The aim of this study was to analyse whether the insulin to glucose relationship following an intravenous glucose load in non-diabetic patients delivered during haemodialysis was affected by extracorporeal clearance and whether this relationship could be determined by an abridged sampling protocol.

**References**


**Insulinogenic index during haemodialysis**

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**Abstract**

**Background.** The aim of this study was to analyse whether the insulin to glucose relationship following an intravenous glucose load in non-diabetic patients delivered during haemodialysis was affected by extracorporeal clearance and whether this relationship could be determined by an abridged sampling protocol.

**Methods.** Studies were done during routine haemodialysis following the infusion of 0.5 g glucose per kilogram body mass. Extracorporeal effects were measured by online clearance ($K_{OCM}$) and insulin clearance ($K_I$). The insulin to glucose relationship was examined for a period of 1 h following the infusion of glucose. The integral response measured as the insulinogenic index ($I_G$) was compared...
to the relationship between insulin and glucose concentrations measured at the whole period ($k_{IG}$) as well as from only two samples taken at baseline and after 10 min ($k_{l10}$).

**Results.** Eight non-diabetic haemodialysis patients (three females) with a dry body mass of $76.9 \pm 18.2$ kg completed the study. $I_G$ was $5.4 \pm 4.4$ U/mol and not different from normal reference values. A linear relationship showing characteristic slopes $k_{IG}$ was observed between arterial insulin and glucose levels. $k_{IG}$ was $6.1 \pm 5.0$ U/mol and not different from $k_{l10} = 5.9 \pm 4.8$ U/mol measured after 10 min of glucose infusion and ongoing dialysis. $I_G$, $k_{IG}$ and $k_{l10}$ were highly correlated ($P < 0.0001$), and $k_{l10}$ showed substantial concordance ($r_s = 0.99$) with $I_G$. Moreover, $I_G$, $k_{IG}$ and $k_{l10}$ were independent of $K_{OCM}$ or $K_t$. 

**Conclusions.** The insulin to glucose relationship is measurable within 10 min of glucose administration and unaffected by extracorporeal clearance. This could be helpful to characterize the insulin response to a glucose stimulus during haemodialysis.

**Keywords:** clearance; extracorporeal system; glucose; insulin

**Introduction**

Impaired glucose control is a major feature of today’s end-stage renal disease population, both because of reduced peripheral glucose utilization, impaired insulin secretion and reduced insulin degradation [1]. These issues are considered to play a major role in the high morbidity and mortality of haemodialysis patients [2]. An important question in this regard is the identification of impaired insulin secretion and the control of glucose levels [3,4]. There are well-established techniques to identify reduced peripheral glucose utilization (insulin resistance) and various patterns of impaired insulin secretion (β-cell exhaustion) [5–7]. However, these techniques require considerable effort, time and resources. On the other hand, the maintenance haemodialysis patient spends much time on the dialysis machine, and the question arises, whether this time together with the extracorporeal equipment and the direct access to the circulation could be used for the purpose of identifying important characteristics of the patient’s glucose–insulin system. Glucose is a small molecule, easily dialysed and a component of standard dialysate [8–10]. Therefore, one would assume that the glucose–insulin system is affected by haemodialysis.

The aim of this study was to analyse whether extracorporeal clearance was an important confounder when estimating the insulin response to a glucose stimulus and to propose an abridged test to identify the insulin response in patients during their regular haemodialysis treatment.

**Materials and methods**

**Patients**

Studies were done in stable and non-diabetic maintenance haemodialysis patients during a regular mid-week treatment and repeated the following week. Patients with recent signs of infection or inflammation such as fever or elevated C-reactive protein levels were excluded from the study. Patients provided written informed consent to participate in the study approved by the Internal Review Board of the Medical University of Graz.
Insulinogenic index during haemodialysis

was also measured by the slope (\(k\)) of the linear regression of plasma insulin (I) upon plasma glucose (G) concentrations in each subject,

\[ I = kG + d, \]

where \(d\) is the intercept of the linear regression, as well as by the change in insulin (\(I\)) relative to the change in glucose concentration (\(G\)) between baseline (\(t = 0\)) and \(t = 10\) min (\(k_{10}\) in U/mol)

\[ k_{10} = \frac{c_I(t=10) - c_I(t=0)}{c_G(t=10) - c_G(t=0)}. \]

The homeostasis model assessment (HOMA) index was calculated as fasting glucose (in mmol/L) times fasting insulin (in mU/L) divided by 22.5.

The relationship between different variables as well as the relationship between identical variables obtained in subsequent measurements was examined by linear regression analysis and by ANOVA. Agreement between different measures of insulinogenic index was determined by the concordance correlation coefficient (\(\rho_c\)) according to Lin [13,14]. A probability \(P < 0.05\) was considered significant to reject the null hypothesis. Data are presented as means ± standard deviation (SD).

Data analysis

The insulinogenic index (\(I_G\) in U/mol) was obtained as the insulin response relative to the glucose stimulus over the observation phase of 1 h as defined by Seltzer et al. [12]

\[ I_G = \frac{A_I}{A_G}, \]

where \(A_I\) (in U/L/min) and \(A_G\) (in mol/L/min) refer to insulin and glucose areas under the curve, respectively. \(A_I\) and \(A_G\) were computed by trapezoidal integration of the time course of arterial line insulin and glucose concentrations between \(t = 0\) and \(t = 60\) min and subtraction of the respective baseline values.

The response of the insulin secretory system to the glucose stimulus was also measured by the slope (\(k_{IG}\), in U/mol) of the linear regression line of plasma insulin (\(I_I\)) upon plasma glucose (\(G_1\)) concentrations in each subject,

\[ I_I = k_{IG}G_{10} + d, \]

where \(d\) is the intercept of the linear regression, as well as by the change in insulin (\(I_I\)) relative to the change in glucose concentration (\(G_{10}\)) between baseline (\(t = 0\)) and \(t = 10\) min (\(k_{10}\) in U/mol)

\[ k_{10} = \frac{c_I(t=10) - c_I(t=0)}{c_G(t=10) - c_G(t=0)}. \]

The relationship between different variables as well as the relationship between identical variables obtained in subsequent measurements was examined by linear regression analysis and by ANOVA. Agreement between different measures of insulinogenic index was determined by the concordance correlation coefficient (\(\rho_c\)) according to Lin [13,14]. A probability \(P < 0.05\) was considered significant to reject the null hypothesis. Data are presented as means ± standard deviation (SD).

Table 3. Insulin and glucose characteristics (n = 16)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Unit</th>
<th>Mean</th>
<th>SD</th>
<th>Min</th>
<th>Max</th>
<th>CV</th>
</tr>
</thead>
<tbody>
<tr>
<td>(A_I)</td>
<td>U/L/min</td>
<td>1.816</td>
<td>0.899</td>
<td>0.009</td>
<td>6.333</td>
<td>1.030</td>
</tr>
<tr>
<td>(A_G)</td>
<td>mol/L.min</td>
<td>0.315</td>
<td>0.099</td>
<td>0.102</td>
<td>0.444</td>
<td>0.315</td>
</tr>
<tr>
<td>(I_G)</td>
<td>U/mol</td>
<td>5.350</td>
<td>4.401</td>
<td>0.330</td>
<td>14.270</td>
<td>0.823</td>
</tr>
<tr>
<td>(k_{IG})</td>
<td>U/mol</td>
<td>6.062</td>
<td>5.037</td>
<td>0.510</td>
<td>19.530</td>
<td>0.831</td>
</tr>
<tr>
<td>(r_{IG})</td>
<td></td>
<td>0.948</td>
<td>0.057</td>
<td>0.840</td>
<td>1.000</td>
<td>0.039</td>
</tr>
<tr>
<td>(k_{10})</td>
<td>U/mol</td>
<td>5.897</td>
<td>4.769</td>
<td>0.530</td>
<td>17.060</td>
<td>0.809</td>
</tr>
</tbody>
</table>

SD, standard deviation; CV, coefficient of variation; \(A_G\), area under the glucose curve; \(A_I\), area under the insulin curve; \(k_{IG}\), insulinogenic index; \(k_{10}\), slope and correlation coefficient (\(r_{IG}\)) of the insulin to glucose relationship; \(k_{10}\), change of insulin relative to change in glucose at \(t = 10\) relative to baseline.

Table 4. Correlation and concordance

<table>
<thead>
<tr>
<th>Variables</th>
<th>(r)</th>
<th>-95%</th>
<th>+95%</th>
<th>(P)</th>
<th>(\rho_c)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(I_G), (M_b)</td>
<td>0.713</td>
<td>0.337</td>
<td>0.893</td>
<td>&lt;0.01</td>
<td>0.021</td>
</tr>
<tr>
<td>(I_G), BMI</td>
<td>0.594</td>
<td>0.140</td>
<td>0.842</td>
<td>&lt;0.05</td>
<td>0.055</td>
</tr>
<tr>
<td>(K_{OCM}, K_I)</td>
<td>0.589</td>
<td>0.023</td>
<td>0.869</td>
<td>&lt;0.05</td>
<td>0.028</td>
</tr>
<tr>
<td>(K_{OCM}, I_G)</td>
<td>0.093</td>
<td>-0.422</td>
<td>0.563</td>
<td>n.s. (0.74)</td>
<td>0.005</td>
</tr>
<tr>
<td>(K_{OCM}, k_{IG})</td>
<td>0.171</td>
<td>-0.354</td>
<td>0.615</td>
<td>n.s. (0.53)</td>
<td>0.001</td>
</tr>
<tr>
<td>(K_{OCM}, k_{10})</td>
<td>0.141</td>
<td>-0.382</td>
<td>0.595</td>
<td>n.s. (0.61)</td>
<td>0.001</td>
</tr>
<tr>
<td>(K_{I}, I_G)</td>
<td>0.197</td>
<td>-0.425</td>
<td>0.693</td>
<td>n.s. (0.55)</td>
<td>0.012</td>
</tr>
<tr>
<td>(K_{I}, k_{IG})</td>
<td>0.234</td>
<td>-0.393</td>
<td>0.712</td>
<td>n.s. (0.47)</td>
<td>0.016</td>
</tr>
<tr>
<td>(K_{I}, k_{10})</td>
<td>0.233</td>
<td>-0.393</td>
<td>0.712</td>
<td>n.s. (0.48)</td>
<td>0.015</td>
</tr>
<tr>
<td>(I_G, k_{IG})</td>
<td>0.955</td>
<td>0.872</td>
<td>0.985</td>
<td>&lt;0.0001</td>
<td>0.935</td>
</tr>
<tr>
<td>(I_G, k_{10})</td>
<td>0.979</td>
<td>0.940</td>
<td>0.993</td>
<td>&lt;0.0001</td>
<td>0.969</td>
</tr>
<tr>
<td>(k_{IG}, k_{10})</td>
<td>0.990</td>
<td>0.971</td>
<td>0.997</td>
<td>&lt;0.0001</td>
<td>0.988</td>
</tr>
</tbody>
</table>

\(r\), correlation coefficient; ±95%, confidence interval; \(P\), probability; \(\rho_c\), concordance correlation coefficient; \(I_G\), insulinogenic index; \(M_b\), body mass; BMI, body mass index; \(K_{OCM}\), online clearance; \(K_I\), insulin clearance; \(k_{IG}\), slope of the insulin to glucose relationship; \(k_{10}\), change of insulin relative to change in glucose at \(t = 10\) relative to baseline; n.s., not significant.
Fig. 2. Insulin to glucose relationship. Insulin to glucose relationship in subjects A to H identified in subsequent studies (1 and 2). The broken line shows the linear regression between arterial insulin (c_I) and glucose concentrations (c_G). Notice the different scale for c_I plotted on the y-axis.
Results

Eight patients (Table 1), three of them female, completed two subsequent studies so that 16 studies were available for the final analysis.

Treatment characteristics are summarized in Table 2. Mean baseline plasma glucose and insulin concentrations were $5.9 \pm 0.9 \text{ mmol/L}$ and $14.7 \pm 15.9 \text{ mU/L}$, respectively, corresponding to a mean HOMA index of $4.2 \pm 5.6 \text{ mU/L}^2$. HbA1c was $4.9 \pm 0.4\%$. $38.4 \pm 8.8 \text{ g}$ of glucose were administered into the drip chamber of the venous blood line within $1.9 \pm 0.4 \text{ min}$. Online clearance $K_{OCM}$ determined by the dialysis machine was $223.2 \pm 24.4 \text{ mL/min}$. Extracorporeal insulin clearance $K_I$ was determined as $62.6 \pm 26.8 \text{ mL/min}$ in a subset of 12 studies. All tests were completed without complications and without changes in mean arterial pressures and heart rates.

Following the infusion at $t = 0 \text{ min}$, arterial glucose and insulin concentrations markedly increased above baseline and returned to high normal values within the observation phase of 60 min (Figure 1). Concentrations as well as areas under the curve ($A_I$, $A_G$) were more variable for insulin than for glucose (Table 3) leading to a marked dispersion of the insulinogenic index ($I_G = 5.35 \pm 4.40 \text{ U/mol}$). To some degree, this dispersion was related to the differences in body mass and body mass index in the patients studied (Table 4). Paired insulin and glucose concentrations measured in the same study showed strong linear relationships (Figure 2). These relationships were characterized by slopes $k_{IG}$ which were reproducible within patients but largely different between patients ($0.5 \text{–} 19.5 \text{ U/mol}$) (Figure 3, Table 3). These slopes $k_{IG}$ were significantly correlated and showed moderate concordance with the insulinogenic index $I_G$ ($r = 0.96, P < 0.0001, \rho_c = 0.94$, Table 4, Figure 4). Sub-

Fig. 3. Reproducibility of insulin response. Identity plot of insulinogenic index ($I_G$, left panel) and slope of the insulin to glucose relationship ($k_{IG}$, right panel) measured in the same patients during first (1) and second (2) treatments ($n = 8$). The full line shows the line of identity.

Fig. 4. Insulinogenic Index. Relationship between insulinogenic index ($I_G$) and the slope ($k_{IG}$) of insulin to glucose concentrations (left panel) compared to the relationship between $I_G$ and the ratio of insulin to glucose change ($k_{10}$) measured within 10 min of glucose administration (right panel). The full line shows the line of identity.
stantial concordance was found between $k_{10}$ and the insulinogenic index $I_G (r = 0.98, P < 0.0001, \rho_c = 0.97)$ as well as between $k_{10}$ and $k_{IG} (r = 0.99, P < 0.0001, \rho_c = 0.99)$ (Table 4, Figure 4). Most importantly, none of these three measures ($I_G, k_{IG}, k_{10}$) correlated with the procedure of haemodialysis as characterized by online clearance ($K_{OCM}$) or extracorporeal insulin clearance ($K_I$) (Table 4).

**Discussion**

This study describes the response of arterial insulin in eight non-diabetic patients during haemodialysis following the delivery of a bolus of glucose through the extracorporeal system. The characteristic response measured within 10 min of glucose administration was not different from the insulinogenic index measured over the course of 1 h of continuing haemodialysis. It was therefore concluded that the insulinogenic index was independent of extracorporeal clearance and could be measured from two blood samples only, the first drawn from the arterial blood line at baseline and the second taken 10 min after the infusion of glucose.

The insulin response to a glucose load has been studied before and after haemodialysis [15,16], but to our knowledge, this is the first study done during haemodialysis. Interestingly, in spite of a higher glucose load of 0.5 g/kg, the area under the glucose curve $A_G$ of 0.315 ± 0.099 mol/L min (Table 3) found in our study was not much higher than that measured before (0.233 ± 0.017 mol/L min) or after haemodialysis (0.311 ± 0.028 mol/L min) using a reduced load of 0.33 g glucose per kilogram body mass [15]. Failure of the larger glucose load to produce a larger area under the curve during haemodialysis can be explained by extracorporeal clearance of glucose. In a companion study, it was found that ~40 ± 10% of a glucose bolus administered during haemodialysis was eliminated extracorporeally [17]. Thus, of the 0.5 g/kg administered during haemodialysis, only 0.3 g/kg are effectively absorbed by the patient, so that the load used in this study is comparable to that of a reduced load reported previously [15,16].

The insulin area under the curve $A_I$ was 1.82 ± 1.87 U/L min (Table 3) and not different from that measured before (1.53 ± 0.24 U/L min) or after haemodialysis (1.83 ± 0.38 mol/L min) reported by Ferrannini et al. [15] for ten patients and comparable to that reported by Allegra et al. [16] for 29 healthy controls (1.56 ± 0.08 U/L min) following a glucose load of 0.33 g per kilogram body mass. The range of values in our study (0.10–6.33 U/L min), however, was much larger, most likely because of the large range in body mass (59–115 kg) and body mass index (20.2–34.0 kg/m²) compared to the body mass (45–80 kg) and body mass index (16.3–28.3 kg/m²) of the earlier study [15].

During haemodialysis, there is a substantial extracorporeal clearance both of glucose and insulin. Clearance of glucose is ~60% of effective urea clearance as measured by an online clearance technique [17,18]. Clearance of insulin was 62.6 ± 26.8 mL/min and ~30% of effective urea clearance (Table 2). The direct effects of extracorporeal clearance can be expected to lower the concentration as well as the area under the curve of both glucose and insulin in arterial blood. However, since glucose and insulin concentrations are not independent of each other, the changes induced by extracorporeal clearance are likely blunted because of mutual negative feedback control. A more detailed analysis of the effects of extracorporeal clearance on glucose and insulin concentrations requires kinetic modelling of the glucose–insulin system, but this is beyond the scope of this study.

The insulinogenic index $I_G$ determined in this study was 5.3 ± 4.4 U/mol (Table 3) and not different from that measured before (6.55 ± 0.92 U/mol) or after haemodialysis (6.17 ± 1.54 U/mol) and reported by Ferrannini et al. [15]. Unsurprisingly, an equivalent behaviour was observed for the slope of the insulin to glucose relationship $k_{IG}$, as both insulinogenic index $I_G$ and $k_{IG}$ measure the insulin response normalized for the glucose stimulus. The linear relationship between insulin and glucose was not affected by dialysis. $k_{IG}$ was 6.06 ± 5.04 U/mol (Table 3) and not different from that measured before (5.94 ± 1.08 U/mol) or after haemodialysis (8.42 ± 2.88 U/mol) reported elsewhere [15]. The insulinogenic index $I_G$ measured in this study was also comparable to that determined in 10 uraemic patients (7.54 ± 0.69 vs. 8.60 ± 0.72 U/mol) using two different glucose loads (0.33 vs. 0.5 g/kg) [16].

The linear relationship between insulin and glucose concentrations (Figure 2) refers to a proportional time course of glucose and insulin traces, $c_G(t)$, and $c_I(t)$, respectively. Integration of the relationship $c_I(t) = k_{IG} c_G(t)$ yields $A_I = A_G k_{IG}$, and further $A_I/A_G = k_{IG}$, which finally confirms the identity of $I_G = k_{IG}$ observed in Figure 4.

There was substantial concordance ($\rho_c > 0.95$) for the change in insulin relative to the change in glucose measured at t = 10 min ($k_{10}$) and the insulinogenic index ($I_G$) as well as the slope of the insulin to glucose relationship for the duration of the whole observation phase of 60 min ($k_{IG}$) (Figure 4, Table 4). Moreover, none of the parameters $I_G$, $k_{IG}$ and $k_{10}$ were related to extracorporeal clearance. These results indicate that the insulin to glucose relationship was independent of technical aspects of ongoing haemodialysis. As there was no difference between $k_{10}$ and $k_{IG}$, the procedure to characterize the insulin response to a glucose stimulus during haemodialysis could be simplified by measuring glucose and insulin concentrations in two blood samples only, at baseline and 10 min after administration of a standardized glucose load. This also decreases the costs for sample analysis.

The insulinogenic index, the ratio of the change in insulin to the change in glucose concentrations following a glucose load, has been proposed as a surrogate indicator of impaired insulin secretion and of the metabolic consequences of diabetes [19]. The focus on a small number of non-diabetic dialysis patients for the purpose of analysing the possible effects of haemodialysis on glucose and insulin levels is a limitation of this study from the clinical point of view. We can only speculate that the approach described in this manuscript is likely to identify impaired insulin secretion in dialysis patients with onset of diabetes. This, however, remains to be tested. Furthermore, patients were studied during dialysis, and pre- and/or post-dialysis control measurements were omitted for the sake of patient comfort and compliance. This could be considered as
Insulinogenic index during haemodialysis

This opens up a new approach for metabolic studies in a population at high risk for metabolic disorders. Such measurements could be helpful to better characterize haemodialysis patients with regard to their glucose metabolism while they are dialysed.

Conflict of interest statement. None declared.

References


Handgrip strength, but not other nutrition parameters, predicts circulatory congestion in peritoneal dialysis patients

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Abstract

Background. Handgrip strength (HGS) is a marker of lean muscle mass. This study aims to test the hypothesis that a low HGS reflects a diseased cardiac status and predicts future risk of circulatory congestion in chronic peritoneal dialysis (PD) patients.

Methods. Two hundred and eighteen chronic PD patients were prospectively recruited from a single regional dialysis unit in Hong Kong. HGS, serum albumin, lean body mass (LBM) by creatinine kinetics (CK) and subjective global assessment (SGA) were assessed at study entry and examined in relation to the risk of developing circulatory congestion over a 4-year follow-up.

Results. Adjusting for age, gender and height, HGS showed significant correlations with LBM by CK, SGA, serum albumin, atherosclerotic vascular disease, left ventricular (LV) mass index and early mitral inflow velocity to peak mitral annulus velocity (E/Em ratio). In the multivariable Cox regression analysis, HGS (P = 0.004) and ejection fraction (P = 0.004) were both second to LV mass index (P < 0.001) as the most significant factors in predicting circulatory congestion at 4 years. Serum albumin, LBM by CK and SGA were not independently predictive of circulatory congestion. Patients with systolic dysfunction and HGS < gender-specific median had an adjusted hazard ratio of 2.77 [95% confidence interval (CI), 1.46–5.28; P = 0.002] in developing circulatory congestion than those with normal systolic function and HGS ≥ gender-specific median.

Conclusions. A low HGS reflects a diseased cardiac status and predicts future risk of circulatory congestion independent of other nutritional, echocardiographic and clinical parameters in PD patients. The important link between skeletal myopathy and myocardial disease in uraemic patients warrants further investigation.

Keywords: circulatory congestion; echocardiography; handgrip strength; nutrition; peritoneal dialysis

Introduction

Heart failure is a common complication in the dialysis population. Harnett et al. reported that nearly one-third of the dialysis patients had heart failure at initiation of dialysis. Of these, over half developed recurrences while on dialysis. Even among patients with no baseline heart failure, 25% developed heart failure subsequently during the course of dialysis [1]. The presence of heart failure at baseline predicts an increased mortality, both in the short term [2] and long term [1], and is often complicated by cachexia that is common in these patients. In the general non-renal failure population, the frequency of body wasting has been reported to be ~12–16% [3,4], but can be up to 50% in those with severe heart failure [5]. Our recent

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