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Research Article

The Impact of Ketoanalogues on Nephropathy Progression in Advanced Chronic Kidney Disease Older Patients

Gustavo Aroca-Martinez[1-3], Angélica Sierra[1,2], Luis Barros-Camargo[4,5], Adolfo Pertuz-Pinzon[4,5], Daniela Dianda[2], Andrés Cadena-Bonfanti[1,2] and Carlos G Musso[1,6]*

[1]*Facultad de Ciencias de la Salud, Universidad Simón Bolivar, Barranquilla, Colombia*

[2]*Clínica de la Costa, Barranquilla, Colombia*

[3]*Universidad del Norte, Barranquilla, Colombia*

[4]*Universidad Libre, Barranquilla, Colombia*

[5]*Asociación Colombiana de Nefrología, Colombia*

[6]*Research Department, Hospital Italiano de Buenos Aires, Buenos Aires, Argentina*

***Corresponding Author:** Carlos G Musso, Research Department, Hospital Italiano de Buenos Aires, Buenos Aires, Argentina.

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Abstract

Introduction: Advanced chronic kidney disease (CKD) can be treated with conservative care or renal replacement therapies. CKD is associated with an increased risk of nephropathy progression, and death. Therefore, slow down CKD progression is crucial, and there is consensus regarding protein intake regulation benefit in delaying this progression. Ketoanalogues are nitrogen-free analogs of essential amino acids which supplements low protein diets. Thus, it was decided to evaluate if keto diet had benefit in reducing CKD progression.

Material and Method: It was evaluated if there was a significant difference in CKD progression between two groups of stage 4-5 CKD patients: one group on keto diet, and one group with standard low protein diet. All patients received standard CKD treatment, and monthly eGFR (CKD-EPI) was documented. All evaluated parameters were compared between their initial and final values (delta value) in each group, and between the groups. Student and Wilcoxon tests were applied for data analysis.

Results: From 140 stage 4-5 CKD old patients, 38 patients were randomly assigned to keto diet, and the rest (n: 102) were assigned to standard reduced protein diet (control group). Both groups were followed up during 12 months. There was no significant difference between initial and final eGFR values neither in keto nor in control groups. Additionally, there was no significant difference between eGFR delta values between the two groups.

Conclusion: There was no significant eGFR in older CKD patients neither on keto diet nor on standard CKD diet.

Keywords: Chronic Kidney Disease; Ketoanalogues; Progression

Introduction

Chronic kidney disease (CKD) shows an increasing worldwide incidence and prevalence, becoming an important public health problem because of their related morbidity and mortality [1]. The current international consensus CKD definition from kidney disease: Improving Global Outcomes (KDIGO 2012) establishes that CKD is defined as renal abnormalities (structural and/or functional) present for more than 3 months [2]. From this perspective, CKD can be diagnosed by detecting at least one of the following four

criteria [3,4]: 1) decreased glomerular filtration rate (GFR) (<60 ml/min/1.73 m^2), 2) increased albuminuria (albumin - creatinine urine index ≥ 30 mg/g) and/or renal hematuria (dysmorphic erythrocytes), 3) serum electrolytes abnormalities due to renal tubular disorders, 4) structural abnormalities detected by renal biopsy or imaging.

Nowadays, patients older than 65 years constitute a significant and growing proportion of the CKD population, a phenomenon which could be explained due to the increasing people longevity, and the improvements achieved treating cardiovascular and oncologic diseases by current medicine [5,6].

Advanced chronic nephropathy, and particularly end-stage renal disease (ESRD) can be associated with serious complications such as anemia, hyperkalemia, hyponatremia, generalized edema, hypocalcemia, hyperphosphatemia, hyperparathyroidism, metabolic acidosis, and symptomatic uremia. In order to avoid the abovementioned complications, alternative therapies currently available for treating this condition includes conservative care or renal replacement therapies (chronic dialysis or kidney transplant) [6].

In addition, CKD is mainly associated with an increased risk of nephropathy progression, death from any cause, cardiovascular death, and acute kidney damage, particularly when patients present pathologic albuminuria, and GFR lower than 45 ml/min/1.73 m^2) [2].

Even though CKD "progression" has been defined in various ways, the most used one is based on the annually reduction of estimated GFR (eGFR). Then, based on the previously mentioned definition CKD progression is considered to be absent (<1 ml/min/1.73 m^2), low (1-3 ml/min/1.73 m^2), moderate (3-5 ml/min/1.73 m^2), or high (≥6 ml/min/1.73 m^2) depending on the eGFR annually reduction rate. Among the main factors reported as associated to CKD progression are diabetes mellitus, older age, systolic hypertension, cardiac failure, as well as proteinuria, and anemia levels. However, it is still controversial the association of cigarette smoking or dyslipidemia with nephropathy progression.

In this sense, the therapeutic objective of slow down CKD progression rate is crucial since the more rapid is CKD progression the worse patient´s clinical outcomes (cardiovascular events and death) are, independently of his/her level of eGFR [7].

Protein intake regulation is the central point of the nutritional treatment in CKD. Its objective is to reduce acidemia, hyperphosphatemia, uremic toxins load (hyperazoemia), and consequently uremia toxicity, avoiding simultaneously malnutrition. In addition, there is consensus regarding the benefit of protein restriction to delay CKD progression, and consequently dialysis requirement [8-10]. It is crucial for human beings to obtain proteins through the diet with essential amino acids, since from total amino acids individuals are only capable of synthesizing nine of them (non-essential amino acids) [11].

Ketoanalogues are nitrogen-free analogs of essential amino acids (without amino groups), whose administration limits protein synthesis avoiding body overload with protein-rich food [12,13]. The "keto diet " refers to a variety of ketoanalogues which supplements low protein diets (LPD): 0.6g/kg per day, or very low protein diets (VLPD) 0.3-0.4g/kg per day). These diets allow a reduced nitrogen intake while avoiding the deleterious consequences of inadequate dietary protein intake and malnutrition. These diets have been shown to be effective in reducing kidney death in selected, well-nourished, CKD patients with low comorbidity, and proven diet adherence; although there is some controversy regarding its benefit in reducing CKD progression [7].

Therefore, it was decided to performed a prospective study in order to evaluate if there would be a significant difference in chronic nephropathy progression between two groups of stage 4 CKD patients which were one on standard reduced protein diet (0.8g/kg/day), and the other on keto diet with LPD.

Material and Method

From a group of CKD patients (stages 3-5) who were assisted by the nephroprevention program of Clinica de la Costa in Barranquilla (Colombia), it was proposed to those patients who were on stage 4-5 CKD (eGFR <30 ml/min/1.73m^2) to receive nephroprevention treatment based on keto diet (Ketosteril) with LPD (0.6g/kg per day).

Then, from those patients who accepted to be on keto diet, one group was randomly assigned to this treatment (keto group), while and the rest was assigned to the standard reduced protein diet for CKD patients: 0.8g/kg/day (control group).

Both study groups also received standard nephroprevention treatment, which entailed treatment of anemia (erythropoietin, iron supply), hypertension (low sodium diet, antihypertensive drugs), dyslipidemia (statins), diabetes mellitus (insulin), metabolic acidosis (bicarbonate supply), serum sodium (loop diuretics), potassium (cationic resins), calcium (calcium supply, calcitriol), phosophorus (phosphorus binders), hyperparathyroidism (cinacalcet), as well as glomerular hyperfiltration (enalapril or losartan).

In all the studied patients, weight, serum hemoglobin, creatinine, urea, sodium, potassium, calcium, phosphorus, were monthly obtained, and eGFR was calculated by applying CKD-EPI equation based on serum creatinine. Besides, serum parathyroid hormone was also measured every three months.

In the keto group particular parameters were monthly obtained, such as abdominal perimeter, body mass index, lean mass and fat mass percentage (impedanciometry).

Dietary compliance was monthly controlled, and patients were followed for up to 12 months (since January 2020 to January 2021).

All evaluated parameters were compared between their initial value (January 2020) to their final value (January 2021) in both, keto and control groups. Additionally, difference between initial and final value (delta value) for each parameter were also compared between keto and control groups.

Student and Wilcoxon tests were applied for data analysis, and p value <0.05 was considered statistically significant.

Informed consent was obtained from all patients included in the study and this study was approved by the Ethics Committee of the Clínica de la Mujer, Bogotá (Colombia).

Results

From 800 CKD patients (stages 3-5) assisted by the nephroprevention program of Clínica de la Costa in Barranquilla (Colombia), 140 stage 4-5 CKD patients accepted to participate in this study, and 38 were randomly assigned to the keto diet with LPD treatment (x: 9 tablets/day), and the rest (n: 102) were assigned to the standard reduced protein diet (control group). Both groups were followed up during 12 months.

In the study population there was moderate proteinuria, and the more prevalent comorbidities were hypertension (84%), and diabetes mellitus (29%).

Keto group (n: 38) had a mean age of 72 years (range 38-94), and 55% were male, while control group (n: 102) had a mean age of 72 years (range 39-94), and 44% were male.

There was no significant difference between initial eGFR (x: 19.8 ± 6 ml/min/1.73 m^2), and final eGFR (19.2 ± 8 ml/min/1.73 m^2) values in keto group. Similarly, there was no significant difference between initial eGFR (x: 20.2 ± 7 ml/min/1.73 m^2), and final eGFR (19.4 ± 7 ml/min/1.73 m^2) values in control group. There was no significant difference between final eGFR and initial eGFR values (delta eGFR) between the two groups. In the keto group, particular nutritional parameters were obtained, such as body mass index, abdominal perimeter, fat mass and lean mass percentage. All these parameters were in normal range, and showed no significant difference between their initial and final value (Table 1).

In both groups, all the evaluated serum parameter were in normal range, except for serum hemoglobin, and initial albumin which were reduced, as well as serum urea, creatinine, and intact parathyroid hormone which were elevated. There was no significant difference between the initial and the final value of each parameter in both studied groups (Tables 2 and 3).

There was no significant difference between delta value (final - initial) of each parameter between the two groups, except for urea (delta: - 4.9, p = 0.02), and albumin (delta: - 0.38, p = 0.007) parameters, which means that there was a significant comparative increased after 12 months in serum urea and albumin values in the keto group. Neither significant changes in nutritional status nor adverse reactions due to the prescribed treatment were documented in the keto group.

Discussion

Prevention of CKD progression is currently one of the main objectives of chronic nephropathy treatment, and keto diet has been proposed by different studies as an effective therapy to slow down this progression. This phenomenon has been supported by the finding that restricted protein diets can delay CKD progression by reducing albuminuria and renal fibrosis [14-16]. This prospective study was performed in order to add more evidence regarding keto diet impact on CKD progression in pre-ESRD patients. It was found that there was no significant change in eGFR (eGFR reduction rate <1 ml/min/1.73 m^2) after 12 months neither in the keto group nor in the control group (standard nephroprevention treatment). Besides, since all the evaluated nutritional parameters (body weight, abdominal perimeter, fat mass percentage, lean mass percentage,

seru albumin) were preserved after 12 months of keto diet treatment, it was documented that this diet was able to preserve an adequate nutritional status in CKD patients (Tables 1 and 2). Even more, the significant relative increased observed in serum urea and albumin without increase in eGFR after 12 months of keto diet can be interpreted as a nutritional improvement secondary to this treatment. This very important since reinforce the concept that keto diet is a safe alternative treatment to chronic dialysis particularly in the oldest old [8].

To the best of our knowledge, this is the study that has evaluated the impact of keto diet on nephropathy progression in the oldest CKD population (72 ± 20 years) on any study until date.

It is worth mentioning that most of the previously performed studies included mainly young adult patients, except for Qiu., *et al.* study whose studied population had 63 ± 9 years old. In addition, our study is the second one in number of studied patients (n: 140), after Garneata., *et al.* study (n: 207) [7].

Even though in our study it was documented no significant change in eGFR value between keto diet and control groups, it was also documented no significant eGFR reduction along 12 moths of follow up, and this is an important finding in an aged population since older CKD patients particularly suffered a greater renal damage progression than the younger people [17].

Menon., *et al.* had also reported that a very low-protein diet did not delay CKD progression [18]. In addition, Malvy., *et al.* documented that a severe protein restriction (0.3 g/kg/day) supplemented by ketoanologues did not limit GFR decrease when GFR is below 20 mL/min/1.73m^2 [19]. Conversely, Li., *et al.* recently have published a meta-analysis, based on 12 studies, where they found that a restricted protein diet supplemented with ketoanalogues could slow down CKD progression in pre-ESRD patients (eGFR > 18 mL/min/1.73 m2) without inducing malnutrition [7]. Therefore, the benefit of ketoanalogues on reversing CKD progression remains inconclusive, and further research is needed in this field.

Regarding other biochemical parameters usually controlled in CKD follow-up, such as serum sodium, potassium, calcium, phosphorus, and parathyroid hormone, they were in normal range, and no significant difference was documented in none of them between the compared CKD groups. Jiang., *et al.* found that keto diet significantly reduced serum phosphorous and parathyroid hormone levels but did not change serum calcium level [8]. However, Li., *et al.* reported, in coincidence with our study, no significant difference in serum phosphorous, calcium, and PTH between pre-ESRD patients on keto diet and placebo group [7]. Therefore, there are controversial findings also in this point, and further research is also needed in this field.

Parameters	Mean SD	P-value
BMI	a: 25.7 ± 4 b: 25.8 ± 4	NS
Abdominal perimeter(cm)	a: 93.7 ± 11 b: 96.2 ± 10	NS
Fat mass (%)	a: 36.7 ± 9 b: 37.5 ± 9	NS
Lean mass (%)	a: 63.2 ± 9 b: 62.4 ± 9	NS

Table 1: Nutritional parameter in keto group.

Parameters	Mean SD	P-value
Body weight (kg)	a: 67.3 ± 14 b: 67.7 ± 14	NS
Hemoglobin (g/dl)	a: 11.5 ± 1.6 b: 11.4 ± 1.4	NS
Serum urea (mg/dl)	a: 71.8 ± 12 b: 81.6 ± 17	NS
Serum creatinine (mg/dl)	a: 3.0 ± 1 b: 3.1 ± 1.2	NS
Serum potassium (mmol/L)	a: 4.8 ± 0.5 b: 4.7 ± 0.4	NS
Serum sodium (mmol/L)	a: 140.4 ± 3 b: 140.6 ± 2	NS
Serum calcium (mg/dl)	a: 9.4 ± 0.5 b: 9.4 ± 0.4	NS
Serum phosphorus (mg/dl)	a: 3.9 ± 0.6 b: 3.9 ± 0.7	NS
PTHi (pg/dl)	a: 109.7 ± 111 b: 85.3 ± 78	NS
Serum albumin (g/dl)	a: 3.9 ± 0.1 b: 4.3 ± 0.2	NS
serum glucose (mg/dl)	a: 97.2 ± 23 b: 101.1 ± 12	NS

Table 2: Main evaluated parameter in keto group.

a: Initial; b: Final; PTHi: Intact Parathyroid Hormone

Parameters	Mean SD	P-value
Weight (kg)	a: 62.4 ± 14 b: 63.6 ± 15	NS
Hemoglobin (g/dl)	a: 10.7 ± 1.8 b: 11.5 ± 1.6	NS
Serum urea (mg/dl)	a: 78.8 ± 22 b: 73.2 ± 62	NS
Serum creatinine (mg/dl)	a: 2.8 ± 0.8 b: 2.9 ± 1.3	NS
Serum potassium (mmol/L)	a: 4.3 ± 0.5 b: 4.3 ± 0.6	NS
Serum sodium (mmol/L)	a: 141 ± 1.4 b: 141 ± 3.2	NS
Serum calcium (mg/dl)	a: 9.3 ± 0.5 b: 9.2 ± 0.4	NS
Serum phosphorus (mg/dl)	a: 4.2 ± 0.9 b: 4.3 ± 0.6	NS
PTHi (pg/dl)	a: 39.5 ± 17 b: 40.8 ± 15	NS
Serum albumin (g/dl)	a: 3.2 ± 0.8 b: 4.6 ± 1.6	NS
Serum glucose (mg/dl)	a: 82.6 ± 10 b: 94.4 ± 27	NS

Table 3: Main evaluated parameter in control group.

Conclusion

There was no significant estimated glomerular filtration rate in older chronic kidney disease patients neither on keto diet nor on standard chronic nephropathy diet.

Compliance with Ethical Standards

- The authors declare that they have no conflict of interest.
- No funds were received for performing this study.

Ethical Approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent was obtained from all the participants included in the study.

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