LETTER TO THE EDITORS

Reply to: Correspondence regarding the impact of kidney transplantation on insulin sensitivity

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Dear Editors,

We thank Bergfeld *et al.* [1] for showing interest in our study regarding insulin sensitivity following kidney transplantation [2]. Using the hyperinsulinaemic–euglycaemic clamp (HEC)—the gold standard method to measure insulin sensitivity—we demonstrate that insulin resistance is developed following kidney transplantation which could contribute to the high incidence of post-transplantation diabetes mellitus (PTDM). We believe that direct measurement of insulin sensitivity such as the HEC is imperative as insulin sensitivity indices may be unreliable in this patient group [3,4], especially in a longitudinal setting [5].

We agree with Bergfeld *et al.* that it would have been interesting to also have measured the insulin secretion following transplantation. Previous studies, including work from Bergfeld *et al.*, indicate that beta-cell dysfunction also contributes to PTDM, but to our knowledge, only few studies have used the hyperglycaemic clamp—the gold standard to measure beta-cell function—and none have used this technique in a longitudinal setting in transplanted patients. We therefore believe that the statement of Bergfeld *et al.* that insulin secretion is the 'central denominator of PTDM' should be accepted with caution.

As also emphasized by Bergfeld *et al.*, PTDM is a unique form of diabetes, where multiple factors such as immunosuppressive drugs, the uraemic environment and altered metabolism of glucose-regulating hormones contribute to both insulin resistance and beta-cell dysfunction. This implicates, though, that the traditional view of the mechanisms which regulates insulin secretion with respect to insulin resistance cannot be expected. It cannot be assumed that a hyperbolic relationship exists between insulin sensitivity and beta-cell function which is a typical prerequisite when using indices of both insulin sensitivity and indices of beta-cell function. We therefore strongly encourage research groups to use direct measures of both insulin sensitivity and beta-cell function in this patient group.

Additional data and comments are requested by Bergfeld *et al.*:

1 At screening, our patients had a higher level of plasma glucose following the oral glucose tolerance test than the healthy controls. As the primary outcome of the study was change in insulin sensitivity, each patient was compared against their own insulin sensitivity prior to transplantation and not the insulin sensitivity of the controls. While impaired glucose tolerance seems to increase the risk of PTDM [6], we are not aware of any data suggesting that patients with impaired glucose intolerance are more susceptible to develop or increase their insulin resistance when treated with immunosuppressive drugs.

2 Following transplantation, the patients gained weight which was primarily due to fat deposition as evaluated by DXA scans. As also stated, this body composition could be associated with some of our findings including the insulin resistance in liver and adipose tissue. A half-century ago, Randle *et al.* [7] showed in a rat heart model that the addition of free fatty acids could induce insulin resistance probably caused by a competing substrate oxidation with glucose—the so-called Randle cycle. Several clinical studies also indicate that peripheral insulin sensitivity (both oxidative and nonoxidative) as well as hepatic insulin sensitivity is reduced in the excess availability of free fatty acids [8,9].

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Interestingly, beta-cell dysfunction may also be caused by an increased lipolytic activity and so an impaired effect of insulin on lipolysis could explain several of the glucometabolic disturbances observed in kidney transplanted patients.

3 Following transplantation, four of the nine patients had short (1–3 days) treatments with methylprednisolone due to a suspected rejection. Kidney biopsies showed one with acute rejection grade 1B, one with borderline rejection and two without rejection. The cited paper by Bergfeld *et al.* reports a biopsy-proven rejection rate of 11 per cent on tacrolimus not including borderline rejections, which corresponds well with the rejection rate in our study. As all the treatments were short and also more than 5 months before the follow-up clamp, it seems unlikely that this could cause a 'disproportionally' effect on insulin sensitivity. The patients receiving rejection therapy had also slightly better insulin sensitivity after transplantation than non-treated patients.

4 As stated by Bergfeld *et al.*, a less than optimal graft function in itself can cause insulin resistance. Creatinine levels at the time of the two clamps are given in Table 2, in the paper. The patients treated for a suspected rejection had a creatinine level of 192 μM after transplantation, which was slightly higher than the average of 163 μM.

5 Although the calcineurin inhibitors have different diabetogenic potential, there was no apparent association with insulin resistance as the patients treated with tacrolimus had better insulin sensitivity after transplantation than patients treated with cyclosporine.

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