Dialysis Time and the Metabolism of Carbohydrates and Lipids

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Summary

The present paper reports some aspects of glycolipid metabolism observed during and after dialysis of varying duration, and the effects of glucose content in dialysate fluid.


MATERIAL AND METHODS

Studies have been made of 34 patients (26 men, 8 women, aged 30 to 53 years), undergoing dialysis treatment from a minimum of six to a maximum of 64 months. Obesity, diabetes or nephrotic syndrome were not present. Average weight was ±5% of ideal body weight. Treatment was as follows (Figure I):

Fourteen patients received short dialysis (3 hr every other day or 4 hr three times per week) with Coil UF2, Coil UF100, Dasco SP75 dialysers (Group 1).

Eight patients received short dialysis (3 hr every other day or 4 hr three times per week) using Coi LF2, Coil UF100, dialysers (Group 2).

Twelve patients received prolonged dialysis (7–12 hr three times per week) using Kiil dialysers (Group 3).

In each case, the dialysis fluid had the same electrolyte composition (Na = 137 mEq/l, K = 1–2 mEq/l, Ca = 4 mEq/l, Mg = 1.5 mEq/l, Cl = 102 mEq/l, acetate = 35 mEq/l) but differed in glucose concentration (Groups 1 and 3 with 2 g/l glucose in dialysis fluid; Group 2 without glucose). Heparin in short dialysis (Groups 1 and 2) was administered as a single initial dose (5,000–8,000 units)
while in prolonged dialysis it was administered as a continuous infusion (total
dose 7,500—16,000 units). Patients had been fasting for at least 6 hr before
dialysis and continued to fast for 4 hr after dialysis.

Evaluation of glycaemia (enzyme technique) insulinaemia (Albano et al, 1972
technique), free fatty acids (Dole technique) and triglycerides (UV technique
with Biochemia Milan reagent kit), was performed before treatment and every
hour during short dialysis, and after the first hour and every two hours during
prolonged dialysis. In the post-dialysis period evaluations were made every hour
up to the fourth hour.

**DIALYSIS FLUID WITH GLUCOSE [2 g/l]**

**PLASMA F.F.A. μEq/l**  

**TRIGLYCERIDES mg%**

**BLOOD GLUCOSE mg%**  

**PLASMA INSULIN μU/ml**

Figure 1. The behaviour of the mean values of plasma triglycerides, free fatty acids, blood
glucose and plasma insulin before, during and after short and prolonged dialysis with glucose
in the dialysis fluid.
<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Short Dialysis With Glucose (2g/l)(u.o. 13)</th>
<th>Short Dialysis Without Glucose (u.o. 8)</th>
<th>Prolonged Dialysis With Glucose (2g/l)(u.o. 13)</th>
<th>B.U.N. mg/400ml</th>
<th>Short Dialysis With Glucose (2g/l)(Dialysate Flow 500ml/min)</th>
<th>Short Dialysis Without Glucose (D.F. 500ml/min)</th>
<th>Prolonged Dialysis With Glucose (2g/l)(D.F. 500ml/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>41 ± 14</td>
<td>44 ± 9</td>
<td>40 ± 5</td>
<td>93 ± 15</td>
<td>94 ± 17</td>
<td>91 ± 15</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Body Weight (kg)</td>
<td>60 ± 6</td>
<td>62 ± 5</td>
<td>61 ± 4</td>
<td></td>
<td>Serum Creatinine mg/100 ml</td>
<td>12.40 ± 1.30</td>
<td>13.00 ± 2.00</td>
</tr>
<tr>
<td>Dialysis (months)</td>
<td>19 ± 13</td>
<td>15 ± 5</td>
<td>25 ± 13</td>
<td></td>
<td>Heparin (Units) Total doses</td>
<td>6,200 ± 900</td>
<td>6,100 ± 700</td>
</tr>
<tr>
<td>Basal Values</td>
<td>643 ± 99</td>
<td>622 ± 184</td>
<td>642 ± 92</td>
<td>Basal Values</td>
<td>235 ± 44</td>
<td>221 ± 69</td>
<td>273 ± 31</td>
</tr>
<tr>
<td>Basal Values</td>
<td></td>
<td></td>
<td></td>
<td>During Dialysis</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>1hr</td>
<td>1,315 ± 299</td>
<td>1,411 ± 204</td>
<td>1,173 ± 323</td>
<td>1hr</td>
<td>101 ± 65</td>
<td>126 ± 59</td>
<td>190 ± 18</td>
</tr>
<tr>
<td>2hr</td>
<td>1,323 ± 230</td>
<td>1,444 ± 204</td>
<td></td>
<td>2hr</td>
<td>109 ± 37</td>
<td>111 ± 33</td>
<td></td>
</tr>
<tr>
<td>3hr</td>
<td>1,261 ± 273</td>
<td>1,356 ± 333</td>
<td>1,233 ± 366</td>
<td>3hr</td>
<td>107 ± 64</td>
<td>128 ± 65</td>
<td>232 ± 29</td>
</tr>
<tr>
<td>4hr</td>
<td>1,281 ± 275</td>
<td>1,400 ± 371</td>
<td></td>
<td>4hr</td>
<td>120 ± 9</td>
<td>142 ± 83</td>
<td></td>
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<tr>
<td>5hr</td>
<td></td>
<td></td>
<td>1,297 ± 316</td>
<td>5hr</td>
<td>231 ± 74</td>
<td></td>
<td></td>
</tr>
<tr>
<td>7hr</td>
<td></td>
<td></td>
<td>1,260 ± 419</td>
<td>7hr</td>
<td>234 ± 75</td>
<td></td>
<td></td>
</tr>
<tr>
<td>12hr</td>
<td></td>
<td></td>
<td>1,176 ± 277</td>
<td>12hr</td>
<td>242 ± 59</td>
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<td></td>
</tr>
<tr>
<td>Free Fatty Acids &amp; E. l</td>
<td></td>
<td></td>
<td></td>
<td>Triglycerides mg%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1hr</td>
<td>1,136 ± 227</td>
<td>1,378 ± 361</td>
<td>1,140 ± 184</td>
<td>1hr</td>
<td>172 ± 50</td>
<td>259 ± 87</td>
<td>235 ± 38</td>
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<tr>
<td>2hr</td>
<td>1,011 ± 274</td>
<td>1,199 ± 289</td>
<td>1,077 ± 254</td>
<td>2hr</td>
<td>177 ± 74</td>
<td>309 ± 90</td>
<td>246 ± 60</td>
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<tr>
<td>3hr</td>
<td>901 ± 173</td>
<td>1,019 ± 210</td>
<td>1,047 ± 253</td>
<td>3hr</td>
<td>181 ± 68</td>
<td>302 ± 120</td>
<td>241 ± 58</td>
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<tr>
<td>4hr</td>
<td>780 ± 168</td>
<td>957 ± 204</td>
<td>901 ± 242</td>
<td>4hr</td>
<td>182 ± 82</td>
<td>336 ± 120</td>
<td>335 ± 50</td>
</tr>
</tbody>
</table>
RESULTS

Dialysis of Varying Duration with Glucose in Dialysis Fluid

Free fatty acids. Pre-dialysis mean values in chronic uraemic patients, treated with periodic dialysis are not only significantly higher than in normal subjects (MV = μEq/l, 525 ± 88) but also by comparison with chronic uraemic patients under conservative therapy (MV = μEq/l, 535 ± 155). After the first hour of dialysis, a clear increase in all patients is observed, which is more pronounced in short-dialysis patients receiving higher doses of heparin.

From the third to the fourth hour of dialysis, free-fatty-acid values do not vary significantly between the two groups. If dialysis is continued for 12 hours, free fatty acids remain elevated and decrease slowly, still remaining above basal levels at the fourth hour after dialysis. On the contrary, free fatty acids decrease rapidly towards values that are closer to basal levels in the four hours that follow short dialysis.

Triglycerides. Pre-dialysis mean values of triglycerides in the same patients are above normal levels (MV = mg%, 162 ± 28) and fall rapidly in the first hour in both groups, at a rate that is more marked in short dialysis subjects receiving higher initial doses of heparin.

If dialysis is continued up to the twelfth hour, triglycerides go up without reaching basal levels; remain steadily elevated, and then go up again reaching values that are above basal levels four hours after dialysis is discontinued. In short-dialysis patients triglycerides remain at the low levels reached at the first hour and go up after the end of dialysis, but still remain below basal levels at the fourth hour.

Glycaemia and insulinaemia. Evaluations of glycaemia and of insulinaemia that were performed every hour during our studies do not show significant variations between groups of patients treated with either short or long dialysis.

Removal of Glucose from Dialysis Fluid. (See Figure 2 and Table 1.)

This effect has been studied only in short-dialysis patients. After removal of glucose, free fatty acids show a more pronounced rise during the four hours of dialysis and a slower decrease in the following hours; at the fourth hour after discontinuation of dialysis they remain above basal values.

Triglycerides, in the absence of glucose, fall at first but during the four hours after dialysis increase and pass basal levels to a clearly greater extent than is observed in the presence of glucose.

Differences between mean values of glycaemia and insulinaemia are scarcely significant in the absence of glucose. In single cases, however, a marked hypoglycaemia is observed during dialysis, which recovers at the end.
Figure 2. The behaviour of the mean values of plasma free fatty acids, triglycerides, blood glucose and plasma insulin before, during and after short dialysis with and without glucose in the dialysis fluid.

DISCUSSION

The increase in free fatty acids, found in all groups of patients, can be explained by two factors: (1) the lipolytic effect of heparin (Robinson and French, 1960; Wolff and Wolff, 1960), and (2) the presence of large amounts of acetate in dialysis fluid (Tsaltas and Freidman, 1968; Ghosal et al, 1969). In effect, heparin dosages nearly equal to those used in short dialysis cause an increase in free fatty acids in normal subjects (Pelkonen et al, 1968) to the same degree as observed in
uraemic patients. However in normals, the increase is sustained for only 1–2 hr
(Castello et al, 1963; Russo et al, 1970). By contrast, in short dialysis the in-
crease in free fatty acids continues up to the fourth hour after a single infusion
of heparin and later drops very slowly.

It can therefore be assumed that in such dialysed patients, after exhaustion
of lipolysis caused by heparin, a neosynthesis of free fatty acids from acetate
becomes evident (Tsaltas and Friedman, 1968; Ghosal et al, 1969), the effects of
which were already present at the beginning of dialysis and continued after the
end, maintaining free fatty acid values above normal levels for several hours. In
prolonged dialysis, the lipolytic activity remains high owing to the administra-
tion of heparin as continuous infusion for 12 hours, its persistence probably being
due to synthesis from an increased amount of metabolised acetate.

The reduction of triglycerides, which is observed at the same time as the
increase in free fatty acids at the beginning of dialysis in all patients, suggests
that it is due to the lipolytic effect of heparin. Post-dialysis attenuation of the
phenomenon may be explained by the reduction of heparin lipolysis and the
presence of glucose in the dialysis fluid (Carlson et al, 1965; Chalmers, 1965).
Furthermore an inhibition of resynthesis of triglycerides by acetate may operate.
(Williamson and Jones, 1964). However in long-dialysis schedules the metabolized
acetate reaches a much higher level, causing an increased synthesis of triglycerides
(Bagdade et al, 1968; Tsaltas and Friedman, 1968).

As for glucose, its removal from dialysis fluid may be responsible for enhanced
lipolysis and therefore for the increase in free fatty acids. During dialysis a loss
of glucose occurs which causes instant variations in glycaemia but is supported
by the presence of different blood glucose concentrations existing between the
input ($MV = mg\%$, $60 \pm 16$) and the output ($MV = mg\%$, $38 \pm 10$) of the dialyser.
This difference means a loss of approximately 16 g of glucose from the body, with
a minimum of 8 g and a maximum of 33 g for every dialysis of four hours.

Under these conditions, the relative lack of carbohydrates can stimulate tissue
glycogenesis, and also enhance the synthesis and increase in blood concentration
of triglycerides in the post-dialysis period. The latter sequence of events is due
to a greater availability of free fatty acids (Assan et al, 1969).

On the other hand, it is known that in normal conditions intravenous infused
glucose reduces the blood concentration of free fatty acids.

In uraemic patients it is also possible that the ingestion of carbohydrates, in
the same quantities that are lost in dialysis fluid, might not be able promptly to
compensate for the loss of glycogen, if there is insufficiency is present in uraemia and is improved but not completely
corrected by dialysis treatment.

Neither the administration of acetate, nor the presence of 2 g/l of glucose
or the absence of glucose in dialysis fluid accounts for the rare variations observed
in insulinaemia and glycaemia. Controversy remains over the extent to which
high values of free fatty acids and of heparin affect insulin secretion (Carrol and
CONCLUSION

Changes in lipid metabolism shown by an increase in free fatty acids are peculiar to the uraemic condition under dialysis treatment (Tsaltas and Freidman, 1968; Hubner et al, 1971) and probably correlated with the lipolytic effect of heparin and the neosynthesis from the acetate of the dialysis fluid.

These changes continue, though at a slightly reduced rate in the interdialysis periods. The accumulation of triglycerides, which is peculiar to uraemia (Bagdade et al, 1968; Losowsky and Kenward, 1968) is only partially corrected during dialysis. Short dialysis seems to be preferable to long dialysis because it results in smaller and less protracted increases in free fatty acids and in a better correction of elevated blood triglycerides. Dialysis, and the administration of heparin and acetate with glucose, do not modify the blood concentration of glucose, or insulin production. However, the removal of glucose from dialysis fluid causes a chronic loss of carbohydrates with periodic lowering of blood glucose concentration, which can worsen the changes of lipid metabolism in uraemia.

Acknowledgments

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References

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Open Discussion

M McGEOWN (Belfast) Some of your patients had very low blood glucose levels when you used glucose-free dialysis. Did they have any symptoms of hypoglycaemia?

MIGONE Sometimes, but the symptoms were not always related to the blood glucose.

J. WINCHESTER (Glasgow) I wonder if you had the opportunity to measure lipoprotein lipase in your patients? As I am sure you know, there is correlation between a rise in free fatty acids and cardiac arrhythmias. Did you notice this in any of your patients?

MIGONE No we didn't measure lipoprotein lipase, and no arrhythmias were observed.

ROODVOETS (Holland) In short dialysis, did you have higher triglyceride levels between dialyses?

MIGONE We had high triglyceride blood levels in all patients in intermediate periods, and the pre-dialysis blood levels are always higher than normal. This difference is due to the fact that the blood level of free fatty acids is higher in uraemic patients treated with haemodialysis than in uraemic patients under conservative treatment. Free fatty acids are higher for patients treated with
prolonged dialysis, than for short dialysis.

Comment

ROODVOETS But if short dialysis did not influence triglycerides, then there would not be any benefit on, for instance, long-term vascular damage.

B COHEN (New York) What is the concentration of acetate in your dialysis solution, and do you know how much of this is absorbed.

MIGONE 40 mEq/l, the high concentration being because we have short dialysis. We haven’t measured the rate of absorption directly. Only the change in bicarbonate, which is high after dialysis.