Insulin Resistance after Renal Transplantation: The Effect of Steroid Dose Reduction and Withdrawal

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Abstract. Cardiovascular disease is a prevalent and serious complication after solid organ transplantation. Treatment with glucocorticoids is associated with increased risk for diabetes mellitus, insulin resistance, weight gain, hypercholesterolemia, and hypertension, all shown to be independent risk factors for cardiovascular disease. We sought to test the hypothesis that tapering of prednisolone (TAP) the first year after renal transplantation improves insulin sensitivity (IS), and to assess the effect of complete steroid withdrawal (SW) on IS in patients on a cyclosporine-based immunosuppressive regimen. All patients (n = 57) completed two consecutive hyperinsulinemic euglycemic glucose clamp procedures, a TAP group (n = 34) and a control group (n = 12) at 3 and 12 mo after transplantation, and a SW group (n = 11) before and 5 mo after SW. The IS index (ISI) was calculated as the glucose disposal rate divided by mean serum insulin the last 60 min of the clamp. In the TAP group, the mean (range) daily prednisolone was reduced from 16 (10 to 30) to 9 (5 to 12.5) mg accompanied by an average increased ISI of 24% (P = 0.008). In contrast, no significant change in ISI was observed in the control group (0%, P = 0.988). In the SW group, withdrawal of 5 mg prednisolone did not influence mean ISI significantly (−8%, P = 0.206). Lowering daily prednisolone toward 5 mg/d has beneficial effects on insulin action after renal transplantation, but withdrawal of 5 mg prednisolone may not influence IS significantly.

The success of renal transplantation in extending patient and graft survival has uncovered an increased risk of cardiovascular disease (CVD) in allograft recipients. At present, glucocorticoid drugs are included in most immunosuppressive protocols used after organ transplantation. Treatment with glucocorticoids is associated with increased risk for diabetes mellitus, insulin resistance, weight gain, hypercholesterolemia, and hypertension, all independent risk factors for CVD (1–5).

During the last 50 yr, the term “steroid diabetes” has been used to characterize the type of diabetes that may develop in humans treated with glucocorticoids (6,7). More specifically, corticosteroid-induced diabetes may be considered a part of the group IIIE, drug- or chemical-induced diabetes, as suggested by the American Diabetes Association Expert Committee (8). The diabetogenic effect of glucocorticoids is primarily caused by insulin resistance that has been explained by enhanced gluconeogenesis in the liver and decreased glucose uptake and glycogen synthesis in skeletal muscle cells (1,2).

We have previously reported that posttransplantation diabetes mellitus occurs in up to 20% of renal transplant recipients receiving a cyclosporine A (CsA, Neoral) based triple immunosuppressive regimen, and even more patients (30%) have impaired glucose tolerance (9). Moreover, data from two prospective observational studies indicate that tapering of daily prednisolone is associated with improved glucose tolerance, whereas long-term improvement of glucose tolerance is associated with enhanced insulin sensitivity (IS) (10,11).

Ekstrand et al. (12) have shown that even renal transplant recipients with normal glucose tolerance are insulin resistant when compared with control subjects from the general population. The mean total glucose disposal during a hyperinsulinemic euglycemic glucose clamp (HEC) was 25% lower in normoglycemic kidney transplant recipients treated with 8.2 ± 1.5 mg methylprednisolone/d than in age- and weight-matched healthy control subjects.

Weight gain is common after renal transplantation (13–15) and may represent an important and modifiable risk factor for impaired insulin action and the development of diabetes (4). In a cross-sectional study of 167 patients, we reported that daily prednisolone dose, body mass index (BMI), and triglyceride (TG) concentrations were independent predictors of insulin resistance 3 mo after renal transplantation (16).

In a 6-yr follow-up study, decreasing daily prednisolone dose from a median of 10 to 5 mg was independently associated with improved IS (11). An oral glucose tolerance test–derived IS index (ISI_TG) was used to assess IS in our previous studies (11,16).

It is well known that treatment with calcineurin inhibitors, tacrolimus and CsA, increases the risk for new-onset posttransplantation diabetes mellitus. Recently, van Duijnhoven and coworkers (17) evaluated glucose metabolism in patients receiving tacrolimus or CsA the first 3 yr after transplantation but did not address changes in prednisolone dose specifically. In
the same issue of the journal, Boots et al. (18) reported that withdrawal of 10 mg prednisolone in tacrolimus treated recipients tended to be associated with lower insulin resistance (HOMA-IR, $P = 0.17$; insulin/glucose ratio $P = 0.10$).

To our knowledge, no prospective longitudinal study has been conducted using gold standard methods (HEC technique) to address the effects of steroid dose tapering, steroid withdrawal, or weight change on IS in solid organ transplant recipients. The main objectives of the present prospective observational study were first, to assess whether tapering of daily prednisolone dose (TAP) during the first year after transplantation has beneficial effects on insulin action as measured by HEC, and further, to evaluate the effect of steroid withdrawal (SW) on IS in a group of patients treated with low-dose prednisolone (5 mg/d).

**Materials and Methods**

The study was approved by the Regional Committee for Medical Research Ethics and was performed in accordance with the Declaration of Helsinki (19). All patients ($n = 57$) gave informed consent to participate. All patients were given a triple immunosuppressive regimen, including prednisolone, CsA (Sandimmun Neoral; Novartis, Basel), and azathioprine. The immunosuppressive protocol has previously been described in detail (9).

**Procedures.** The HEC procedures were performed with a modification of the method by DeFronzo et al. as described previously (20,21). Lean body mass (lbm) was estimated by Hume’s formula (22). The glucose disposal rate (GDR) was calculated from the amount of glucose infused during the last 60 min, and the IS index (ISI) was calculated as GDR ($\mu$mol/kg (lbm) $\times$ min) divided by mean serum insulin (pmol/L) during the last 60 min of the clamp.

Overweight was defined as BMI between 25.0 and 29.9 kg/m$^2$, obesity as BMI $\geq$30.0 kg/m$^2$, and underweight as BMI $<18.5$ kg/m$^2$ (3). The waist circumference (WC) was measured at the midpoint between the lowest rib and the iliac crest (23). The body fat percentage was calculated by the formula suggested by Deurenberg et al. (24): Body fat percentage = $1.20 \times$ BMI + $0.23 \times$ age $-10.8 \times$ sex $-5.4$ (male $= 1$, female $= 0$).

**Tapering of Prednisolone.** A total of 46 renal transplant recipients completed two consecutive HEC procedures, the first at a median (range) of 3 (2 to 5) mo, and the second at 12 (7 to 22) mo, after renal transplantation. In 34 patients (TAP group), the daily prednisolone dose was tapered by 1.25 to 20 mg, whereas the steroid dose was stable (median 10 mg/d) in 12 patients who served as controls (CON group). No patient had previously known diabetes, and the majority ($n = 45$) were examined with an oral glucose tolerance test about 3 mo after transplantation (9). At baseline, six patients (13%) had post-transplantation diabetes mellitus (none received glucose-lowering drugs), 22 patients had impaired glucose tolerance or impaired fasting glucose (IFG), and 17 normal glucose tolerance. A total of 11 patients (24%) were overweight, only one was obese, and none was underweight.

**Corticosteroid Withdrawal.** A total of 11 renal transplant recipients were included in the TAP group at a median of 91 mo (range, 26 to 201 mo) after transplantation (SW group). All patients had a normal fasting whole-blood glucose concentration (HemoQuest; Norway). Patients receiving a CsA-based immunosuppressive therapy with a stable serum creatinine (<20% variation) lower than 200 $\mu$mol/L, and who for personal reasons wanted to withdraw prednisolone, were asked to participate in the study. Patients with early (within 21 d post-transplant) or steroid-resistant rejection episodes, and PRA (panel reactive antibodies) positive (>0%) recipients were excluded. At inclusion, all patients received a daily prednisolone dose of 5 mg. Prednisolone was then tapered to 2.5 and 5 mg on alternate days for 1 mo, then 2.5 mg daily for the second month, and finally 2.5 mg each second day for the third month before withdrawal. All 11 patients were successfully withdrawn from prednisolone and were steroid-free at a median of 3 yr after SW. All patients completed two consecutive HEC procedures within a median time interval of 11 mo (range, 6 to 20 mo) and the second 5 mo (range, 3 to 11 mo) after complete SW.

**Statistical Analyses.** The data are presented as mean (SD), median (range), or proportions, as appropriate. Comparison between groups for continuous data with a normal distribution were performed with one-way ANOVA and unpaired or paired t tests; otherwise, the Kruskal-Wallis test or Mann-Whitney test were implemented. Pearson’s $x^2$, Fisher’s exact test, or the McNemar test was used to analyze proportions as appropriate. Univariate or multiple linear regression was implemented as appropriate. $P$ values $<0.05$ were considered statistically significant. The analysis was implemented by SPSS 10.0.

**Results**

**Baseline Characteristics**

At baseline, the members of the TAP, CON, and SW groups were comparable with respect to age, BMI, hypertension, antihypertensive medication, rejections, and donor source, but differed significantly with respect to daily prednisolone dose, gender, and the proportion of patients treated with $\beta$-blockers (Table 1). The mean baseline ISI did not differ significantly between the TAP group and CON group (unpaired t test, $P = 0.528$), but was significantly higher in the SW group as compared with both other groups (SW versus TAP; $P < 0.001$, SW versus CON; $P = 0.004$). The median baseline GDR was significantly higher ($P = 0.007$), whereas median fasting blood glucose, insulin, and TG concentrations were lower ($P = 0.075$, $<0.001$, and $<0.001$, respectively) in the SW group as compared with the TAP group (data not shown, but can be inferred from Tables 2 and 3).

**TAP versus CON Groups**

The average ISI increased significantly from baseline to follow-up ($\Delta$ISI $= 24\%$, $P = 0.008$) in the TAP group (Table 2), as compared with no significant change ($\Delta$ISI $= 0\%$, $P = 0.988$) in the CON group (Figure 1). The mean $\Delta$ISI was
higher, although not statistically significant, in the former than
the latter group (1.72 \times 10^{-2} \text{mol} 	imes \text{min} \times \text{pmol} \ versus \ 0.01 \times 10^{-2}, P = 0.152).

**TAP**

The mean (range) daily prednisolone dose was tapered from
16 mg (range, 10 to 30 mg) to 9 mg (range, 5 to 12.5 mg) (0.22
to 0.12 mg/kg per d) (Table 2), mean daily CsA dose from 370
to 282 mg, and the mean CsA trough level declined from 229
to 150 \mu g/L (all P < 0.001). The patients had a significant
overall 5% increase in mean body weight and BMI, 7% in-
crease in mean body fat mass percentage, and 2% increase in
mean lean body mass and WC (Table 2). The proportion of
overweight or obese patients rose significantly from 26% (9 of
34) at baseline to 41% (14 of 34) at follow-up (P = 0.039).

There was a trend toward lower HbA1c at follow-up; no
significant changes were observed in fasting whole blood glu-
cose or insulin. Mean creatinine clearance (25) increased sig-
ificantly (from 59 to 68, 8 ml/min; 95% CI, 4 to 11, P <
0.001), but the change in creatinine clearance did not correlate significantly with ISI ($P = 0.682$). Mean baseline systolic BP (137 mmHg), diastolic BP (86 mmHg), total cholesterol (6.3 mmol/L), HDL cholesterol (1.3 mmol/L), TG level (2.2 mmol/L), and serum albumin (42 g/L) did not change significantly during the study. The proportion of patients who received beta-blockers, furosemide, ACE inhibitors, or calcium-channel antagonists did not change significantly from baseline to follow-up.

**Effect of Weight Change (TAP)**

To address the effect of changes in body weight on insulin action, the group of patients with a stable weight or moderate weight loss (median 2.0 kg; $n = 5$) and the group who gained weight (median 4.0 kg; $n = 29$) were analyzed separately (Figure 2). The former group had a significantly higher median increase in ISI than the latter ($3.82 \times 10^{-2}$ versus $1.18 \times 10^{-2}$, $P = 0.039$).

**Correlations between Variables**

To assess any potential linear relationship between ISI as the dependent variable and changes in prednisolone dose, BMI, WC, and serum TG, both univariate and multiple linear regression analyses were carried out. In the univariate analysis, $\Delta$TG and $\Delta$BMI tended to be associated with ISI ($P = 0.061/0.084$, $\beta = -0.01/-0.006$ and $r = 0.316/0.258$), whereas neither change in prednisolone ($P = 0.478$, $\beta = -0.0008$ and $r = 0.107$) nor $\Delta$WC ($P = 0.776$, $\beta = 0.0003$ and $r = 0.043$) correlated significantly with ISI. However, after converting weight gain and TAP to categorical variables (yes/no), a significant association between weight gain and ISI was revealed ($P = 0.041$, $\beta = -0.028$ and $r = 0.302$), and a

**Table 3. Metabolic and anthropometric parameters in 11 renal transplant recipients assessed before and after corticosteroid withdrawal (SW)**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Before SW</th>
<th></th>
<th>After SW</th>
<th></th>
<th>Mean Difference</th>
<th>95% CI</th>
<th>$P$ Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
<td>Mean</td>
<td>SD</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ISI ($\mu$mol × L × $10^{-2}$/kg × min × pmol)</td>
<td>14.76</td>
<td>6.89</td>
<td>13.56</td>
<td>6.48</td>
<td>-1.20</td>
<td>-3.18 to 0.78</td>
<td>0.206</td>
</tr>
<tr>
<td>GDR ($\mu$mol/kg × min)</td>
<td>66.3</td>
<td>24.5</td>
<td>67.6</td>
<td>24.4</td>
<td>1.2</td>
<td>-6.6 to 9.1</td>
<td>0.734</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>25.1</td>
<td>5.0</td>
<td>24.6</td>
<td>4.3</td>
<td>-0.5</td>
<td>-1.5 to 0.4</td>
<td>0.252</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>73.4</td>
<td>15.7</td>
<td>71.9</td>
<td>14.1</td>
<td>-1.5</td>
<td>-4.2 to 1.2</td>
<td>0.251</td>
</tr>
<tr>
<td>Lean body mass (kg)</td>
<td>50.7</td>
<td>6.4</td>
<td>50.3</td>
<td>6.1</td>
<td>-0.5</td>
<td>-1.3 to 0.4</td>
<td>0.250</td>
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<tr>
<td>Body fat mass percentage</td>
<td>32.5</td>
<td>8.7</td>
<td>31.9</td>
<td>7.9</td>
<td>-0.5</td>
<td>-1.7 to 0.6</td>
<td>0.312</td>
</tr>
<tr>
<td>Waist circumference (cm) ($n = 8$)</td>
<td>83.6</td>
<td>16.4</td>
<td>82.9</td>
<td>13.0</td>
<td>-0.8</td>
<td>-6.5 to 5.0</td>
<td>0.765</td>
</tr>
<tr>
<td>Triglyceride concentration (mmol/L) ($n = 10$)</td>
<td>1.0</td>
<td>0.3</td>
<td>1.1</td>
<td>0.4</td>
<td>0.0</td>
<td>-0.2 to 0.2</td>
<td>0.817</td>
</tr>
<tr>
<td>Fasting blood glucose (mmol/L)</td>
<td>4.2</td>
<td>0.6</td>
<td>4.8</td>
<td>0.6</td>
<td>0.6</td>
<td>0.0 to 1.2</td>
<td>0.036</td>
</tr>
<tr>
<td>Fasting insulin (pmol/L)</td>
<td>57</td>
<td>24</td>
<td>58</td>
<td>25</td>
<td>1</td>
<td>-12 to 13</td>
<td>0.901</td>
</tr>
</tbody>
</table>

*a* ISI, insulin sensitivity index; BMI, body mass index.
tendency toward a correlation between TAP and ΔISI was observed \((P = 0.152, \beta = 0.017, \text{and } r = 0.214)\). In the multiple linear regression analysis, tapering of daily prednisolone \((\text{yes} = 1, \text{no} = 0)\) was independently associated with ΔISI \((\text{standardized } \beta = 0.401, P = 0.015)\), whereas weight gain and ΔTG failed to reach statistical significance. This model explained 27% of the variation in ΔISI.

No significant associations were found between changes in CsA dose or trough levels and ΔISI. Moreover, no significant correlations were observed between changes in prednisolone dose (independent) and changes in TG, WC, BMI, fat mass percentage, or lean body mass (data not shown).

**Corticosteroid Withdrawal**

Table 3 shows metabolic and anthropometric parameters before and after cessation of prednisolone. Mean ISI, GDR, and anthropometric measures were not significantly affected by SW. Mean HDL cholesterol decreased significantly from \(1.6 \pm 0.3\) to \(1.4 \pm 0.2\) mmol/L \((P < 0.001)\), whereas no significant changes in total cholesterol \((5.5 \pm 5.2\) mmol/L, \(P = 0.211)\) or TG levels were observed. Mean fasting blood glucose increased significantly from \(4.2\) to \(4.8\) mmol/L \((P = 0.036)\). The mean daily dose of CsA did not change significantly during the study, nor did the mean CsA trough level (data not shown). Creatinine clearance did not change significantly.

**Discussion**

Immunosuppressive treatment of transplant recipients may \textit{per se} have negative effects on cardiovascular risk factors, and importantly, posttransplant mortality is largely attributable to CVD. Glucocorticoids provoke insulin resistance, which may be associated with increased risk for CVD (4).

**Tapering or Withdrawal of Prednisolone?**

To our knowledge, the study presented here is the first to indicate that insulin action, as assessed by the HEC technique, significantly improves during tapering of steroids the first year after renal transplantation. The overall 24% improvement of average ISI despite a concomitant 5% increase in body weight may be explained by a mean daily prednisolone dose reduction of 7 mg. Our findings add support to the hypothesis that reducing daily prednisolone from relatively high doses (10 to 30 mg) early posttransplant to medium/low doses (5 to 12.5 mg) during the first year has a beneficial effect on insulin action.

The failure to document any further beneficial effect of low-dose (5 mg) SW on insulin action was somewhat unexpected, but may have several explanations. First, the 11 patients who underwent SW were assessed in a more stable phase (2 to 16 yr after therapy) and were on average clearly less insulin resistant than those examined early after transplantation, with a lower potential for further improvement. Second, the administration of prednisolone 5 mg/d \((0.07\) mg/kg), the glucocorticoid equivalent to 20 mg hydrocortisone (cortisol), after years of steroid therapy may not be sufficient to diminish IS significantly. Finally, it is well known that adverse effects of glucocorticoids such as weight gain, enhanced deposition of intraabdominal fat, and increased appetite (26–29) may induce insulin resistance. However, neither SW nor a modest prednisolone dose reduction was associated with a significant weight loss or reduced WC in our study.

**Potential Mechanism for Beneficial Effect of Corticosteroid Tapering on Insulin Action**

In 1995, Steiger and coworkers (30) reported a close and linear relationship between reduction in daily prednisolone dose the first year after transplantation \((0.45\) to \(0.15\) mg/kg; \(30\) to \(10\) mg/d) and enhanced fat oxidation. Moreover, results from very recent studies indicate that reduced fatty acid oxidation, intracellular lipid accumulation, and impaired mitochondrial function may represent important pathogenic mechanisms for insulin resistance and diabetes (31–33). In addition, dexamethasone has been shown to inhibit hepatic fatty acid β-oxidation in mice (34). Although these issues were not addressed in the study presented here, it is tempting to speculate that inhibition of fat oxidation may represent a possible mechanism for steroid-induced insulin resistance after renal transplantation.

**Comparison with Other Studies**

In contrast to previous studies addressing changes in IS during SW by the use of surrogate measures of insulin action (18,35), the gold standard method HEC was implemented in the study presented here. Furthermore, previous studies addressing SW included patients receiving larger steroid doses (≥10 mg/d) and may therefore not be comparable.

Nevertheless, our results are in line with a recent retrospective study arguing that most metabolic benefits (reduction of body weight, BP, Hba1c, diabetic medication) of prednisolone tapering are seen down to 5 mg/d, whereas no further benefits are observed after SW (36). Moreover, in a cross-sectional study of 77 renal transplant recipients treated with either 0, 5, or 10 mg prednisolone per day, no major differences in body fat mass percentage, lean body mass, waist-to-hip ratio, or substrate (glucose, protein, fat) oxidation rates were observed between groups (37).

However, partly contrasting our results, a significant reduction in fasting insulin was observed after cessation of prednisolone (≤10 mg/d) in a Canadian study including 26 renal transplant recipients (35). As mentioned above, the results from a Dutch trial indicate that withdrawal of 10 mg prednisolone may have a borderline beneficial effect on IS (18), whereas our results suggest that withdrawal of 5 mg prednisolone does not influence IS significantly.

**Body Weight and TG**

The mean ISI did not improve significantly in patients who gained weight, whereas patients maintaining or losing weight had a >50% increased mean ISI from 3 to 12 mo after transplantation. This is in accordance with findings in the general population (26–28). We have previously reported that increasing TG concentration is correlated with insulin resistance, but in the study presented here, no significant association between ΔTG and ΔISI was found. Moreover, the overall mean TG level did not change significantly, despite a significant improvement of insulin action
in the TAP group. This may partly be explained by the concomitant increase in body weight and fat percentage.

**Conclusions**

Our results indicate that lowering of daily prednisolone down toward 5 mg/d and moderate weight loss both have beneficial effects on insulin action the first year after renal transplantation. On the other hand, withdrawal of low-dose prednisolone (5 mg/d) in stable renal transplant recipients did not influence IS significantly.

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**References**


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