Plasma glucose turnover and oxidation during hemodialysis: nutritional effect of dialysis fluid¹-³

Charles L Skutches and Miles H Sigler

ABSTRACT  Mass transfer of glucose from dialysis fluid into patients is a source of energy and a form of nutrition during hemodialysis. The effect of glucose mass transfer on endogenous glucose metabolism and the overall nutritional importance of glucose transfer is not known. Rates of plasma glucose turnover and oxidation were determined by radioisotope-dilution techniques in patients with chronic renal failure (CRF) in the basal state, during hemodialysis, and during the infusion of glucose at a rate similar to the mass transfer rate (M; 6.6 ± 0.7 μmol·min⁻¹·kg⁻¹). Rates of plasma glucose turnover (11.8 ± 0.8 μmol·min⁻¹·kg⁻¹) and oxidation (4.0 ± 0.4 μmol·min⁻¹·kg⁻¹) and contribution of glucose oxidation to the metabolic rate were similar to those of control subjects both in the basal state and during glucose infusion. During hemodialysis with acetate and glucose, the plasma glucose turnover rate was similar to that in the basal state, but the energy from glucose oxidation was less (P < 0.02) even though energy expenditure was increased by 21%. Immediate oxidation of plasma glucose and acetate accounted for 65% of the patients' energy expenditure. Energy (1172 kJ) from acetate and glucose M; surpassed the patients' energy requirements, offsetting the utilization of endogenous fuels, a sparing effect equivalent to 31 g fat or 70 g carbohydrate. Rates of plasma glucose turnover and oxidation during bicarbonate-glucose and glucose-free acetate hemodialysis were similar to that during acetate-glucose hemodialysis. However, without glucose or acetate in the bath fluid, a deficit as much as 669 kJ must be met by the oxidation of endogenous fuels. Addition of organic nutrients that supply energy to dialysis fluids may over time be a beneficial supplemental treatment for the malnutrition and body wasting commonly observed in CRF. Am J Clin Nutr 1997;65:128–35.

KEY WORDS Glucose turnover and oxidation, energy metabolism, hemodialysis, nutritional status, malnutrition, chronic renal failure, acetate, bicarbonate, dialysis fluid, body wasting

INTRODUCTION

General body wasting is commonly encountered in hemodialysis patients. The clinical causes of body wasting are not clearly understood, but inadequate energy intake may be a contributing cause, and therefore, may be a contributing factor leading to increased morbidity and mortality in this patient population (1). As early as the 1960s, hemodialysis was used to acutely supply energy to severely traumatized patients (2). Because dietary intervention alone has been largely ineffective (3), we believe that the dialysis bath fluid can serve as a source of needed energy to help offset the slow progressive body wasting associated with end-stage renal disease. To illustrate this, we selected patients undergoing hemodialysis with acetate with glucose because the mass transfer of both acetate and glucose provides energy to the patient. We determined previously the energy contribution of acetate in the bath (4); however, we are unaware of similar studies that measured the effect of glucose mass transfer on the rates of plasma glucose turnover and oxidation during hemodialysis or that attempted to define the possible effect of energy derived from the mass transfer of glucose and/or other organic nutrients into the patient on the overall nutritional status of the patient. Consequently, the present studies were undertaken in patients with chronic renal failure (CRF) to determine the rates of plasma glucose turnover and oxidation in the basal state, during hemodialysis with acetate and glucose, during intravenous infusion of glucose in an amount equivalent to the glucose mass transfer rate into the patient during hemodialysis with acetate and glucose, and during hemodialysis with glucose-free acetate and bicarbonate with glucose.

SUBJECTS AND METHODS

Subjects

Four male and eight female stable hemodialysis outpatients ranging in age from 27 to 74 y and three male and two female nonuremic control subjects ranging in age from 40 to 66 y were studied. Each subject gave his written voluntary consent after being informed of the nature, purpose, and potential risks of the procedure.

The etiologies of the patient's CRF are shown in Table 1. The patients were dialyzed with hemodialyzers in the single-pass mode. Patients 1–9 were dialyzed against an acetate-glucose bath that contained 37 mmol acetate, 12.4 mmol glu-

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cose, 130 mmol Na, 2.5 mmol Ca, 2.0 mmol K, 1.5 mmol Mg, and 99 mmol Cl/L. For the purpose of the study, patient 10 was dialyzed with this bath fluid omitting glucose, whereas patients 11 and 12 were dialyzed against a bicarbonate bath fluid that contained 39 mmol bicarbonate, 11.1 mmol glucose, 140 mmol Na, 106 mmol Cl, 1.0 mmol Mg, and 2.5 mmol Ca/L. Patient 11 had insulin-dependent diabetes and patient 8 was treated previously by continuous ambulatory peritoneal dialysis for 2 y before her 1 mo of acetate-glucose hemodialysis. Access routes were either a Quinton Scribner shunt (Quinton Instrument Co, Seattle), arteriovenous fistula, or a Gortex graft (WL Gore and Associates, Inc, Flagstaff, AZ). During hemodialysis, blood and dialysis fluid flow rates were established at 200 and 500 mL/min. A Drake Willock model 4500 blood pump (Portland, OR) was used and calibrated by either in vitro volumetric collection or bubble transit time with a 50-cm race track. Neither positive nor negative pressures were applied to minimize the ultrafiltration rate. Dialysis flow rates were verified by volumetric calibration.

Metabolic studies in the basal state and during glucose infusion

**Plasma glucose turnover and oxidation**

Rates of plasma glucose turnover and oxidation were determined by the constant-infusion, radioisotope-dilution technique in overnight fasted control subjects and CRF patients in the basal state and during the intravenous infusion of glucose; the validity of the assumptions in the use of this technique for measurement of the rates of plasma substrate turnover and oxidation were thoroughly discussed by Steele (5). After an overnight fast by the control subjects and 1 d after the CRF patients’ last dialysis, the subjects were studied at rest in a well-ventilated room. A polyethylene catheter was inserted into an antecubital vein of one arm for the primed continuous infusion of 1.67 $\times$ 10\(^6\) Bq (45 $\mu$Ci) [\(^{1-14}\)C]glucose (New England Nuclear, Wilmington, DE) over 7 h and in the other arm for the withdrawal of blood. The ratio of the priming dose (Bq) to the infusion rate (Bq/min) was 100. The intravenous infusion of ~450 $\mu$mol glucose/min, an amount equivalent to the mass transfer of glucose from the dialysis bath to the patient during acetate-glucose hemodialysis (4, 6), was initiated after the third hour. Samples of heparinized blood and expired air were taken at hours 1, 2, 2.5, 3, 5, 6, 6.5, and 7. Expired air was collected in Douglas bags for indirect calorimetry measurements as described by Isserof et al (7, 8). The specific activity of the expired 14CO\(_2\) was determined according to Fredrickson and Ono (9).

The specific activity of glucose was determined as described by Holroyde et al (10) in ultrafiltrates of plasma prepared through membranes with a 10 000 nominal molecular weight cutoff (Millipore Corp, Bedford, MA). Within 1 h of the radioisotope and the radioisotope plus glucose infusions, plasma glucose specific activity was constant, indicating that steady state conditions were established, i.e., the rates of plasma glucose production and utilization were equal. The rates of plasma glucose turnover and oxidation were calculated as described by Paul and Bortz (11) by using the following equations:

\[
\text{Plasma glucose turnover (μmol min}^{-1}\text{kg}^{-1}) = \frac{[1 - ^{14}\text{C}]\text{glucose infusion rate (Bq/min)}}{\text{plasma glucose specific activity (Bq/μmol) × body wt (kg)}} \tag{1}
\]

\[
\% \text{CO}_2 \text{ from plasma glucose oxidation} = \frac{\text{CO}_2 \text{ specific activity (corrected) × 6 × 100}}{\text{plasma glucose specific activity}} \tag{2}
\]

\[
\text{Plasma glucose oxidation rate (μmol min}^{-1}\text{kg}^{-1}) = \frac{\% \text{CO}_2 \text{ from plasma glucose oxidation} \times \text{CO}_2 \text{ output}}{6 \times \text{body weight (kg)}} \tag{3}
\]
\[
\% \text{ Plasma glucose turnover oxidized} = \frac{\text{plasma glucose oxidation rate}}{\text{plasma glucose turnover rate}} \times 100 \tag{4}
\]

**Plasma fatty acid turnover and oxidation**

The rates of plasma fatty acid turnover and oxidation were measured in patient 9, after an overnight fast, by the constant-infusion, radioisotope-dilution technique described above (7, 12). Albumin-bound \([1-^{14}\text{C}]\text{palmitate} (1.85 \times 10^6 \text{ Bq, or 50 } \mu\text{Ci})\) (Amersham Corp, Arlington Heights, IL) was infused in an antecubital vein for 4 h. The ratio of the priming dose to infusion rate was 50. Plasma fatty acid specific activity was determined in hourly Na-EDTA blood samples from the plasma fatty acid concentration (13) and the radioactivity in the heptane extract. Samples of expired air were also collected hourly for oxygen and carbon dioxide analysis and the determination of carbon dioxide specific activity. The rates of plasma fatty acid turnover and oxidation were calculated by using the equations described above by substituting 16 as the average fatty acid chain length.

**Metabolic studies during hemodialysis**

**Plasma glucose turnover and oxidation**

The rates of plasma glucose turnover and oxidation were determined by the constant-infusion, radioisotope-dilution technique described above with the following modifications. Within 1 h of the onset of hemodialysis, a radioisotopic steady state was established for plasma glucose. \([1-^{14}\text{C}]\text{glucose}\) was infused in the venous return line of the hemodialyzer. Hourly samples of heparinized blood were taken simultaneously from the arterial and venous lines of the dialyzer upstream from the site of the infusion of \([1-^{14}\text{C}]\text{glucose}\). A polyethylene catheter was inserted into an opposite antecubital vein of patients with either a fistula or graft from which hourly blood samples were withdrawn in conjunction with those taken from the arterial and venous lines to determine the specific activity of glucose. The specific activity of plasma glucose was determined in the arterial blood sample from patients with a Quinton Scriber shunt. With each hourly withdrawal of blood, a 20-mL sample of spent dialysate fluid was collected anaerobically to measure the carbon dioxide and bicarbonate concentrations in the fluid by standard fluid gas procedures and an additional deciliter was taken for analysis of \(^{14}\text{CO}_2\) in dialysis fluid as described in detail previously (4).

The quantity of glucose that diffused into the plasma per unit time (mass transfer rate, \(M_r\)) was determined from the difference in the plasma glucose concentration between the arterial blood entering the dialyzer and the venous blood leaving the dialyzer \((A-V)\) multiplied by the plasma flow rate.

**Plasma fatty acid turnover and oxidation**

A primed, continuous infusion of albumin-bound \([1-^{14}\text{C}]\text{palmitic acid}\) was administered to patient 9 via the venous return line as described for the infusion of \([1-^{14}\text{C}]\text{glucose}\). Blood samples were withdrawn hourly from an antecubital vein into Na-EDTA-containing tubes for the determination of plasma fatty acid specific activity. The specific activity and concentration of carbon dioxide and bicarbonate in the dialysis fluid and the analysis of expired gases were determined as described above.

**Additional analysis**

The plasma fatty acid \((13)\) concentration was measured in peripheral venous blood from control subjects and CRF patients in the basal state and during glucose infusion and in either the arterial line or peripheral venous blood from CRF patients during hemodialysis.

**Isotope calculations**

We observed that \([1-^{14}\text{C}]\text{glucose}\) is lost to the dialysis bath at a constant rate during the dialytic period. If the loss of \([1-^{14}\text{C}]\text{glucose}\) is not subtracted from the radioisotope-infusion rate, plasma glucose turnover will be overestimated. The becquerels of \([1-^{14}\text{C}]\text{glucose}\) lost to the bath were calculated from \(A-V\) multiplied by the plasma flow rate, and the \([1-^{14}\text{C}]\text{glucose}\) infusion rate was corrected accordingly. In addition, to calculate the immediate oxidation of either plasma glucose or fatty acid, the specific activity of carbon dioxide must be corrected to a value that represents complete isotope equilibration in the bicarbonate pool. During the constant infusion of tracers, the rise in the specific activity of exhaled \(^{14}\text{CO}_2\) and the percentage recovery of \(^{14}\text{CO}_2\) are due to the relatively slow diffusion of carbon dioxide derived from tissue oxidation into the large uneabeled bicarbonate pool as well as to exhalation from the lungs. The development of the fractional recovery curves to convert the observed specific activity of \(^{14}\text{CO}_2\) to the ideal for the calculation of the immediate rate of plasma glucose oxidation during hemodialysis as well as in the basal state and during glucose infusion was described by Skutch et al (4) and Isselbacher et al (7).

**Statistical analysis**

Comparisons between groups of control subjects and CRF patients were analyzed by one-way analysis of variance (ANOVA). Paired observations within groups of control subjects and CRF patients were analyzed by using matched paired \(t\) tests. In Table 2, the Studentizing method of analysis for an obvious outlier observation within a paired data set was used to develop a more valid comparison in percentage carbon dioxide output from glucose oxidation in the basal state compared with during acetate-glucose hemodialysis (14).

**RESULTS**

The fasting plasma glucose concentrations displayed in Figure 1 were similar in control subjects and CRF patients. From the beginning of an acetate-glucose hemodialysis treatment, \(6.62 \pm 0.74 \mu\text{mol} \cdot \text{min}^{-1} \cdot \text{kg}^{-1} (M_r)\) or \(\approx 450 \mu\text{mol glucose}\) diffuses into the bloodstream per minute (Table 2), resulting in an approximate 15% increase in the plasma glucose concentration. In both overnight-fasted control and CRF subjects, the intravenous infusion of glucose at a quantity and rate similar to glucose \(M_r\) increased the plasma glucose concentration by 11.0% and 12.3%, respectively. This suggested that the elevation of plasma glucose during acetate-glucose hemodialysis was solely related to glucose \(M_r\).

As shown in Table 2, the basal rates of plasma glucose turnover were similar in overnight-fasted control subjects and...
TABLE 2
Plasma glucose turnover in the basal state and during glucose infusion in control subjects and patients with chronic renal failure (CRF) and in CRF patients during acetate-glucose hemodialysis†

<table>
<thead>
<tr>
<th>Subjects</th>
<th>Infusion rate</th>
<th>M̄2</th>
<th>Basal Glucose infusion</th>
<th>Dialysis Glucose infusion</th>
<th>Endogenous Glucose production</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>6.20 ± 0.56</td>
<td>—</td>
<td>11.77 ± 0.81</td>
<td>10.46 ± 0.74</td>
<td>4.25 ± 0.40</td>
</tr>
<tr>
<td>CRF patients (no hemodialysis)</td>
<td>6.22 ± 0.56</td>
<td>—</td>
<td>11.57 ± 0.93</td>
<td>11.38 ± 0.97</td>
<td>5.16 ± 1.16</td>
</tr>
<tr>
<td>CRF patients (hemodialysis)</td>
<td>—</td>
<td>6.62 ± 0.74</td>
<td>13.57 ± 1.16</td>
<td>16.20 ± 2.78</td>
<td>9.58 ± 2.22</td>
</tr>
</tbody>
</table>

†x ± SEM of measured rates in control subjects 1–5 and in CRF patients 4–7 and 10–12 in the basal state and during glucose infusion and in CRF patients 1 and 3–6 in the basal state and during acetate-glucose hemodialysis.

‡Glucose mass transfer rate (the amount of glucose entering the plasma from the dialysis fluid).

§Glucose turnover rate minus glucose infusion rate or glucose M̄.

¶Significantly different from basal glucose turnover, P ≤ 0.05.

CRF patients. During the infusion of glucose, the mean plasma glucose turnover rate in control subjects was slightly below (P ≤ 0.05) their basal rate, but not significantly different from the turnover rate in CRF patients given a comparable infusion of glucose. In addition, the mean rate of plasma glucose turnover in CRF patients during hemodialysis was similar to the basal rate. Within this group, the rate of plasma glucose turnover in patient 3 was elevated 1.6-fold above the basal rate during hemodialysis, which accounted for the apparent difference in the mean values. In the three patients (patients 4, 5, and 6) studied during glucose infusion and hemodialysis, the rates of plasma glucose turnover were similar during both procedures. The respective rates of plasma glucose turnover in patients 4, 5, and 6 were 10.80, 16.07, and 11.67 μmol·min⁻¹·kg body wt⁻¹ in the basal state; 10.21, 16.50, and 12.09 μmol·min⁻¹·kg⁻¹ during glucose infusion; and 13.98, 18.83, and 10.63 μmol·min⁻¹·kg⁻¹ during acetate-glucose hemodialysis. Therefore, from these paired studies we concluded that endogenous plasma glucose production was not elevated during acetate-glucose hemodialysis.

In control subjects and CRF patients studied in the basal state and during intravenous administration of glucose (Table 3), mean rates of plasma glucose oxidation, fraction of the plasma glucose turnover oxidized, and percentage of the carbon dioxide output originating from the immediate oxidation of plasma glucose were similar. As shown in Table 3, the mean rate of plasma glucose oxidation was slightly elevated (P ≤ 0.05) compared with the basal rate in CRF patients during glucose infusion.

During acetate-glucose hemodialysis, the mean rate of plasma glucose oxidation and fraction of the glucose turnover oxidized (Table 3) were similar to basal rates. The percentage of carbon dioxide output from the immediate oxidation of plasma glucose was reduced by as much as 40% in four of five patients during hemodialysis. In one patient (patient 5), this percentage was increased 1.4-fold above the basal value, a response completely opposite that of the other patients. However, the use of Windsorizing method of analysis (14) for an obvious outlier within a paired data set substantiated that the mean percentage decrease was significant (P ≤ 0.02). Even though the percentage carbon dioxide output from plasma glucose oxidation was reduced, the mean energy expenditure of these patients was increased from 13.0 ± 1.3 kJ·h⁻¹·kg⁻¹ in the basal state to 15.7 ± 1.1 kJ·h⁻¹·kg⁻¹ during acetate-glucose hemodialysis (P ≤ 0.02).

Patient 10 was studied while undergoing glucose-free acetate hemodialysis. Without glucose in the bath, glucose passed from the bloodstream into the dialysis fluid at a rate of 4.25 μmol·min⁻¹·kg⁻¹ (Table 4). The rate of plasma glucose turnover shown in Table 4 was not stimulated above the basal rate (10.47 μmol·min⁻¹·kg⁻¹) to compensate for this reverse glucose M̄. Consequently, the plasma glucose concentration dropped from 4.78 mmol/L before to 3.81 mmol/L during dialysis. The reverse glucose M̄ was equivalent to 45.1% of the
Table 3
Rate of plasma glucose oxidation, fraction of plasma glucose turnover oxidized, and carbon dioxide output from plasma glucose oxidation in the basal state and during glucose infusion in control subjects and patients with chronic renal failure (CRF) and in CRF patients during acetate-glucose hemodialysis.

<table>
<thead>
<tr>
<th>Subject</th>
<th>Glucose氧化</th>
<th>Fraction turnover oxidized</th>
<th>Carbon dioxide output from glucose oxidation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Basal</td>
<td>Glucose infusion</td>
<td>Dialysis</td>
</tr>
<tr>
<td></td>
<td>μmol·min⁻¹·kg⁻¹</td>
<td>%</td>
<td>%</td>
</tr>
<tr>
<td>Control</td>
<td>5.01 ± 0.48</td>
<td>4.81 ± 0.46</td>
<td>—</td>
</tr>
<tr>
<td>CRF patients</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(no hemodialysis)</td>
<td>4.02 ± 0.37</td>
<td>4.42 ± 0.33²</td>
<td>—</td>
</tr>
<tr>
<td>CRF patients</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(hemodialysis)</td>
<td>5.08 ± 0.87</td>
<td>—</td>
<td>5.62 ± 1.23</td>
</tr>
</tbody>
</table>

¹ x ± SEM of measurements in control subjects 1-5 and CRF patients 4, 5, 6, 8, 10, and 12 in the basal state and during glucose infusion and in CRF patients 1 and 3-6 in the basal state and during acetate-glucose hemodialysis.

² Significantly different from basal glucose oxidation, P ≤ 0.05.

³ Significantly different from basal carbon dioxide output, P ≤ 0.02.

Plasma glucose turnover rate in patient 10, leaving 54.9%, or 5.18 μmol·min⁻¹·kg⁻¹, of the plasma glucose turnover rate metabolically available. Even though 36.4% of the total plasma glucose turnover was immediately oxidized for energy as shown in Table 4, this actually represented 66.2% (3.34 μmol·min⁻¹·kg⁻¹ ÷ 5.18 μmol·min⁻¹·kg⁻¹ · 100) of the portion metabolically available to the patient.

Patients 11 and 12 were dialyzed against a bicarbonate-glucose fluid. The predialysis plasma glucose concentration was not measured in patient 11, but in patient 12 the glucose concentration in plasma increased by 16% from 4.49 mmol/L before to 5.20 mmol/L during dialysis, an increase similar to that during acetate-glucose hemodialysis (Figure 1). Unlike in patients undergoing acetate-glucose hemodialysis, rates of plasma glucose turnover in patients 11 and 12 shown in Table 4 were elevated 1.6-fold above their basal rates, which are not shown in Table 4 but were measured at 13.15 and 8.36 μmol·min⁻¹·kg⁻¹, respectively. The contribution made by the immediate oxidation of plasma glucose to carbon dioxide output during dialysis in these patients was within the range observed in patients dialyzed against acetate-glucose fluid.

Figure 2 illustrates the effect of dialysis on the concentrations of fatty acids in plasma. There was no significant change in the plasma fatty acid concentration during acetate-glucose hemodialysis; however, in the absence of glucose the plasma fatty acid concentration was elevated 5.3-fold in patient 10. In the absence of acetate, plasma fatty acid concentrations were elevated 2.5-fold and 2.9-fold in patients 11 and 12, respectively. The rates of plasma fatty acid turnover and oxidation were measured in patient 9 in the basal state and during acetate-glucose hemodialysis. The plasma fatty acid concentration in patient 9 decreased by 19% during acetate-glucose hemodialysis (Figure 2 and Table 5). Together with the fall in the plasma fatty acid concentration, the plasma fatty acid turnover rate was reduced by 35% during hemodialysis. Also, the fraction of the plasma fatty acid turnover immediately oxidized for energy was markedly decreased, contributing only 6.2% to the patient’s energy expenditure during hemodialysis.

Discussion

We showed that the rates of basal plasma glucose turnover and oxidation and the contribution of plasma glucose oxidation to the basal metabolic rate in our hemodialysis patients were similar to those of healthy nonuremic control subjects. During acetate-glucose hemodialysis and the intravenous infusion of glucose at a quantity and rate comparable with glucose $M_{glucose}$ during acetate-glucose hemodialysis, our dialysis patients responded as did normal control subjects, ie, the rate of endogenous plasma glucose production was inhibited to the extent that glucose entered the bloodstream. Also, during acetate-glucose hemodialysis and infusion of glucose, the fraction of plasma glucose turnover oxidized was similar to that in the basal state, a response also observed in our nonuremic control subjects and by Wolfe et al (15) in nonuremic subjects given a comparable infusion of glucose. The rates of glucose mass transfer during acetate-glucose hemodialysis and glucose infusion were approximately equivalent to 50% of the basal plasma glucose production in both our dialysis patients and nonuremic patients.

Table 4
Plasma glucose turnover and oxidation during glucose-free acetate and bicarbonate-glucose hemodialysis

<table>
<thead>
<tr>
<th>Subject</th>
<th>Dialysis protocol</th>
<th>$M_{glucose}$</th>
<th>Turnover</th>
<th>Oxidation</th>
<th>Turnover oxidized</th>
<th>Carbon dioxide output from plasma glucose oxidation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>μmol·min⁻¹·kg⁻¹</td>
<td>μmol·min⁻¹·kg⁻¹</td>
<td>μmol·min⁻¹·kg⁻¹</td>
<td>%</td>
<td>%</td>
</tr>
<tr>
<td>10 Glucose-free acetate</td>
<td>—4.25</td>
<td>9.43</td>
<td>3.43</td>
<td>36.4</td>
<td>15.9</td>
<td></td>
</tr>
<tr>
<td>11 Bicarbonate-glucose</td>
<td>4.36</td>
<td>21.11</td>
<td>2.69</td>
<td>12.7</td>
<td>15.9</td>
<td></td>
</tr>
<tr>
<td>12 Bicarbonate-glucose</td>
<td>3.76</td>
<td>13.36</td>
<td>3.81</td>
<td>29.7</td>
<td>27.4</td>
<td></td>
</tr>
</tbody>
</table>

Glucose mass transfer rate (the amount of glucose entering the plasma from the dialysis fluid).
GLUCOSE TURNOVER AND OXIDATION DURING HEMODIALYSIS

FIGURE 2. Plasma fatty acid concentrations in patients with chronic renal failure (CRF) before and during acetate-glucose, glucose-free acetate, and bicarbonate-glucose hemodialysis. Means ± SEMs are given for patients 5, 6, 7, and 9.

control subjects. Thus, our studies showed that, in nondiabetic hemodialysis patients, the regulatory mechanisms that control plasma glucose turnover and oxidation remain intact in response to an infusion of glucose that is within the normal physiologic range of plasma glucose production as occurs during acetate-glucose hemodialysis. The normal physiologic response to glucose $M_1$ during hemodialysis is somewhat surprising because of the long-recognized glucose intolerance associated with renal failure and is contrary to the impression gained from glucose clamp studies performed in this patient population (16–18). This normal physiologic response to glucose $M_1$ is particularly important in the extended care of these patients, considering they undergo $\geq 150$ hemodialysis treatments/y.

During acetate-glucose hemodialysis, the percentage of carbon dioxide output from the immediate oxidation of plasma glucose was less than that during the basal state, even though the energy expenditure of patients was increased. We have no explanation for this change in energy expenditure except that the metabolism of dialysis fluid glucose and acetate may have a thermic effect similar to that observed after the ingestion of a meal (19). Interestingly, the energy expenditures of patients 11 and 12 were not elevated during bicarbonate-glucose hemodialysis with cuprophane membranes, suggesting that membrane biocompatibility was not a factor (20).

The decreased contribution to the patient’s energy requirement from the immediate oxidation of plasma glucose during hemodialysis suggested that the oxidation of plasma acetate spared the oxidation of plasma glucose, a sparing action we postulated previously to have an even greater effect on plasma fatty acid metabolism (4). Even though plasma fatty acid kinetics were determined in only one patient, the decrease in the immediate oxidation of plasma fatty acid was so profound that it is reasonable to assume that the combined oxidation of plasma acetate and glucose spares plasma fatty acid oxidation such that plasma fatty acid becomes a minor contributor to energy homeostasis during acetate-glucose hemodialysis. The fatty acids thus spared are available to meet the patient’s energy needs during the off-dialysis period. The combined effect of glucose and acetate on plasma fatty acid metabolism during acetate-glucose hemodialysis is indirectly supported by the large increase in the plasma fatty acid concentration in patients 11 and 12 during bicarbonate-glucose hemodialysis and in patient 10 during glucose-free acetate hemodialysis (Figure 2). Even though these patients had less energy in their dialysis fluid, $< 30\%$ of their energy requirement (percentage of carbon dioxide output) was supplied by the oxidation of plasma glucose. Therefore, the remainder of their energy requirement must have been supplied by the oxidation of another metabolic fuel, the most likely being fatty acids and hence the marked increase in their plasma concentration. This conclusion is further supported by the observations of Wathen et al (6), who reported more than a twofold increase in the concentration of ketone bodies in plasma after glucose-free acetate hemodialysis compared with acetate-glucose hemodialysis.

From our previous work and the data presented herein, we can now accurately estimate that the immediate oxidation of plasma acetate (4) and glucose accounts for 40.3% and 24.3% of the energy requirement, respectively, during acetate-glucose hemodialysis. We can also speculate with a degree of certainty that plasma fatty acid oxidation contributes $\approx 10.0\%$. If we assume the average catabolic rate of protein in our patients to be $1.1 \, \text{g} \cdot \text{kg}^{-1} \cdot \text{d}^{-1}$ as shown by Sargent et al (21), and the catabolic rate represents complete oxidation, 19% of the energy expenditure is provided by the oxidation of protein:

\[
\% \text{ of the energy expenditure from the oxidation of protein} = \frac{1.1 \, \text{g} \cdot \text{kg}^{-1} \cdot \text{d}^{-1} \times 72.3 \, \text{kg} \times \frac{1}{6} \, \text{d} \times 16.74 \, \text{kJ/g} \times 100}{1135 \, \text{kJ/4 h dialysis}}
\]

(5)

Therefore, in summary, we can identify and account for the source of $\approx 90\%$ of the patient’s energy expenditure during an acetate-glucose dialysis treatment.

### TABLE 5

<table>
<thead>
<tr>
<th>Fatty acids</th>
<th>Turnover</th>
<th>Fraction turnover oxidized</th>
<th>Carbon dioxide output from fatty acid oxidation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>mmol/L</td>
<td>$\mu\text{mol} \cdot \text{min}^{-1} \cdot \text{kg}^{-1}$</td>
<td>%</td>
</tr>
<tr>
<td>Basal</td>
<td>0.594</td>
<td>9.53</td>
<td>42.9</td>
</tr>
<tr>
<td>Hemodialysis</td>
<td>0.486</td>
<td>6.16</td>
<td>7.4</td>
</tr>
</tbody>
</table>
We expected to observe that endogenous plasma glucose production would be stimulated to counteract the loss of glucose during hemodialysis. Instead, the physiologic response was one of recognition of the dialysis machine as another organ of the body taking up glucose from the bloodstream as needed. This false recognition resulted in a 45\% reduction in the rate of plasma glucose production that normally would be utilized for metabolic purposes (Table 4). Obviously, more studies in more patients are necessary to more closely quantify these initial observations; however, sufficient meaningful data were derived from these initial studies to allow a discussion of how the composition of dialysis fluid might significantly affect energy metabolism and the nutritional status of hemodialysis patients.

During acetate-glucose hemodialysis, approximately 55.3 \( \mu \text{mol acetate} \cdot \text{min}^{-1} \cdot \text{kg}^{-1} \) enters the patient’s bloodstream from the dialysis bath (4, 22-24), or in the patients included in the present study, an average of 0.96 mol (57.6 g) in 4 h of dialysis. This acetate load is equivalent to an energy gain of 841 kJ (57.6 g \( \times 14.6 \text{kJ/g acetate} \)) to the patient. In addition, 331 kJ (6.33 \( \mu \text{mol} \cdot \text{min}^{-1} \cdot \text{kg}^{-1} \times 72.3 \text{kJ} \times 240 \text{min} \times 1.80 \times 10^{-4} \text{g/\mu mol} \times 16.74 \text{kJ/g} \)) are simultaneously provided by the mass transfer of glucose. Collectively, the mass transfer of acetate and glucose to the patient supplies a net gain of 1172 kJ, or 38 kJ more than the patient’s energy requirement (94.2 kJ \( \cdot 24 \text{ h}^{-1} \times 72.3 \text{kJ} + 6 \)) during a dialysis treatment. Thus, the gain in energy equivalents from acetate and glucose is sufficient to meet the energy needs of the patient, and, in so doing, offsets the utilization of endogenous energy stores to maintain energy homeostasis.

The combined energy effect of acetate and glucose is theoretically equivalent to sparing the oxidation of 31 g fat or 70 g either carbohydrate or protein. In contrast, as much as 14.2 g plasma glucose, or 238 kJ, is lost to the dialysis bath during glucose-free acetate hemodialysis as shown in patient 10. Consequently, in this patient the net energy gain between acetate diffusing into and glucose passing out of the bloodstream is only 603 kJ, which translates into an energy deficit of 544 kJ per dialysis treatment. Therefore, patient 10 must mobilize and immediately oxidize an equivalent of 14 g fat or 33 g carbohydrate or protein from endogenous tissue stores to satisfy the energy deficit incurred during glucose-free acetate hemodialysis. Over time, this net utilization of endogenous tissue stores, to satisfy energy requirements during hemodialysis, could contribute significantly to a malnourished condition. Using patient 12 as an example of a patient on bicarbonate-glucose dialysis, an even greater energy deficit (695 kJ) resulted from the absence of acetate in the dialysis fluid. As for patient 10, endogenous tissue stores must be mobilized to make up for this energy deficit.

Malnutrition and general body wasting are commonly encountered in hemodialysis patients. Current studies illustrate that the energy content of the dialysis fluid does significantly affect the energy metabolism of patients and that the manipulation of the energy content of the dialysis fluid could have a positive nutritional benefit. In the discussion of these studies, emphasis was placed on the energy benefit gained from the mass transfer of acetate and glucose in a single dialysis treatment. If projected over a year or more of treatments, the energy provided by acetate and glucose could conceivably have a significant effect on the nutritional status of the patient. Thus, hemodialysis has the potential to serve as an important adjunct therapy to the more conventional nutritional interventions that are used to treat the malnutrition and body wasting associated with end-stage renal disease. However, acetate may not be a satisfactory source of energy because of its hypotensive action (25-27). Therefore, the challenge will be to develop a fluid that provides the energy equivalents of acetate without its clinical side effects. Future studies must be undertaken to test the hypothesis that increasing the energy density of the dialysis bath fluid by supplementing the fluid with energy-yielding nutrients will provide a long-term prophylactic nutritional benefit to the hemodialysis patient.

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