Increased subcutaneous insulin requirements in diabetic patients recently commenced on peritoneal dialysis

Cheuk-Chun Szeto, Kai-Ming Chow, Chi-Bon Leung, Bonnie Ching-Ha Kwan, Kwok-Yi Chung, Man-Ching Law and Philip Kam-Tao Li

Department of Medicine and Therapeutics, Prince of Wales Hospital, The Chinese University of Hong Kong, Shatin, Hong Kong, China

Abstract

Background. Diabetic patients often have reduced insulin requirements when they progress to renal failure. Since peritoneal dialysis (PD) solution contains glucose, the insulin requirement of these patients often increases after commenced on PD. However, the change in insulin requirement has not been studied systematically.

Methods. We study 60 consecutive patients (32 male) with diabetic nephropathy newly started on PD. Their insulin requirement before and 6 months after initiation of dialysis is compared. Clinical factors affecting insulin requirement are explored.

Results. All patients received a standard 6 l/day dialysis exchange. The mean age was 60.3 ± 8.9 years. Twelve patients did not require insulin before PD; four of them were started on insulin 6 months after dialysis. The average dosages of insulin 6 months before and after PD were 0.27 ± 0.08 and 0.37 ± 0.29 unit/kg/day, respectively (paired t-test, \( P < 0.001 \)). The increment in dosage was 0.103 ± 0.216 unit/kg/day. The dosage of insulin requirement correlates with the small solute transport of the peritoneal membrane, as represented by the mass transfer area coefficient (MTAC) of creatinine (\( r = -0.307, P = 0.017 \)) and haemoglobin level (\( r = 0.284, P = 0.028 \)), but not with body mass index (BMI). The change in insulin dosage correlates with the number of 2.5% dialysis cycle required per day (\( r = 0.433, P = 0.001 \)), but not with peritoneal transport status or BMI. In patients who did not receive hypertonic exchange, the dosage of insulin increased by 1.5 ± 1.1 unit/day. Each extra 2.5% 2 l exchange results in a 7.5 unit/day (95%CI 3.2–11.8, \( P = 0.001 \)) increase in insulin requirement.

Conclusion. Diabetic patients have a minimal increase in insulin requirement after initiation of PD per se, but the dosage of insulin increased markedly after exposure to hypertonic glucose solution. Our result provides a basis for the dosage adjustment of insulin in diabetic patients newly commenced on PD.

Keywords: glucose; obesity; renal failure

Introduction

In diabetic and non-diabetic patients with renal failure, insulin secretion by the \( \beta \)-islet cells of the pancreas is reduced, and there is insulin resistance in peripheral tissue [1]. However, insulin catabolism is also decreased. It is often difficult to achieve a tight control of serum glucose in dialysis patients because of the variations in dietary intake and food absorption, as well as the confounding effect of dialysis therapy.

In patients with diabetic nephropathy treated with peritoneal dialysis (PD), blood glucose control is even more difficult because of the additional glucose load from the dialysis solution. In general, the objectives of insulin treatment during peritoneal dialysis are to maintain ‘euglycaemia’ during the dwell time, to prevent post-prandial hyperglycaemia, and to avoid hypoglycaemia in the morning.

The optimal mode of insulin injection for PD patients remains controversial [1–3]. Traditionally, intraperitoneally administered insulin is regarded as the most physiological therapy, with a lower peripheral insulin concentration and reduced atherogenic effect, but equal or better glycaemic control than subcutaneous insulin. Nevalainen et al. [4] found that intraperitoneal insulin therapy offers better glycaemic control and insulin sensitivity than subcutaneous insulin. However, there is a controversial effect of intraperitoneal insulin on serum lipids. In type 1 diabetic patients, the replacement of continuous insulin infusion by intraperitoneal insulin has been associated with modifications of lipoprotein triglyceride or cholesterol content [5–7]. One study showed that the
transition from subcutaneous to intraperitoneal insulin induced a decrease in lipoprotein lipase and cholesteryl ester transfer protein activities [8], while another study reported an increase in hepatic lipase activity [7]. More importantly, some reports suggest that the use of intraperitoneal insulin is associated with an increased incidence of peritonitis or with reduced efficacy [9]. For practical purposes, good glycaemic control may be achieved with either subcutaneous intensive insulin therapy or intraperitoneal insulin administration [10]. The latter method allows a reduction of circulating free insulin levels, but requires a higher dose of insulin per day [10].

Although diabetic nephropathy is the most common cause of dialysis-dependent renal failure in many parts of the world, the insulin requirement of these patients after commenced on PD has not been well studied. In Hong Kong, most diabetic patients with advanced renal failure are treated with subcutaneous insulin. The same route of insulin administration is generally continued when these patients are started on PD. This policy provides an excellent opportunity for us to examine the change in insulin requirement in these patients.

Patients and methods

Patient selection

We reviewed 60 consecutive Chinese patients with type 2 diabetes and clinically diagnosed diabetic nephropathy newly started on PD in the dialysis unit of a single university hospital in Hong Kong from 2002 to 2004. Baseline data including age, sex, underlying renal disease and PD regimen were recorded. Comorbid conditions, including coronary artery disease, heart failure, peripheral vascular disease, cerebrovascular disease, dementia, chronic pulmonary disease, connective tissue disorder, peptic ulcer disease, liver disease, diabetes with and without complications, hemiplegia, malignancy and acquired immunodeficiency syndrome (AIDS), were also recorded. The modified Charlson’s Comorbidity Index, which was validated in PD patients [11], was used to calculate a comorbidity score.

Insulin requirement and clinical management

The dosage of subcutaneous insulin was recorded at three time points: 6 months before Tenckhoff insertion, the day before Tenckhoff insertion, and 6 months after patients were stable on PD. Body weight was also recorded at the three time points. None of the patients received intraperitoneal insulin. Fasting plasma glucose, HbA1C and serum parathyroid hormone levels were measured every 6 months, after overnight fast but with continuation of PD with 1.5% dextrose dialysate. HbA1C was measured using an automated ion-exchange chromatographic method (BioRad, Hercules, CA, USA; normal range 5.1–6.4%). Serum intact parathyroid hormone was measured using a chemiluminescence assay (Immulite, Diagnostics Products Corporation, Los Angeles, CA, USA), with a sensitivity of 0.1 pmol/l and normal range 1.6–6.9 pmol/l. Medications that might affect plasma glucose, notably corticosteroid, were also recorded. All patients received structured counselling from a dietitian during training for PD. The dosage of subcutaneous insulin was adjusted according to clinical need as decided by the individual nephrologist. In general, we adjusted the insulin dosage according to the home haemoglucostix record, report of hypoglycaemic symptoms, fasting plasma glucose, as well as the HbA1C level. In general, the PD regimen (i.e. dialysate glucose concentration) remained stable during the 6-month review period. We neglected short-term alteration of PD regimen for simplicity of analysis.

Study of the peritoneal transport

Standard peritoneal equilibration test (PET) was performed by the method of Twardowski et al. [12] when the patients were in a euvoalaemic state. Briefly, a 4 h dwell study was carried out with 2 l of glucose 2.5% dialysis fluid (Baxter-Travenol, Deerfield, IL, USA). Dialysate creatinine and glucose levels at 0, 2 and 4 h, and plasma creatinine and glucose levels at 2 h were measured. Drainage and ultrafiltration volumes (UF) at 4 h were documented. Creatinine concentration in dialysate was corrected according to a validated formula in our laboratory [13]. Dialysate-to-plasma ratios of creatinine (D/P) at 0, 2, and 4 h were calculated after correction of glucose interference. Results were plotted on a PET graph. Mass transfer area coefficients (MTAC) of creatinine normalized for body surface area (BSA) was calculated by the formula described by Krediet et al. [14]. BSA was determined from body weight and height by a nomogram [15].

Statistical analysis

Statistical analysis was performed by SPSS for Windows software version 11.0 (SPSS Inc., Chicago, IL, USA). Results were expressed as mean ± SD unless otherwise specified. Comparisons between parameters were performed by chi-square test, Student’s t-test or Pearson’s correlation coefficient as appropriate. In order to quantify the effect of dialysate glucose load on insulin requirement, we constructed simple linear regression models, using the change in dialysate glucose load as the dependent variable and dialysate glucose load or the number of 2.5% dextrose exchanges per day as the independent variable. A P-value of <0.05 was considered statistically significant. All probabilities were two-tailed.

Results

We studied 60 patients with diabetic nephropathy. Baseline demographic and clinical data are summarized in Table 1. All patients were treated with continuous ambulatory peritoneal dialysis (CAPD) and received a standard 6 l/day dialysis exchange; 18 patients (30%) required one 2.5% 2 l exchange per day, 9 patients (15%) required two daily 2.5% 2 l exchanges. Utilization of a 2.5% exchange was related to low peritoneal transport status but not residual renal function. For patients requiring 0, 1 and 2, 2.5% exchanges per day, the mean D/P at 4 h was 0.74 ± 0.10, 0.68 ± 0.12 and 0.65 ± 0.10, respectively.
Insulin requirements in PD

The dosage of insulin is summarized in Table 2. Of the 51 patients who required insulin 6 months after PD, 38 had intermediate-acting insulin and 13 had mixed short-intermediate acting insulin. There was no significant change in insulin dosage from 6 months before PD to the day of Tenckhoff insertion. Within the first 6 months of PD, patients gained an average of 1.27 ± 2.94 kg of weight. During the same period, the average increase in insulin dosage was 6.1 ± 13.4 unit/day or 0.103 ± 0.216 unit/kg/day. Twelve patients (20%) needed only dietary restriction 6 months after PD. In addition, actual dosage of insulin also correlates with body mass index (BMI) (r = 0.190, P = 0.15). The actual dosage of insulin correlates with the body weight (r = 0.351, P = 0.006) (Figure 1), but not with body mass index (BMI) (r = 0.190, P = 0.15). In all patients, insulin dosage increased 2.0 ± 6.8 unit/day (95% CI 0.0015–0.0083, P = 0.001). The correlation remained statistically significant after adjusting the insulin dosage by body weight (r = 0.406, P = 0.001). With simple linear regression, each gram of glucose from peritoneal dialysate per day is related to 0.362 unit/day (95% CI 0.159 to 0.566, P = 0.001), or 0.0049 unit/kg/day (95% CI 0.0015–0.0083, P = 0.005), increment of insulin requirement.

The change in insulin dosage did not correlate with body weight, BMI, peritoneal transport characteristics, serum parathyroid hormone level, or the change in body weight within the first 6 months of PD. However, the change in insulin requirement during the first 6 months of PD directly correlated with the daily glucose load (r = 0.433, P = 0.001). The correlation remained statistically significant after adjusting the insulin dosage by body weight (r = 0.406, P = 0.001). With simple linear regression, each gram of glucose from peritoneal dialysate per day is related to 0.362 unit/day (95% CI 0.159 to 0.566, P = 0.001), or 0.0049 unit/kg/day (95% CI 0.0015–0.0083, P = 0.005), increment of insulin requirement.

The relation between change in insulin requirement and number of 2.5% 2 l exchanges per day was further analysed and summarized in Figure 3. In patients who did not receive the 2.5% 2 l exchange, the dosage of insulin increased by 1.5 ± 11.1 unit/day or 0.040 ± 0.203 unit/kg/day during the first 6 months of PD. In patients who received one 2.5% 2 l exchange per day, the insulin dosage increased by 9.7 ± 13.7 unit/day, or 0.155 ± 0.223 unit/kg/day. In patients with two 2.5% 2 l exchanges per day, the increment was 16.0 ± 14.0 unit/day or 0.229 ± 0.184 unit/kg/day. With simple linear regression, each extra 2.5% 2 l exchange per day was related to a 7.5 unit/day (95% CI 3.2–11.8, P = 0.001) or 0.099 unit/kg/day (95% CI 0.027–0.171, P = 0.008), increase in insulin requirement.

Table 1. Demographic and baseline clinical data of the patients at the initiation of dialysis

<table>
<thead>
<tr>
<th>No. of patients</th>
<th>60</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (M:F)</td>
<td>32:28</td>
</tr>
<tr>
<td>Age (years)</td>
<td>60.3 ± 8.9</td>
</tr>
<tr>
<td>Body weight (kg)</td>
<td>61.0 ± 10.5</td>
</tr>
<tr>
<td>Body height (cm)</td>
<td>159.6 ± 7.8</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>24.1 ± 3.8</td>
</tr>
<tr>
<td>Major comorbidity, No. of cases (%)</td>
<td></td>
</tr>
<tr>
<td>Coronary heart disease</td>
<td>24 (40.0%)</td>
</tr>
<tr>
<td>Cerebrovascular disease</td>
<td>10 (16.7%)</td>
</tr>
<tr>
<td>Peripheral vascular disease</td>
<td>9 (15.0%)</td>
</tr>
<tr>
<td>Liver disease</td>
<td>9 (15.0%)</td>
</tr>
<tr>
<td>Charlson’s Index score</td>
<td>6.7 ± 1.7</td>
</tr>
<tr>
<td>Parathyroid hormone level (pmol/l)</td>
<td>28.5 ± 24.8</td>
</tr>
<tr>
<td>Residual renal function (ml/min/1.73 m²)*</td>
<td>3.84 ± 2.18</td>
</tr>
</tbody>
</table>

*At 6 months after dialysis.

Table 2. Serial trends of body build, glycaemia control and insulin dosage

<table>
<thead>
<tr>
<th>Modality of diabetic control, No. of patients (%)</th>
<th>6 months before PD</th>
<th>On the day before Tenckhoff insertion</th>
<th>6 months after PD</th>
<th>P-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diet only</td>
<td>13 (21.7%)</td>
<td>12 (20.0%)</td>
<td>8 (13.3%)</td>
<td></td>
</tr>
<tr>
<td>Oral agents</td>
<td>1 (1.7%)</td>
<td>0</td>
<td>1 (1.7%)</td>
<td></td>
</tr>
<tr>
<td>Insulin</td>
<td>46 (76.7%)</td>
<td>48 (80.0%)</td>
<td>51 (85.0%)</td>
<td></td>
</tr>
<tr>
<td>Insulin dosage</td>
<td>Total dosage (unit/day)</td>
<td>17.9 ± 18.8</td>
<td>17.1 ± 14.3</td>
<td>23.2 ± 18.9</td>
</tr>
<tr>
<td></td>
<td>Dosage adjusted for body weight (unit/kg/day)</td>
<td>0.27 ± 0.28</td>
<td>0.26 ± 0.20</td>
<td>0.37 ± 0.29</td>
</tr>
<tr>
<td></td>
<td>Body weight (kg)</td>
<td>61.5 ± 10.9</td>
<td>61.6 ± 11.5</td>
<td>62.9 ± 11.6</td>
</tr>
<tr>
<td></td>
<td>Body mass index (kg/m²)</td>
<td>24.1 ± 3.8</td>
<td>24.1 ± 4.0</td>
<td>24.6 ± 4.0</td>
</tr>
<tr>
<td></td>
<td>Haemoglobin A1c (%)</td>
<td>6.7 ± 2.0</td>
<td>6.8 ± 2.0</td>
<td>6.9 ± 2.0</td>
</tr>
<tr>
<td></td>
<td>Fasting plasma glucose (mmol/l)</td>
<td>7.8 ± 4.6</td>
<td>7.9 ± 4.7</td>
<td>7.6 ± 4.2</td>
</tr>
</tbody>
</table>

PD, peritoneal dialysis. *Paired Student’s t-test comparing the day of Tenckhoff insertion and 6 months after PD.
Discussion

In the present study, we examined the change in insulin requirement in diabetic patients after initiation of PD. We found that daily glucose load from dialysate was an important factor that determined the increase in insulin dosage after PD. Nonetheless, there was a substantial inter-individual variation in insulin requirement.

Since the early report by Amair et al. [16], PD with intraperitoneal administration of insulin is often regarded as a suitable alternative treatment for diabetics with end-stage renal disease. Previous study shows that after initiation of PD, there is often a deterioration of glycaemic control, as represented by HbA1c, if the patients remain on subcutaneous insulin, which may be partly due to the absorbed energy from the dialysate [4]. Intraperitoneal insulin therapy offers better glycaemic control and insulin sensitivity than subcutaneous insulin [4,17]. Compared with the subcutaneous route, intraperitoneal insulin may display more consistent absorption, produce more physiological insulin concentrations, and be more convenient to administer [2,3]. However, intraperitoneal insulin therapy seems to have detrimental effects on serum lipids [4,17]. Scarpioni et al. [10] found that in uraemic diabetic patients on PD, good glycaemic control may be achieved either with subcutaneous intensive insulin therapy or with intraperitoneal insulin administration. The latter method allows reduction of circulating free insulin levels, but requires a higher dose of insulin per day [10]. In practice, the route will remain a matter of patient preference. In our centre, continuation of subcutaneous insulin is preferred because patients often get used to the technique and a single daily subcutaneous dosage of medium-to-long acting insulin is usually more convenient than multiple intraperitoneal dosage.

Similar to previous study [4] and common belief, we observed a substantial weight gain in diabetic patients during the first 6 months of PD, which may be a result of the absorbed glucose from the dialysate, as well as improved oral intake following the improvement in uraemic symptoms. Although body weight was related to the absolute dosage of insulin, we found that the increase in body weight did not correlate with the change in insulin requirement after PD, indicating that increase in obesity, and hence insulin resistance, is not the major cause of higher insulin requirement in PD patients.

The correlation between increase in insulin requirement and daily glucose load is weak. A correlation coefficient of 0.433 means that only 19% of the variability in change in insulin requirement was explained by the daily glucose load. It remains obscure what other determinants of the change in insulin

![Fig. 1. Relation between dosage of insulin and body weight.](https://academic.oup.com/ndt/article/22/6/1697/1924982)

![Fig. 2. Relation between dosage of insulin and (A) mass transfer area coefficient (MTAC) of creatinine; and (B) haemoglobin level.](https://academic.oup.com/ndt/article/22/6/1697/1924982)
requirement are. The data showing the effect of a 2.5% PD exchange is apparently more impressive, despite the small sample size. Theoretically, more glucose would be absorbed from the dialysate in high peritoneal transporters, resulting in higher insulin need. We find that the overall insulin dosage relates to body weight, peritoneal transport characteristics and haemoglobin level. However, none of these factors correlates with the change in insulin requirement after PD. Because of the retrospective nature of our study, we do not have fasting insulin level or measures of the degree of insulin resistance (for example, the homeostasis model assessment of insulin resistance, HOMA-IR) in our patients. On this aspect, it is important to note that PD treatment per se may lead to insulin insensitivity in non-diabetic end-stage renal disease patients and the high glucose content of PD solutions may be responsible for insulin resistance [18]. Recently, Amici et al. [19] further showed that chronic use of icodextrin solution in the long night-time dwell can reduce serum insulin levels and increase insulin sensitivity in PD patients.

In the present study, we found that PD patients treated with a standard regimen of 1.5% 21 exchange thrice daily did not often require increase in insulin dosage. Each daily exchange of 2.5% dialysate, however, would on average require an extra 7.5 units of insulin per day. Since the 95% CI of our result is wide, we recommend that for each 2.5% exchange, the dosage of subcutaneous insulin should be increased empirically by 4 unit/day (i.e. close to the lower limit of the CI), and given the highly variable individual need, the blood haemoglucostix should be carefully monitored. Although none of our patients required 4.25% dextrose dialysate, the increase in insulin requirement is likely to be directly proportional to the dextrose concentration. It is interesting to note that this empirical need is identical to the Toronto Western Hospital Protocol for intraperitoneal insulin [20].

Our result, however, should be extrapolated to the western population with caution. All of our patients were Chinese and received a 21 exchange thrice daily, a regimen that is standard in our region but rare elsewhere in the world [21,22]. All of our patients had type 2 rather than type 1 diabetes. Moreover, the haemoglobin level of our patients (Figure 2) was much lower than that suggested by the USA or European guidelines [23,24]. It is known that in uroaemic patients, insulin resistance is associated with anaemia [25], and correction of anaemia by erythropoietin reverses insulin resistance and hyperinsulinaemia [26]. On the whole, the insulin requirement of our patients was small (around 0.3 unit/kg/day), indicating either some residual pancreatic islet cell function or enhanced insulin sensitivity. In general, obesity is less common in our patients. It should be noted that despite similar body fat contents, the BMI cut-off value used to define obesity in Chinese should be lower as compared with Caucasians, and a BMI over 23 kg/m2 should be taken as the definition of overweight in Chinese subjects [27]. Although we did not find any relation between peritoneal transport characteristics and increase in insulin dosage, low and low-average transporters are common in our population [28,29]. It remains possible that in patient populations with a higher prevalence of high peritoneal transporters (and therefore higher glucose absorption from dialysate), the increase in insulin requirement would be higher. The basis of adjusting insulin dosage from our result may not always be applicable in other PD patients, who may have a higher BMI, be less anaemic and have different peritoneal membrane characteristics. In addition, our result is probably not applicable to patients treated with automated PD, which has a short dwell time.

Acknowledgement. This study was supported in part by the CUHK research account 6901031.

Conflict of interest statement. None declared.
References


Received for publication: 3.10.06
Accepted in revised form: 21.12.06