Adiposity and insulin resistance in nondiabetic hemodialysis patients: effects of high energy supplementation

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ABSTRACT

Background: In contrast to the general population, a higher body mass index is associated with better survival among hemodialysis patients. Theoretically, high energy supplementation in these patients ought to lead to weight gain over time, but the benefits of this strategy are unclear.

Objective: The objective was to assess whether high energy supplementation in nondiabetic hemodialysis patients might adversely affect insulin resistance—a known risk factor for cardiovascular disease.

Design: We first investigated the association between body fat mass and insulin resistance (homeostasis model assessment of insulin resistance; HOMA-IR) in nondiabetic hemodialysis patients in a cross-sectional analysis (study 1). Of the 106 individuals studied, 55 were randomly assigned to either high energy supplementation (an extra 475 kcal/d; n = 28) or not (n = 27) for 12 wk to assess prospective changes in body fat mass and insulin resistance (study 2).

Results: In study 1, body fat mass (P < 0.05) and C-reactive protein (CRP) (P < 0.05) each contributed independently to HOMA-IR. In study 2, 41 patients completed the study. The 20 patients who received high energy supplementation had a significantly greater increase in body fat mass (P < 0.05), CRP (P < 0.05), and HOMA-IR (P < 0.001) than did the 21 controls.

Conclusions: Body fat mass and CRP are primary determinants of insulin resistance in nondiabetic hemodialysis patients. High energy supplementation, because it increases adiposity and inflammation, exacerbates insulin resistance. A long-term study is needed to clarify the metabolic effects of high energy supplementation on cardiovascular disease outcomes in hemodialysis patients.

INTRODUCTION

Obesity is a well-established risk factor for cardiovascular disease (CVD) in the general population (1). Paradoxically, an increasing number of epidemiologic studies have indicated that there is a survival advantage in having an elevated body mass index (BMI; in kg/m²) among hemodialysis patients (2). In fact, whereas traditional CVD risk factors are associated with an unfavorable outcome in the general population, these factors would appear to be protective in chronic hemodialysis patients. This phenomenon has been referred to as “reverse epidemiology” (3).

Chronic hemodialysis patients frequently have a low energy intake and are underweight. A greater caloric intake by hemodialysis patients to engender a better survival outcome has been hypothesized because of this obesity paradox (4). Nonetheless, obesity is also associated with an increased risk of developing insulin resistance (5), which may contribute to accelerated CVD, which is the major cause of death among chronic hemodialysis patients (6). Hence, the protective effects of excess weight in hemodialysis patients remain debatable and need to be tested with an appropriately designed prospective study (7).

Increased body fat mass is associated with poorer insulin resistance in stage 3–4 nondiabetic chronic kidney disease (CKD) patients who are not receiving dialysis (8). However, potential determinants of insulin resistance in stage 5 CKD patients undergoing chronic hemodialysis have not been studied in detail. We hypothesized that body fat mass may also be independently associated with insulin resistance among nondiabetic chronic hemodialysis patients and an increase in energy intake will result in increased insulin resistance due to the increase in body fat mass. To test this hypothesis, we examined the relation between body fat mass and insulin resistance as determined by homeostasis model assessment of insulin resistance (HOMA-IR) among nondiabetic chronic hemodialysis patients in a cross-sectional observation (study 1). We further conducted a randomized controlled trial to verify whether the level of insulin resistance is associated with the increase in adiposity that occurs after high energy supplementation (study 2).

SUBJECTS AND METHODS

The study consisted of a cross-sectional analysis at baseline (study 1), followed by a prospective randomized controlled intervention over 12 wk (study 2). The protocol was approved by the local medical ethics committee, and all patients gave their
Study 1

Subjects were recruited among chronic hemodialysis patients at the dialysis centers of affiliated hospitals of National Yang-Ming University, Taipei. Inclusion criteria were age >20 y and duration of prior dialysis >6 mo. The patients were being dialyzed for 4–4.5 h three times/wk by using a single-use dialyzer equipped with a membrane surface area of 1.6–1.7 m2 at a blood flow of 300–350 mL/min and a dialysate flow of 500 mL/min. Exclusion criteria were diabetes mellitus, an inadequate dose of dialysis (single-pool K/\(V < 1.2\)), comorbidity with malignancy, liver disease, significant fluid overload, and an infectious disease 4 wk before enrollment.

Baseline information was obtained from each patient, including age, sex, anthropometric measures (eg, body weight, BMI, and body fat mass), routine chemistry, insulin concentration, leptin concentration, and C-reactive protein (CRP) concentration. All laboratory tests were conducted after the patients had fasted and before the start of midweek dialysis. Glucose in the plasma and albumin together with total cholesterol and triglyceride concentrations in the serum were measured by using an autoanalyzer (model 736-60; Hitachi, Naka, Japan). Plasma insulin (Diagnostic Products Corporation, Los Angeles, CA) and leptin (Linco Research Inc, St Louis, MO) were measured by radioimmunoassay according to the procedures recommended by the manufacturers. Serum CRP was measured by immunoturbidimetric assay by using rate nephelometry (Beckman, Galway, Ireland). Insulin resistance was quantified by HOMA-IR. HOMA-IR was calculated with the following formula: fasting plasma glucose (mg/dL) \times \text{fasting plasma insulin} (\mu U/mL)/405, with higher values representing greater degrees of insulin resistance. The validity of HOMA-IR as a surrogate measure of insulin resistance has been established in the CKD population (9, 10). Body fat mass was measured with the multifrequency bioimpedance method (model 310; Biodynamics, Seattle, WA), which was performed within 30 min after a dialysis session at presumed dry weight and involved a single well-trained dietitian to avoid interobserver variation.

Study 2

A subset of patients in study 1 who provided informed consent was randomly assigned to 1 of 2 groups: the high-energy group and the control group. Treatment order was block-randomized with the use of computer-generated random numbers. Patients in the high-energy group received one can of a commercially available oral nutritional supplement (Nepro; Abbott Laboratories, Ross Products Division, Chicago, IL) daily for 12 wk. Each can of supplement contained 16.6 g protein, 22.7 g fat, and 52.8 g carbohydrate and provided 475 kcal. These values for energy and protein were added to the food intake to calculate total intake. Daily dietary records over 3 consecutive days were used to estimate intakes of protein and calories at the beginning and the end of the study (11). Supplements were dispensed weekly. Compliance was verified by dietary interviews during dialysis sessions, as described previously (12).

The primary outcome measures were changes in body fat mass and HOMA-IR over the 12-wk study period. The secondary outcome measures were changes in metabolic variables, including plasma leptin, serum cholesterol, triglyceride, albumin, and CRP. Patients in the control group were observed in parallel to estimate any changes in the main outcome measures. Over the course of the study, the previous level of physical activity was kept constant for both groups. The methods of data collection were the same as those in study 1.

Statistical analysis

Descriptive statistics included means ± SDs for continuous data and percentages for categorical data. The values for HOMA-IR, plasma insulin and leptin, and serum CRP were not normally distributed and are reported as medians with interquartile ranges. In study 1 and study 2, for between-group comparison, Student’s \(t\) test was used for normally distributed data and the Mann-Whitney rank-sum test was used for nonnormally distributed data. Pearson’s chi-square test was used for frequency measures.

In study 1, Pearson’s correlation analysis was performed to examine the association between HOMA-IR and body fat mass as well as other potentially explanatory variables. Forward stepwise multiple regression was performed to assess the independent effect of the 11 covariates, including age, sex, dialysis vintage, urea reduction rate, BMI, body fat mass, serum albumin, cholesterol, triglyceride, CRP, and plasma leptin on the HOMA-IR (dependent variable) in study 1 and the changes in HOMA-IR (dependent variable) in study 2. Statistical analysis was performed by using the computer software Statistical Package of Social Science (SPSS 12.0, 2003; SPSS Inc, Chicago, IL). A \(P\) value \(<0.05\) was considered statistically significant.

On the basis of our previous data (12), we estimated that 40 patients (20 in each group) would be required for study 2 to have a power of 90% to detect an absolute difference in the primary endpoint and a probability of a type I error of 0.05 with the use of a 2-sided test. We allowed for the possibility of a withdrawal rate of 25% by including a total of 55 patients for the study 2.

RESULTS

Study 1

Patient characteristics

A total of 106 nondiabetic hemodialysis patients were enrolled. The etiologies of the end-stage renal disease (ESRD) included glomerulonephritis \((n = 40)\), interstitial nephritis \((n = 19)\), hypertension \((n = 18)\), various polycystic kidney diseases \((n = 9)\), and shrunken kidneys of unknown etiology \((n = 20)\). The patients were subdivided into either low (median: 1.16; interquartile range: 0.86–1.53; \(n = 53\)) or high (median: 3.48; interquartile range: 2.45–6.54; \(n = 53\)) HOMR-IR groups. The baseline characteristics of the patients are shown in Table 1. Patients in the high HOMA-IR group were significantly older than those in the low HOMA-IR group. There were no significant differences between the 2 groups with regard to sex, hemodialysis duration, BMI, and body weight. Plasma leptin, fasting plasma glucose, serum albumin, and total cholesterol also did not differ significantly. Percentage body fat \((P < 0.05)\),
body fat mass (P < 0.05), and fasting plasma insulin concentrations (P < 0.001) were significantly greater in the high HOMA-IR group than in the low HOMA-IR group. Moreover, patients with high HOMA-IR had significantly greater serum triglyceride (P < 0.05) and CRP (P < 0.05) concentrations than did those with low HOMA-IR.

Predictors of insulin resistance

The potential predictors of HOMA-IR are depicted in Table 2. In the unadjusted analysis, there was a strong positive correlation between HOMA-IR and CRP (r = 0.343, P < 0.001), followed by body fat mass (r = 0.296, P < 0.01), BMI (r = 0.279, P < 0.01), and plasma leptin (r = 0.268, P < 0.01). In multiple regression analysis (Table 3), CRP (P < 0.01) and body fat mass (P < 0.05) were independent predictors of HOMA-IR.

Study 2

Patient characteristics

Of the 106 individuals in study 1, 55 were randomly assigned to either the high-energy group (n = 28) or the control group (n = 27) (Figure 1). The high-energy and control groups were not significantly different at baseline with respect to age (58 ± 14 years compared with 57 ± 14 years), sex distribution (63% male compared with 58% male), hemodialysis duration (6.9 ± 6.2 years compared with 6.6 ± 6.1 years), BMI (20.9 ± 2.7 compared with 21.4 ± 2.8 years), body fat mass (16.1 ± 3.5 kg compared with 15.6 ± 5.1 kg), fasting plasma insulin concentration [10.4 (8.2–17.3) μU/mL compared with 13.3 (9.9–19) μU/mL], and HOMA-IR [1.89 (1.29–6.33) compared with 2.80 (2.15–7.46)], respectively.

Effects of high energy supplementation on body fat mass and insulin resistance

Forty-one patients completed the study (20 in the high-energy group and 21 in the control group) (Figure 1). The high-energy group had a significantly greater increase in body fat mass (P < 0.05), plasma leptin (P < 0.001), CRP (P < 0.05), and HOMA-IR (P < 0.001) than did the control group (Table 4). Multivariate regression analysis showed that the change in body fat mass was an independent predictor of the increase in HOMA-IR (P < 0.001), even after adjustment for the change in serum CRP.

DISCUSSION

Insulin resistance and its associated metabolic abnormalities are known complications of advanced CKD. Previous studies that used the glucose clamp technique described by Smith and...
DeFronzo (13) showed that a postbinding defect in insulin action, probably resulting from retained uremic toxins, was the primary cause of glucose intolerance in nondiabetic patients with ESRD. Vitamin D deficiency, metabolic acidosis, and inflammation are other potential contributors to the development of uremic insulin resistance (14). In the present study, we report 2 novel findings. First, in the analysis of the cross-sectional observation (study 1), body fat mass and CRP, independently predicted insulin resistance in nondiabetic ESRD patients receiving maintenance hemodialysis. Second, in the randomized controlled trial (study 2), an increase in energy intake beyond current recommendations (15), because it increases adiposity and inflammation, significantly augmented insulin resistance evaluated in terms of HOMA-IR.

The role of body fat mass in the development of uremic insulin resistance can be attributed to adipocyte-derived hormones such as leptin, adiponectin, and resistin, which regulate peripheral insulin sensitivity (16). Leptin, a protein that is secreted exclusively by adipocytes, plays an important role in insulin resistance and participates in the pathogenesis of arterial hypertension (17, 18). As expected, plasma leptin concentrations correlated positively with HOMA-IR in the present study. Proinflammatory adipokines, such as tumor necrosis factor-α, have also been shown to mediate insulin resistance (19). Ramos et al (20) found that percentage body fat independently predicted the concentrations of markers of oxidative stress and inflammation among patients with moderate-to-severe CKD. CKD is a chronic inflammatory state. Therefore, increased adiposity can enhance the inflammatory responses that accompany CKD and cause a further increase in insulin resistance. Because of the cross-sectional design of the study, however, the cause-effect relation between body fat mass and HOMA-IR could not be completely elucidated. Study 2 showed that an increase in calorie intake appears to increase body fat mass and subsequently increase HOMA-IR in hemodialysis patients. Further analysis showed an independent metabolic effect of fat mass on HOMA-IR, even after adjustment for the change in serum CRP. In fact, high energy supplementation alone can induce immediate oxidative stress and inflammation (21). Therefore, the direct effect of body fat mass on insulin resistance should be evaluated after suppressing inflammation in hemodialysis patients to eliminate confounding factors, such as systemic proinflammatory cytokines.

The interrelation between body fat mass, insulin resistance, and inflammation in the nondiabetic hemodialysis patients in the present study was of interest because a deleterious combination might explain the overwhelming CVD risk of ESRD patients. Nonetheless, in contrast with the general population, overweight and obese hemodialysis patients (BMI ≥ 27.5) have a significantly higher survival rate than do persons who are normal in weight (BMI = 20–27.5) or underweight (BMI < 20) (2). One recent study in chronic hemodialysis patients showed that those with increased body weight over time had a better survival rate than did those with stable or decreased body weight (22). This “obesity paradox” in ESRD might be explained by statistical fallacies such as age-related mortality patterns and time discrepancies between competing risk factors. In a recent study, de Mutsert et al (23) found no reverse epidemiology of BMI and mortality in hemodialysis patients compared with a general population of equal baseline age and duration of follow-up. It is possible that, in the long term, overweight ESRD patients may experience more CVD events if they survive long enough (3). In the United States, Asian dialysis patients have a better survival rate than do white patients. Indeed, the relation between BMI

<table>
<thead>
<tr>
<th>Variable</th>
<th>Unit of increase</th>
<th>Regression coefficient</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>ln C-reactive protein</td>
<td>ln 1 mg/L</td>
<td>0.626</td>
<td>0.330, 0.923</td>
<td>0.002</td>
</tr>
<tr>
<td>Body fat mass</td>
<td>1 kg</td>
<td>0.042</td>
<td>0.001, 0.083</td>
<td>0.041</td>
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</table>

\(n = 106\). The dependent variable was ln HOMA-IR. The independent variables included were age, sex, dialysis vintage, urea reduction rate, BMI, body fat mass, plasma albumin, cholesterol, triglycerides, and C-reactive protein. All variables that were significant \(P < 0.05\) were left in the model.

![FIGURE 1](image-url) Numbers of patients who entered the study for a cross-sectional analysis at baseline (study 1), who were later randomly assigned to receive either high energy supplementation or no supplementation (study 2), and who completed the study.
and survival was U-shaped rather than reversed in the Asian dialysis patients (24).

A limitation of this study was the lack of a placebo control or a supplement with protein in the control group, which may have affected the outcome of any treatment effect. Another limitation was that body composition analysis with the bioimpedance method may be confounded by excessive extracellular volume in patients with uremia. Nevertheless, persons with potential significant fluid overload were excluded from this study, and bioimpedance was performed after a dialysis session when patients had reached their dry weight. Furthermore, because of limitations associated with the use of bioimpedance analysis for assessing body fat mass, the differentiation between subcutaneous and metabolically active visceral fat could not be assessed in the present study (25). Finally, insulin resistance is a consequence of high energy intake in nondiabetic hemodialysis patients, but it was not possible to infer that the increase in HOMA-IR was causally related to an adverse CV outcome in a 12-wk intervention. However, in a cohort study with a mean follow-up period of 67 mo, Shinohara et al (6) showed that HOMA-IR independently predicted a higher risk of CV mortality among chronic hemodialysis patients. Long-term, adequately sized randomized controlled studies of CV outcomes among chronic hemodialysis patients receiving high energy supplementation are needed to better define the appropriate clinical role, if any, of this therapy.

In conclusion, the present study showed that body fat mass and CRP each closely correlate with insulin resistance in nondiabetic chronic hemodialysis patients. Moreover, high energy supplementation results in increased insulin resistance, which is a novel risk factor for CVD in ESRD (6). Our present findings have important implicatons for chronic hemodialysis patients who are willing to gain weight because of the “obesity paradox.” Simply increasing energy intakes above current recommendations might worsen insulin resistance and other associated metabolic disorders. Strategies to attenuate adverse metabolic responses without negating the beneficial effects of increases in energy intake need to be evaluated in future studies (26). Agents that enhance insulin sensitivity, such as peroxisome proliferator–activated receptor γ agonists (27) and angiotensin II blockade (28), might hold promise as adjunctive therapies that improve insulin resistance among chronic hemodialysis patients receiving high energy supplementation.

The authors’ responsibilities were as follows—D-CT: protocol design and overall conduct of the study; and D-CT and S-CH: data analysis and manuscript preparation. Neither of the authors had a conflict of interest.

REFERENCES


<table>
<thead>
<tr>
<th>Variable</th>
<th>High-energy group (n = 20)</th>
<th>Control group (n = 21)</th>
<th>p2</th>
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<tbody>
<tr>
<td>Total energy intake at baseline (kcal · kg⁻¹ · d⁻¹)</td>
<td>29.9 ± 6.7</td>
<td>29.2 ± 5.7</td>
<td>0.705</td>
</tr>
<tr>
<td>ΔTotal energy intake, 12 wk − baseline (kcal · kg⁻¹ · d⁻¹)</td>
<td>7.9 ± 2.6</td>
<td>0.1 ± 2.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>BMI at baseline (kg/m²)</td>
<td>20.8 ± 2.5</td>
<td>21.7 ± 2.7</td>
<td>0.410</td>
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<tr>
<td>ΔBMI, 12 wk − baseline (kg/m²)</td>
<td>0.6 ± 1.0</td>
<td>0.3 ± 1.5</td>
<td>0.327</td>
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<td>Body fat mass at baseline (kg)</td>
<td>15.1 ± 3.2</td>
<td>16.9 ± 4.8</td>
<td>0.337</td>
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<tr>
<td>ΔBody fat mass, 12 wk − baseline (kg)</td>
<td>2.5 ± 1.2</td>
<td>−0.4 ± 2.0</td>
<td>0.031</td>
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<tr>
<td>Fasting plasma glucose at baseline (mg/dL)</td>
<td>81 ± 14</td>
<td>87 ± 15</td>
<td>0.100</td>
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<tr>
<td>ΔFasting plasma glucose, 12 wk − baseline (mg/dL)</td>
<td>25 ± 12</td>
<td>4 ± 13</td>
<td>0.072</td>
</tr>
<tr>
<td>Fasting plasma insulin at baseline (μU/mL)</td>
<td>10.3 (8.0–14.9)</td>
<td>13.2 (8.6–18.7)</td>
<td>0.877</td>
</tr>
<tr>
<td>ΔFasting plasma insulin, 12 wk − baseline (μU/mL)</td>
<td>7.7 (3.4–14.6)</td>
<td>0.9 (1.7–3.9)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>HOMA-IR at baseline</td>
<td>1.73 (1.25–4.88)</td>
<td>2.61 (1.42–5.32)</td>
<td>0.546</td>
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<tr>
<td>ΔHOMA-IR, 12 wk − baseline</td>
<td>2.31 (1.07–7.91)</td>
<td>0.04 (~0.89 to 2.44)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Plasma leptin at baseline (ng/mL)</td>
<td>11.8 (7.7–18.5)</td>
<td>12.5 (9.3–15.1)</td>
<td>0.623</td>
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<tr>
<td>ΔPlasma leptin, 12 wk − baseline (ng/mL)</td>
<td>14.7 (6.6–25.6)</td>
<td>3.3 (1.3–7.2)</td>
<td>&lt;0.001</td>
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<td>Total cholesterol at baseline (mg/dL)</td>
<td>171 ± 37</td>
<td>174 ± 32</td>
<td>0.877</td>
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<tr>
<td>ΔTotal cholesterol, 12 wk − baseline (mg/dL)</td>
<td>15 ± 19</td>
<td>6 ± 20</td>
<td>0.724</td>
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<td>Triglycerides at baseline (mg/dL)</td>
<td>125 ± 55</td>
<td>138 ± 53</td>
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<td>ΔTriglycerides, 12 wk − baseline (mg/dL)</td>
<td>16 ± 24</td>
<td>1 ± 36</td>
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<td>CRP at baseline (mg/L)</td>
<td>3.0 (3.2–7.0)</td>
<td>3.4 (3.0–8.9)</td>
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<td>ΔCRP, 12 wk − baseline (mg/L)</td>
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<td>1.3 (0.5–2.3)</td>
<td>0.038</td>
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<td>Serum albumin at baseline (g/dL)</td>
<td>3.8 ± 0.3</td>
<td>3.9 ± 0.3</td>
<td>0.301</td>
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<tr>
<td>ΔSerum albumin, 12 wk − baseline (g/dL)</td>
<td>0.2 ± 0.1</td>
<td>0.0 ± 0.1</td>
<td>0.864</td>
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