Inflammation is associated with increased energy expenditure in patients with chronic kidney disease

Simone Unaka, Carla M Avesani, Sergio A Draibe, Maria A Kamimura, Solange Andreoni, and Lilian Cuppari

ABSTRACT

Background: Inflammation, a clinical condition observed in patients with chronic kidney disease (CKD), may be related to increased resting energy expenditure (REE).

Objectives: The main objective was to investigate the relation between inflammation and REE in patients with CKD who are not undergoing dialysis. We also aimed to analyze whether a decrease in C-reactive protein (CRP) would result in a reduction in REE.

Design: This study enrolled 132 patients with CKD who were not undergoing dialysis, who had creatinine clearance from 5 to 65 mL · min⁻¹ · 1.73 m⁻², and who were 53.6 ± 16 y old; 82 (62.1%) were men. Twenty-nine patients had clinical signs of infection. REE was measured by using indirect calorimetry, and inflammation was evaluated by using high-sensitivity CRP measurement. Patients were divided according to tertiles of CRP with the following tertile ranges: first tertile, CRP 0.15–0.59 mg/dL (n = 43); second tertile, CRP 0.55–1.39 mg/dL (n = 43); and third tertile, CRP ≥ 1.40 mg/dL (n = 43). REE was measured before and after treatment in 10 patients who had inflammation or infection.

Results: After adjustment for age, sex, and lean body mass, the REE of the third (1395 kcal/d; P = 0.02) and second (1355 kcal/d; P = 0.04) tertiles was significantly higher than that of the first tertile (1286 kcal/d). In the multiple linear regression analysis (n = 132), the independent determinants of REE were lean body mass, CRP, and age (R² = 0.55). After treatment of infection in a subgroup of 10 patients, it was observed that a significant reduction in CRP concentration was accompanied by a significant reduction of 174 ± 165 kcal that accounted for 13% of the initial REE.

Conclusion: This study showed that inflammation is associated with increased REE in patients with CKD.

INTRODUCTION

Protein-energy malnutrition is common among patients with chronic kidney disease (CKD) (1–3). The cause of malnutrition in CKD is complex and includes many factors, such as poor food intake (4, 5), enhanced protein catabolism (6), hormonal disturbances (6), and increased resting energy expenditure (REE) (7). More recently, inflammation has also been pointed to as an important factor in a worsening of the nutritional status. Clinical and subclinical infections are frequent complications that lead to an inflammatory response in patients with CKD (8).

KEY WORDS Chronic kidney disease, resting energy expenditure, inflammation, C-reactive protein, protein-energy malnutrition

SUBJECTS AND METHODS

Subjects

This study enrolled 132 nondialysis patients with CKD from the renal outpatient clinic of the Federal University of São Paulo—

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Oswaldo Ramos Foundation (São Paulo, SP, Brazil). Exclusion criteria included the following: age < 18 y, altered thyroid function, diabetes mellitus, pregnancy, and the use of corticosteroid or immunosuppressive agents. Of the entire group, 29 patients had clinical signs or laboratory data (or both) that were indicative of infection, such as urinary infection, diagnosed by positive urine culture (n = 10); gastric ulcer, diagnosed by the presence of Helicobacter pylori (n = 1); and renal tuberculosis, diagnosed by presence of the Koch bacillus in the urine sample (n = 1). Other infections were varicose ulcer (n = 2), erysipelas (n = 1), herpes zoster (n = 1), pneumonia (n = 1), pharyngitis (n = 1), and influenza (n = 11), which were diagnosed by clinical symptoms. Of the 132 enrolled patients, 118 (89.4%) were taking diuretics or both; and 43 (32.6%) were taking β-blockers. Vitamin supplementation (folic acid, B vitamins, or both) was taken by 57 patients (43.2%). A diet containing 30–35 kcal · kg⁻¹ · d⁻¹ and 0.6–0.8 g protein · kg⁻¹ · d⁻¹ had been prescribed for 111 patients (84%).

For the second part of the study, we selected the patients with the following conditions: presence of clinical sign of infection plus CRP concentrations >0.5 mg/dL and a decrease in CRP concentration after treatment of the infection condition. Of 29 patients with infections, only 10 met these criteria. This subgroup of 10 patients had infections such as influenza (n = 4), urinary infection (n = 2), pharyngitis (n = 1), pneumonia (n = 1), renal tuberculosis (n = 1), and varicose ulcer (n = 1). All patients were treated, and antibiotics were administered when appropriate.

Written informed consent was obtained from each subject. The study was approved by the Human Investigation Review Committee of the Federal University of São Paulo.

Study protocol

All patients participated in an initial interview to verify the inclusion criteria and to provide informed consent. The patients were also instructed to collect urine over a 24-h period. On the same day of REE measurement, the subjects underwent fasting blood tests (including CRP) and body-composition and nutritional assessments. In the subgroup of 10 patients, these measurements were repeated after treatment of infection. The mean interval between the 2 measurements was 102 ± 69 d.

Biochemical data

Blood samples were drawn after an overnight fast of 12 h. Serum creatinine, urea, and glucose were measured by using a standard autoanalyzer. We measured bicarbonate (normal range: 23–27 mmol/L) with an automated potentiometer, thyroid-stimulating hormone (normal range: 0.3–4.0 mIU/L) with immunofluorometric assays, and albumin (normal range: 3.4–4.8 g/dL) by using the green bromocresol technique. Intact parathyroid hormone (normal range: 10–65 pg/mL) and high-sensitivity assay for CRP (inflammatory state: >0.5 mg/dL) were ascertained by using immunochemiluminescence. In all but the 10 patients whose CRP had been measured before and after treatment of infection, only a single measurement of CRP was taken. Assay analytic sensitivity for CRP was 0.02 mg/dL, and the interassay variability was 10%, 6%, 5%, and 7% for very low, low, medium, and high values, respectively. Intraassay variation was 5%, 5.3%, 4.2%, and 6.4% for very low, low, medium, and high CRP values, respectively. Glomerular filtration rate was evaluated by using standard creatinine clearance (CrCl) corrected for body surface area (1.73 m²).

Resting energy expenditure

REE was measured by indirect calorimetry with the use of an open-circuit, ventilated, computerized metabolic system (Vmax series 29n; SensorMedics Corp, Yorba Linda, CA). Initially, the flow sensor was calibrated with a syringe piston to adjust it for measuring high and low inspiratory and expiratory flow. Before each REE measurement, the oxygen and carbon dioxide sensors were calibrated by using mixed reference gases of known composition. All subjects had been instructed to maintain their regular medication, to refrain from any unusual physical activity in the 24-h period before the test, and to maintain their usual sleep schedule the night before REE measurement. They were admitted to the clinic at 0800 after a 12-h overnight fast. After 30 min of rest in a recumbent position, subjects breathed through a clear plastic canopy, placed over their heads, for 30 min in a quiet, dimly lit, thermally neutral room. They were instructed to avoid hyperventilation, fidgeting, or falling asleep during the test. Oxygen consumption (V\text{O}_2) and carbon dioxide production (V\text{CO}_2) were measured at 1-min intervals, and the mean of the final 20 min was used to calculate REE without using the urinary urea nitrogen, according to the Weir equation (23) as follows:

\[
\text{Basal metabolic rate (in kcal/min)} = 3.9[V\text{O}_2 \text{ (in L/min)}] + 1.1[V\text{O}_2 \text{ (in L/min)}] \quad (1)
\]

\[
\text{REE (in kcal/d)} = \text{BMR} \times 1440 \text{ min} \quad (2)
\]

The intranidividual variation coefficient for REE obtained from 9 healthy subjects studied on 2 consecutive occasions was 5%. The respiratory quotient was calculated as the ratio between the volume of carbon dioxide exhaled and that of the oxygen consumed (23).

Body composition

Body composition was measured by bioelectrical impedance with the use of a portable device (Quantum model BIA 101; RJL Systems, Detroit, MI) and the FLUIDS & NUTRITION software (release 3.0; RJL Systems). The measurements were made in the morning, after a 12-h fast and while the patient was in the supine position with the arms lying parallel and separated from the trunk and the legs separated so that the thighs were not touching. Two electrodes were placed on the right hand and wrist and 2 were placed on the right foot and ankle. An electrical current of 800 μA at 50 kHz was introduced, and resistance and reactance were measured. The software provided by the manufacturer calculated the total body water, lean body mass, and body fat.

Nutritional assessment

Anthropometric measurements were performed in the morning and included body weight, height, triceps skinfold thickness, and midarm circumference. Triceps skinfold thickness was measured with the use of a Lange caliper (Cambridge Science Industries, Cambridge, MA). The measurements were performed on the nondominant arm. Midarm muscle circumference was calculated by using the following formula (24):

\[
\text{Midarm muscle circumference} = \text{arm circumference} - 0.314 \times \text{triceps skinfold thickness} \quad (3)
\]
The standard percentages of triceps skinfold thickness and of midarm muscle circumference were obtained by using the National Health and Nutrition Examination Survey percentile distribution tables adapted by Frisancho (24). Body mass index (BMI; in kg/m²) was calculated (25), and desirable body weight was calculated on the basis of data in the Metropolitan Life Insurance table as adapted by Grant et al (26).

Protein equivalent of nitrogen appearance (PNA) was measured by using 24-h urinary nitrogen urea, according to the equation of Sargent and Gotch (27) for use in patients with CKD who were not undergoing dialysis. PNA was normalized by desirable body weight.

Statistical analysis

Data are expressed as means ± SDs. Distribution of variables of interest was examined and tested for normality by using the Kolmogorov-Smirnov test. The variables not normally distributed were log transformed (natural base), and their values are shown as geometric means and ranges. Pearson’s correlation analysis for the whole group (n = 132) was performed to ascertain which variables had linear correlation with REE and CRP. Multiple linear regression analysis was applied to evaluate the determinants of REE in the whole group. Variables tested in the regression model were those that correlated significantly with REE or those that are known to influence REE. The whole group was subdivided according to CRP tertile, by the following intertertile ranges: first tertile, CRP ≤ 0.14 mg/dL; second tertile, CRP: 0.15–0.59 mg/dL; and third tertile, CRP ≥ 0.60 mg/dL.

RESULTS

The main characteristics of the 132 patients are shown in Table 1. Overall, patients did not show signs of malnutrition, because the mean standard percentages of midarm muscle circumference and the standard percentages of triceps skinfold thickness were within the normal range. In addition, BMI was indicative of overweight. The protein intake evaluated by normalized PNA was higher than the amount of protein prescribed, indicative of overweight. The protein intake evaluated by normalized PNA was higher than the amount of protein prescribed, indicative of overweight. BMI was calculated on the basis of data in the Metropolitan Life Insurance table as adapted by Frisancho (24). Body mass index (BMI; in kg/m²) was calculated (25), and desirable body weight was calculated on the basis of data in the Metropolitan Life Insurance table as adapted by Grant et al (26).

TABLE 1

<table>
<thead>
<tr>
<th>Characteristics of the patients¹</th>
<th>Mean [n (%)]</th>
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<tbody>
<tr>
<td>Age (y)</td>
<td>53.6 ± 16²</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td>49.5: 50.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BMI</td>
<td>26.0 ± 4.5</td>
<td></td>
<td></td>
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<tr>
<td>Serum creatinine (µmol/L)</td>
<td>111.0 ± 55.5</td>
<td></td>
<td></td>
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<tr>
<td>Creatinine clearance (mL/min)</td>
<td>30.2 ± 14.3</td>
<td></td>
<td></td>
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<tr>
<td>Albumin (g/dL)</td>
<td>4.1 ± 0.4</td>
<td></td>
<td></td>
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<tr>
<td>CRP (mg/dL)</td>
<td>0.31 (0.01–0.92)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>REE (kcal/d)</td>
<td>1346 ± 222</td>
<td></td>
<td></td>
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</tbody>
</table>

¹ n = 132. MAMC, midarm muscle circumference; TSF, triceps skinfold thickness; nPNA, normalized protein equivalent of nitrogen appearance; TSH, thyroid-stimulating hormone; CRP, C-reactive protein; REE, resting energy expenditure.

² x ± SD (all such values).

Geometric x; range in parentheses.

TABLE 2

<table>
<thead>
<tr>
<th>Multiple linear regression analysis with resting energy expenditure (REE) as a dependent variable¹</th>
<th>Coefficient, kcal</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lean body mass</td>
<td>15.8</td>
<td>11.6, 20.1</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Age</td>
<td>27.1</td>
<td>5.71, 48.5</td>
<td>0.01</td>
</tr>
<tr>
<td>Sex</td>
<td>−2.56</td>
<td>−4.37, −0.76</td>
<td>0.006</td>
</tr>
<tr>
<td>nPNA</td>
<td>49.5</td>
<td>−43.2, 142.2</td>
<td>0.29</td>
</tr>
<tr>
<td>Intercept</td>
<td>79.6</td>
<td>−61, 220</td>
<td>0.26</td>
</tr>
</tbody>
</table>

¹ n = 132. CRP, C-reactive protein; nPNA, normalized protein equivalent of nitrogen appearance. R² = 0.55.
Creatinine clearance by Student’s paired t test. CRP, C-reactive protein.

The results of this study show that inflammation was associated with increased REE in patients with CKD who were not undergoing dialysis. In fact, REE was significantly higher in the patients who have undergone long-term hemodialysis (16). On the contrary, in the current study, we did not find any association between CRP and nutritional indicators of muscle mass, and no differences in lean body mass were observed among the CRP tertiles. The low-sensitivity methods used for assessing muscle mass and the cross-sectional design of this study can partly explain the lack of association between CRP and muscle mass indicators. Moreover, a chronic inflammatory condition rather than occasional inflammation might be necessary for a negative effect on the muscle to be observed. However, in the current study cannot be fully identified. However, if one considers the metabolic disorders of the inflammatory response, such as fever (29), elevated V̇O₂ (29), enhanced lipolysis and fat utilization (17), elevated concentration of catabolic hormones, and extensive protein catabolism (15), an elevation in REE can be expected. In addition, the maintenance of immune function was estimated to account for as much as 15% of daily energy expenditure (30). Thus, the deleterious effects of the inflammatory response can result in loss of body proteins and ultimately in malnutrition. This possibility is in accordance with the concept that the metabolic derangements of CKD (ie, inflammation, metabolic acidosis, and insulin resistance) are involved in the loss of body proteins that often is observed in these patients (6). Indeed, a negative correlation between inflammatory markers and increased REE also was observed in other diseases, such as AIDS with opportunistic infections (20), rheumatoid arthritis (21), sepsis (18), and pancreatic cancer (19). Similar results in patients with CKD with a low degree of inflammation were observed recently by our group (22).
study, we observed that patients with elevated CRP (second and third tertiles) had a higher amount of markers of body fat. In addition, CRP correlated directly with markers of fat mass, such as BMI and a standard percentage of triceps skinfold thickness. These associations may be related to inflammatory cytokines released by adipose tissue (31). Similar results have been reported in the general population (32) and more recently in patients with CKD who were not undergoing dialysis (33).

Finally, to investigate whether inflammation leads to increased REE, we evaluated REE after treatment of infection in a subgroup of 10 patients. This analysis showed that a significant decrease in CRP was accompanied by a significant reduction in REE of $\pm 13\%$. Because lean body mass, the greatest determinant of REE, did not change during the treatment, we can attribute the reduction in REE to a decrease in CRP concentration.

The importance of our findings relates to the deleterious effects of a sustained elevated REE. Besides its negative effect on nutritional status, increased REE has been associated with a high rate of mortality in patients who receive dialysis. In a group of 251 patients receiving continuous ambulatory peritoneal dialysis, it was found that those with higher REE had a rate of mortality higher than that in patients with lower REE (34). In addition, our findings highlight the importance of treating infection, because it might lead to an elevation of REE and thereby become another factor that contributes to aggravating the nutritional condition.

In conclusion, our findings showed that inflammation was associated with increased REE and that the reduction of CRP, subsequent to the treatment of subjacent infection, was accompanied by a significant decrease in REE. Further prospective studies focusing on treatment of chronic inflammation in patients with CKD could contribute to a better understanding of the effects of inflammation on both REE and malnutrition.

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SU and CMA were responsible for the data collection, interpretation of the results, and writing of the manuscript. SAD and MAK contributed to the interpretation of the results. SA contributed to the statistical analysis of the results. LC contributed to the conception and design of the study and to the writing of the manuscript. None of the authors had a personal or financial conflict of interest.

REFERENCES