Inflammatory, nutritional and clinical parameters of individuals with chronic kidney disease undergoing conservative treatment

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Abstract

Introduction: due to the relevance of inflammation in individuals with chronic kidney disease (CKD), inflammation should be taken into account in the interpretation of the clinical-nutritional status.

Objective: assess the association between inflammation, nutritional and clinical parameters in patients with CKD.

Materials and methods: 92 patients with CKD. C-reactive protein (CRP) was used as an inflammation marker. Assessed nutritional parameters were anthropometry and biochemical exams. Evaluated clinical parameters were comorbidities, CKD characteristics, lipid profile, lipid-lowering agents, urea, creatinine and total leukocytes. Comparisons between two groups (with or without inflammation) were performed using Student’s t-test or chi-square test.

Results: 15 (16.3%) patients had CRP above ≥ 10mg/L and were considered with inflammation. In the group with inflammation, 05 (33%) had hypoalbuminemia compared with 05 (6.5%) in the group without inflammation (p = 0.002). Lipid values were lower in the group with inflammation, with mean total cholesterol 171 (± 41.2) mg/dL and mean LDL-C 95 (± 31.2) mg/dL as compared with the group without inflammation, which had a mean total cholesterol 198 (± 46) mg/dL and mean LDL-C 124 (± 40.1) mg/dL, p = 0.038 and p = 0.011, respectively. No other statistically significant differences between groups were found.

Conclusion: inflammation was associated with changes in the total cholesterol and LDL levels and with an increased incidence of hypoalbuminemia. We suggest that serum albumin levels should only be used to assess nutritional status in the absence of inflammation and...
CRP levels ought to be considered in nutritional status interpretation in patients with CKD.

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Key words: Chronic kidney disease. C-reactive protein. Inflammation. Nutritional status. Hypoalbuminemia.

Introduction

In patients with chronic kidney disease (CKD), inflammation contributes to the pathogenesis of atherosclerosis and is a predictor of cardiovascular events and increased mortality rate. Clinical reports suggest that inflammatory mediators may induce anorexia, anemia, muscle proteolysis, and reduced protein production, resulting in hypoalbuminemia and malnutrition.

The results of a study conducted with individuals with CKD suggested that inflammation can lead to the misinterpretation of nutritional markers as a result of muscle proteolysis, particularly anthropometric indicators of body composition. Inflammation can also alter biochemical markers, including serum albumin, hemoglobin, transferrin and ferritin levels.

Due to the relevance of inflammation in individuals with CKD, inflammation should be taken into account in the interpretation of the clinical-nutritional status of patients and in the development of therapeutic interventions. C-reactive protein (CRP) has been widely used as a serum marker of inflammation and is considered a reliable biomarker of inflammation and atherosclerotic cardiovascular disease.

The relationship between inflammation and nutritional and clinical parameters is not well understood in CKD patients not undergoing dialysis. Therefore, the aim of the present study was to establish whether a relationship exists between inflammatory markers and nutritional and clinical parameters in CKD patients undergoing conservative treatment.

Materials and methods

Design and sampling

The present cross-sectional study was conducted in a university hospital nutrition and nephropathy outpatient clinic, between September 2012 and November 2013. The study included clinically stable, from both genders, adult (≥ 20 and < 60 years old) and elderly adult (≥ 60 years old) outpatients with glomerular filtration rates (GFRs) between 15 and 89 ml/min/1.73 m².

The exclusion criteria were as follows: admission to a hospital within the past month, limb amputation, malignant disease, chronic infectious disease, acquired immunodeficiency syndrome, history of dialysis or transplantation, use of immunosuppressant drugs, acute kidney failure, severe liver failure, leukocytosis (defined as total leukocit count higher than 10,000 cells/mm³) and terminal CKD.

Data collection

Data collection was standardized and performed by previously trained nutrition trainees and nutritionists. Anthropometric measurements included body weight and height, as recommended by the World Health Organization. Body height and weight were used to calculate the body mass index (BMI), which was evaluated using the cutoff points suggested by the WHO for adults and older adults, based on the classification recommended by Nutrition Screening Initiative (NSI). For adult patients, four skinfolds measurements were summed, and for elderly patients, the tricipital skinfold measurement alone was taken. Corrected arm muscle area was calculated for adult patients, whereas arm muscle circumference was calculated for elderly patients. Waist circumference (WC) was calculated for all patients.

All biochemical tests were performed in the hospital laboratory. Hemoglobin, total protein serum levels and albumin serum levels, urea, creatinine, lipid profile and CPR levels were evaluated. The albumin serum levels were measured by bromocresol green method. Inflammation was evaluated through the measurement of CRP levels by turbidimetry, and the patients were defined as inflamed if CRP ≥ 10 mg/L. Serum urea levels were measured enzymatically and the serum creatinine levels were measuring using the modified Jaffe method. The lipid profile included measurements of total cholesterol (TC), cholesterol fractions and triglycerides (TG), following the recommendations of the National Cholesterol Education Program. The serum TC and TG levels were measured by means of an automated enzymatic method using a colorimetric assay. The high-density lipoprotein (HDL) level was measured by means of the direct method, and the low-density lipoprotein (LDL) and very low-density lipoprotein (VLDL) levels were estimated using the Friedewald equation.

Clinical data were collected from patients’ charts and included time since CKD diagnosis in months, estimated GFR, presence of diabetes mellitus and use of hypolipidemic drugs. Demographic data, such as age and gender, and behavioral data, including smoking and physical activity level, were also evaluated.
Statistical Analysis

For statistical analysis, the Kolmogorov–Smirnov test was used to determine if the data followed a normal (parametric) or non-normal (non-parametric) distribution. The data were expressed as the mean and standard deviation or as the median and interquartile range in the case of the continuous variables and as percentages in the case of the categorical variables.

Comparisons between two groups (with or without inflammation) were performed using Student’s t-test in the case of parametric data and the Mann-Whitney test in the case of non-parametric data. Proportions were compared by means of the chi-square or Fisher’s exact test.

The significance level was set to 5% (p≤ 0.05) in all of the analyses. The analyses were performed using the statistical package SPSS version 20.0®.

The study protocol was approved by the research ethics committee.

Results

Among 92 patients evaluated, 50 (54.3%) were male and elderly, 71 (77.2%) were sedentary and 6 (6.5%) were smokers. The median CRP value was 2.5 mg/L [0.1-7.0 mg/L]. 15 (16.3%) patients had CRP ≥ 10 mg/L and were considered with inflammation, 77 (83.7%) had CRP < 10 mg/L and were considered without inflammation. In the group exhibiting inflammation, 9 (60%) of the participants were male, the mean age was 63.4 (±10.3) years old, 10 (66.7%) were elderly and sedentary patients, and 2 (13.3%) were smokers. Statistically significant differences were not detected between the groups with respect to the demographic and behavioral characteristics.

In the nutritional parameters analysis, 5 (33.3%) in the inflammation group as compared with 5 (6.5%) in the group without inflammation had serum albumin level < 3.8 mg/dL (p = 0.002). Anthropometric indicators, BMI and body composition were not different between groups. The mean WC values were not different between groups. Half of patients with inflammation had increased WC as compared with 41.7% in the group without inflammation (Table II).

Lipid values were lower in the inflammation group, with mean total cholesterol 171 mg/dL (± 41.2) and mean LDL-C 95 mg/dL (± 31.2) as compared with non-inflammation group, which had a mean total cholesterol 198 mg/dL (± 46) and mean LDL-C 124 mg/dL (± 40.1) (p = 0.038 and p = 0.011, respectively). 9 (60%) of patients with inflammation were using hypolipidemic drugs.

No other statistically significant differences between groups were found.

Discussion

The prevalence of chronic inflammation is high among individuals with CKD, including patients not undergoing dialysis, and is strongly associated with morbidity and mortality. Several factors influence this association, including with the presence of uremia, metabolic acidosis and infection.

CRP is the most frequently used markers of inflammation and is associated with an increased risk of cardiovascular disease and mortality in the overall population and among individuals with CKD. In the present study, 16.3% of the participants exhibited CRP ≥ 10 mg/L, which indicates that predialytic patients may exhibit inflammation. A Swedish study that applied the same CRP cutoff value as the present study reported that the prevalence of inflammation was 36% among the 300 CKD participants. These findings suggest that inflammation might contribute to the clinical and nutritional complications exhibited by this population of patients.

An association between nutritional parameters and inflammatory markers has been reported in both the overall population as well as among individuals undergoing dialysis. However, few studies have investigated this association in CKD patients undergoing conservative treatment.

We did not detect any association between CRP and BMI, which is consistent with the results of a study conducted in India involving 100 CKD patients undergoing conservative treatment.
In individuals undergoing conservative treatment, inflammation may activate catabolic pathways, thereby causing a reduction in lean body mass. In the present study, we did not observe an association between inflammation and insufficient muscle mass in CKD patients not undergoing dialysis.

Although central obesity is associated with inflammation, insulin resistance, dyslipidemia and oxidative stress among CKD patients, in the present study we did not observe any relationship between high CRP levels and WC. The mean WC in the group with inflammation was higher than the group without inflammation (94.9 cm (±16.4) vs. 91.0 cm (±12.8); respectively); however, the difference was not statistically significant. Contrary to the results of the present study, Chen and colleagues (2013) reported a positive association between WC and CRP. CRP was also found to be positively associated with WC in a group of 44 individuals with stage 3 or 4 CKD.

Outpatient nutritional follow-up may have contributed to the results of the present study, as dietary pattern can influence inflammation.

Table II

<table>
<thead>
<tr>
<th>Variables</th>
<th>Total 92</th>
<th>Inflammation</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMI (kg/m²)²</td>
<td>25.3 (4.8)</td>
<td>25.1 (4.9)</td>
<td>25.3 (4.8)</td>
</tr>
<tr>
<td>Waist circumference (cm)²</td>
<td>91.7 (13.4)</td>
<td>94.9 (16.4)</td>
<td>91.0 (12.8)</td>
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<tr>
<td>Muscle tissue (cm)¹</td>
<td>33 (35.9)</td>
<td>05 (33.3)</td>
<td>28 (36.4)</td>
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<tr>
<td>Adipose tissue (mm)¹</td>
<td>40 (44.4)</td>
<td>05 (33.3)</td>
<td>35 (46.7)</td>
</tr>
<tr>
<td>Arm circumference¹</td>
<td>32 (35.2)</td>
<td>07 (46.7)</td>
<td>25 (32.9)</td>
</tr>
<tr>
<td>Total proteins (g/dl)¹</td>
<td>7.6 (0.65)</td>
<td>7.6 (0.74)</td>
<td>7.6 (0.74)</td>
</tr>
<tr>
<td>Albumin (g/dl)³</td>
<td>4.2 (4.1-4.5)</td>
<td>4.2 (3.7-4.6)</td>
<td>4.3 (4.1-4.5)</td>
</tr>
<tr>
<td>Hipoalbuminemia (%)¹</td>
<td>10 (10.9)</td>
<td>05 (33.3)</td>
<td>05 (6.5)</td>
</tr>
<tr>
<td>Hemoglobin (g/dl)²</td>
<td>11.8 (1.8)</td>
<td>11.3 (2.4)</td>
<td>11.9 (1.7)</td>
</tr>
</tbody>
</table>

¹Percent, X² test; ²mean and standard deviation, Student's t-test; ³median and interquartile range, Mann-Whitney test.

Table III

<table>
<thead>
<tr>
<th>Variables</th>
<th>Total 92</th>
<th>Inflammation</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetes (%)¹</td>
<td>38 (41.3)</td>
<td>05 (33.3)</td>
<td>33 (42.9)</td>
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<tr>
<td>CKD duration (months)³</td>
<td>48 (12-120)</td>
<td>72 (12-144)</td>
<td>42 (12-105)</td>
</tr>
<tr>
<td>eGFR (ml/min)²</td>
<td>39.7 (19.5)</td>
<td>43.5 (23.3)</td>
<td>38.9 (18.7)</td>
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<tr>
<td>CKD stages 3 and 4 (%)³</td>
<td>81 (88.0)</td>
<td>13 (86.7)</td>
<td>68 (88.3)</td>
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<tr>
<td>Total cholesterol (mg/dl)²</td>
<td>194.3 (46.2)</td>
<td>171.7 (41.2)</td>
<td>198.7 (46.0)</td>
</tr>
<tr>
<td>LDL (mg/dl)²</td>
<td>119.5 (40.0)</td>
<td>95.8 (31.2)</td>
<td>124.1 (40.1)</td>
</tr>
<tr>
<td>HDL (mg/dl)²</td>
<td>45.4 (13.9)</td>
<td>44.6 (14.1)</td>
<td>45.6 (13.9)</td>
</tr>
<tr>
<td>TG (mg/dl)³</td>
<td>131 (95.5-183)</td>
<td>197</td>
<td>183</td>
</tr>
<tr>
<td>TG/HDL ratio³</td>
<td>3.3 (1.8-5.0)</td>
<td>3.7 (1.7-5.7)</td>
<td>3.2 (1.8-5.0)</td>
</tr>
<tr>
<td>Use of hypolipidemic drugs (%)³</td>
<td>41 (44.6)</td>
<td>09 (60)</td>
<td>32 (41.6)</td>
</tr>
<tr>
<td>Urea (mg/dl)²</td>
<td>80.5 (42.1)</td>
<td>81.2 (44.3)</td>
<td>80.4 (42.0)</td>
</tr>
<tr>
<td>Creatinine (mg/dl)²</td>
<td>2.02 (1.1)</td>
<td>1.8 (1.0)</td>
<td>2.0 (1.1)</td>
</tr>
<tr>
<td>Leukocyte count (/mm³)²</td>
<td>6829.2 (1855.6)</td>
<td>1932.8</td>
<td>(1850.3)</td>
</tr>
</tbody>
</table>

¹Percent, X² test; ²mean and standard deviation, Student's t-test; ³median and interquartile range, Mann-Whitney test.
With respect to clinical parameters, the frequency of hypoalbuminemia (serum albumin < 3.8 mg/ml) was higher in the group with inflammation. Abraham et al, 2009, reported similar results, with higher CRP levels among the participants with lower serum albumin levels. Furthermore, other studies have reported an association between increased levels of CRP and a reduction in the serum albumin concentration.

The National Kidney Foundation Kidney Disease Outcomes Quality Initiative (NKF/KDOQI) recommends that the routine assessment of the nutritional status should be based on the serum albumin level. Nevertheless, some studies have found that serum albumin levels decrease in individuals with inflammation.

Our results support an association between inflammation and hypoalbuminemia. In individuals with CKD, hypoalbuminemia is mainly associated with inflammation and thus does not necessarily indicate dietary inadequacy. Therefore, serum albumin is considered a poorly sensitive marker of malnutrition. Inflammation induces earlier changes in the albumin level than does malnutrition, and early albumin changes exhibit a negative correlation with changes in CRP, as confirmed by the present study.

One study of individuals with CKD did not detect a strong correlation between nutritional status and serum albumin. The serum albumin levels were considered to a weak and limited predictor of nutritional status and were poorly correlated with other markers, such as global subjective assessment and handgrip strength.

Cardiovascular morbidity and mortality are not associated with hypoalbuminemia or inflammation. In a retrospective cohort including 452,000 CKD patients from 25 countries across five continents, most deaths were due to cardiovascular disease, and the patients who died exhibited a gradual reduction in their serum albumin levels and an increase in their CRP levels.

Other studies have reported that hypoalbuminemia and increased CRP are strong predictors of clinical prognosis and mortality. Clinical parameters, including the results of biochemical tests, can reveal clinical abnormalities in CKD patients sufficiently early to being interventions.

CKD is characterized by dysregulated lipid metabolism, oxidative stress, inflammation, and dyslipidemia. Inflammation is inversely correlated with cholesterol levels, consistent with the results of the present study. However, in the present study, 60% of the participants with inflammation were treated therapeutically with statins, which may have promoted a reduction in the TC and LDL levels. Statins are able to reduce the CRP and LDL levels as well as morbidity and mortality due to cardiovascular disease and are able to delay the progression of CKD.

Based on the results described above, we conclude that the clinical and nutritional parameters assessed in the present study ought to be evaluated in conjunction with inflammatory parameters. Most of those indicators are widely available and can be used in clinical practice.

References
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