LETTER TO THE EDITORS

Correspondence regarding the impact of kidney transplantation on insulin sensitivity

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Dear Editors,

The hyperinsulinaemic–euglycaemic clamp (HEC) experiments performed in nine living donor kidney transplant recipients from before to after transplantation by Jørgensen *et al.* [1] show a reduction in insulin sensitivity, but post-transplantation diabetes mellitus (PTDM) is also a result of beta-cell dysfunction coinciding with a period of excessive insulin demand [2]. Although the authors have thoroughly cited several previous studies that showed evidence for either component as the main cause of PTDM, we feel obliged to bring forth that PTDM is a unique form of diabetes, as acknowledged in the recent statement from the American Diabetes Association [3]. The overall secretory deficit after kidney transplantation is likely a product of calcineurin inhibitor action, glucotoxicity, lipotoxicity, but also corticosteroid action on the pancreatic beta-cell [4,5].

What surprises us is the fact that insulin secretion as the central denominator of PTDM pathophysiology was not addressed in this study. The HEC is limited by exclusive specificity for insulin sensitivity; however, insulin sensitivity and secretion stand in hyperbolic relationship [6]. One can only be pronounced inadequate in context of the other: assuming insulin resistance was the predominant cause of PTDM, some corresponding increase in insulin secretion must be observed. Unfortunately, no euglycaemic clamp or oral glucose tolerance test (OGTT) was performed after transplantation; therefore, we suggest disclosing surrogates for beta-cell function after transplantation, such as homeostatic model assessment of beta-cell function (HOMA-%B), derived from fasting values of glucose and insulin (or c-peptide, if available).

We kindly ask the authors to provide additional data on insulin secretion and comment on our following observations:

1. At screening: Were you concerned with the significantly lower carbohydrate tolerance identified by OGTT in the transplant group? Naturally, patients with lower glucose tolerance before transplantation are more susceptible to develop insulin resistance when corticosteroid use, perioperative stress and metabolic syndrome coincide. The assumption of equal glucose tolerance on the basis of fasting plasma glucose (FPG) and glycated hemoglobin (HbA1C), disregarding the screening OGTT, cannot be justified in a population of transplanted patients due to several well-known reasons [7,8].
2. Visceral fat is a major mediator of insulin resistance [9]. Participants receiving a transplant gained a significant average of 4.5 kg body weight, primarily due to increasing total fat mass (+5.7 kg), whereas body composition in the control group remained unaffected. May this change in body composition also explain your finding of impaired suppression of lipolysis and endogenous glucose production?
3. Acute rejection affects 10–15% of patients receiving living donor grafts in the general transplant population [10]. However, four of nine participants (45%) were treated with up to 500 mg methylprednisolone for suspected acute rejection. Do you believe that the unusually high need for high-dose steroid therapy disproportionally caused insulin resistance?
4. In addition to metabolic syndrome and steroid excess, less than optimal graft function fails to alleviate uraemia, contributing to insulin resistance. Do you have any data on graft function (e.g. estimated glomerular filtration rate, urine albumin-to-creatinine ratio) at the time of the clamp, especially for those patients who were treated for suspected rejection?

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5. Four of nine patients received cyclosporine A which is potentially less diabetogenic than tacrolimus, and one patient was converted to everolimus with clear diabetogenic potency. Given the small sample size, how did the heterogeneous immunosuppression affect your results?

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