study in HD patients [22].

The most recent nutrition guidelines, in non-diabetic, metabolically stable adults with stage 3-5 CKD, when strictly supervised VLPD is recommended (aiming to reduce the risk of CKD progression toward end-stage renal disease/death and to improve quality of life), in order to meet protein needs, it must be supplemented with KA/EAA [11].

ENERGY SUPPLEMENTS IN CKD

In order to adapt to the protein-restricted diet, it is necessary to correct the metabolic acidosis and to take appropriate energy/calorie. Caloric intake, including energy supplements, play a crucial role in the dietary treatment of patients with CKD. The higher the caloric intake, the lower the nitrogen requirements.

Recent guidelines, for maintaining a stable nutritional state in adults with stage 1-5 CKD in a stable metabolic state, recommend an intake of 25-35 kcal/kg body weight/day based on age, gender, level of physical activity, body structure, ideal weight, CKD stage, comorbidities or the presence of malnutrition [11].

The ideal products for renal patients are those protein-free, which contain almost zero nitrogen, have negligible amounts of phosphorus, potassium and sodium and are a source of energy from fats and carbohydrates. These products are essential for the implementation of LPD or VLPD, as they allow the reduction of proteins in the diet, while maintaining the high/necessary energy intake. Protein-free foods are available and their palatability has been improving [23]. Protein-free bread and pasta contain a high percentage of fiber, to lower glycemic index, as a significant number of CKD patients are diabetic.

CALCIUM AND VIT D SUPPLEMENTS IN CKD

Calcium supplements in the form of calcium carbonate are recommended as phosphorus binders (obtained with food), to reduce phosphorus retention and prevent negative calcium balance in CKD patients, contributing to the reduction of parathyroid hormone (PTH) levels. The dosing of these supplements should be careful, especially in patients with evidence of vascular calcifications, the so-called "adynamic bone disease" and low bone turnover. The risk of positive calcium balance is real in patients treated with calcium supplements. It has been reported that CKD patients with a daily intake of 800 mg calcium in the diet, are in conditions of a neutral balance, perhaps even negative. Taking 2000 mg results in positive calcium balance in normal subjects and even more pronounced in CKD patients [24]. The risk of a positive balance is more pronounced in patients who do not consume a protein/phosphate-restricted diet and in those who are under active Vit D supplementation. A low protein/low phosphate diet is associated with about 500-600 mg calcium and under these conditions, a low dose of calcium carbonate is beneficial.

According to the 2020 guidelines, it is suggested, that in adults with stage 3-4CKD, who do not receive active Vit D analogs, to maintain a neutral calcium balance, 800-1000 mg/day of elemental calcium should be prescribed (includes dietary calcium, calcium supplements, and calcium-based phosphate binders) [11].

The combination of calcium with Vit D_3 has resulted in a positive effect on the rate bone density decrease in women with moderate CKD [25]. Vit-D hypovitaminosis is very common in CKD population. The first intervention, to avoid Vit D deficiency and to prevent or treat secondary hyperparathyroidism in non-dialysis CKD, is Vit D supplementation, until 25(OH)Vit D levels > 30 ng/ml are reached. Data from various observational studies indicate that supplementation of native Vit D (ergocalciferol or cholecalciferol) is safe and effective in non-dialysis CKD patients, while it is advisable to measure serum levels of 25(OH) Vit D, calcium and phosphorus [26,27]. Meta-analysis of observational studies suggests that vitamin D supplementation improves biochemical parameters, but it is unknown whether this further translates into significant clinical benefits [26].

Regarding the effect on CKD progression, the VITAL-DKD study [28], as a sub-study of VITAL [29] did not observe any significant effect of daily supplementation of 2000 IU Vit D on measured glomerular filtration ($_m$GFR) in diabetic CKD patients. After 5 years, no difference in the rate of $_m$GFR decline was found in the vitamin D3 supplemented group versus the placebo group (−12.3 vs −13.1 mL/min/1.73 m^2, respectively). These findings do not support the use of Vit.D for preserving residual renal function and delaying CKD progression.

According to the KDIGO 2020 guidelines, in adults with stage 1-5 CKD, the prescription of Vitamin D supplements in the form of cholecalciferol or ergocalciferol is suggested to correct the deficiency/insufficiency of 25-hydroxyvitamin D (25(OH)D). In adults with stage 1-5 CKD with nephrotic range proteinuria, it is reasonable to consider the supplementation of cholecalciferol, ergocalciferol or other precursors of 25(OH)D (opinion) [11].

THE ROLE OF UNSATURATED FATTY ACIDS IN CKD

Due to the cardioprotective effects, the intake of unsaturated fatty acids called PUFA (poly unsaturated fatty acids) is of interest in CKD [30]. Thus omega-3 PUFA can reduce oxidative stress, platelet activity, inflammation, triglycerides and have antiarrhythmic effect in CKD patients [31], similar to those in general population. Several studies have demonstrated the potential benefits of n-3 fatty acids in reducing cardiovascular risk. Reduction of arterial pressure is a confirmed effect of omega-3 fatty acids in CKD and is probably attributed to the reduction of plasma levels of 20-hydroxyeicosatetraenoic acid [32]. In IgA nephropathy, omega-3 intake may reduce proteinuria and result in a more favorable prognosis. One study in patients with CKD showed that omega-3 supplementation was associated with reduced oxidative stress (seen as increased telomere length in leukocytes) [33]. In patients with CKD, during the short-term supplementation of omega-3, an increase in the so-called Pro Resolving lipid Mediators (PRM's) [31] was observed. PRM's act as active anti-inflammatory agents through a unique mechanism. Anti-inflammatory effects and reduction of oxidative stress may be key factors in reducing cardiovascular risk in CKD patients. Fish oil consumption is likely to have beneficial effects in CKD. This is attributed to its low content in saturated fatty acids and high content in linoleic acid, which is the most well-known omega-6 fatty acid with beneficial cardiovascular effects [30]. Regarding the effect on CKD progression, the VITAL-DKD study [28], as a sub-study of the VITAL [29] in diabetic patients with CKD, did not show any significant effect of daily supplementation of 1g of omega-3 fatty acids (eicosapentaenoic acid and docosahexaenoic acid) on GFR at year 5. The mean change of $_m$GFR was −12.2 (95% CI, −13.3 to −11.1) mL/min/1.73 m^2 within omega-3 fatty acids supplemented group versus −13.1 (95% CI, −14.2 to −12.0) mL/min/1.73 m2 within placebo group (difference 0.9 [95% CI, −0.7 to 2.6] mL/min/1.73 m2). These findings do not support the use of omega-3 fatty acids to preserve residual renal function and reduce CKD progression.

Current guidelines, in adults with stage 3-5 CKD, suggest the prescription of 2 g/day of LC (long chain) n-3 PUFA to lower triglycerides [11].

SUPPLEMENTS OF IRON, VITAMIN B12 AND FOLATES IN CKD

In cases of vegan or vegetarian diets, as well as in cases of iron deficiency, its (iron) supplementation is recommended [34]. Data on iron deficiency anemia in CKD are limited. Actually, understanding the clinical effect of iron deficiency and its correction, independent of anemia, is recommended by experts as an area of primary interest for research [35]. Intravenous (iv) iron administration, compared to oral administration, is more efficient in terms of deficit correction, ESA demand reduction and has a good safety profile.

Regarding iron supplements and CKD progression, one study of interest is REVOKE, which questioned whether intravenous (iv) iron supplements accelerated the GFR decline compared to oral supplements. This study compared ferrous sulfate 325 mg 3 times/day for eight weeks, with iv iron sucrose 200 mg every two weeks (total 1g). The likelihood of a 50% reduction in eGFR after two years was low, and the results of this study were non-conclusive. Because of a higher risk of infections and cardiovascular complications after iv iron supplementation, its oral administration was the preferred route in patients with stage 3 & 4 CKD and iron deficiency anemia. The results of a 1-year analysis in the FIND-CKD study support the conclusion that the correction of iron deficiency anemia with iv ferric carboxymaltose is safe in non- dialysis CKD patients [36].

In ischemic CKD on subjects with congestive heart failure, known as a cardiorenal syndrome, iron supplementation in patients with its deficiency is associated with improved renal function[37].

Vit B6, Vit B12 and folates have received special attention in relation to cardiovascular disease in CKD, as they reduce serum levels of homocysteine (participating in its conversion to methionine). Also, vegetarian or vegan diets do not contain Vit B12, therefore its supplementation is necessary in cases of deficiency. Regarding the effect of folic acid, a randomized controlled trial tested (as a sub-study of a larger study) the effects of folic acid supplementation on the progression of CVD [38]. 15,104 participants (sub-study) with stage 3 CKD, with high blood pressure, under ACE inhibitor (enalapril) were randomly divided into two groups. One group received 0.8 mg/day folic acid added to usual 10 mg Enalapril for an average period of 4.4 years. Folic acid intake resulted in a significant (adjusted) risk reduction for CKD progression (HR, 0.45 [95% CI, 0.27-0.76]; P = 0.003 [38]. This study did not include a control group with placebo and this has been considered one of its drawbacks. Meanwhile, two other

randomized, controlled trials have not found any positive effect of folic acid supplementation, Vit B_6 and Vit B_{12} on the risk of starting dialysis treatment (achieving ESRD) [39,40].

Recent guidelines, in patients with stage 1-5 CKD, suggest the prescription of folate, Vit B_{12} and/or Vit B-complex, to correct the lack/insufficiency of folates or Vit B_{12} based on the signs and clinical symptoms [11].

Routine folate or Vit B-complex supplementation is not recommended. In relation to zinc and selenium supplements, in adults with stage 1-5 CKD, guidelines do not suggest their routine supplementation, as there is very little evidence that this intervention would improve the nutritional and inflammatory state [11].

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