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LETTER

Donor insulin use during stay in the intensive care unit should not preclude pancreas transplantation. Reply to Ventura-Aguiar P, Montagud-Marrahi E, Amor AJ et al [letter]

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To the Editor: We welcome the correspondence from Ventura-Aguiar et al [1] regarding our recent publication in *Diabetologia* [2] and value the opportunity to respond.

Ventura-Aguiar et al commented on the uncertainties relating to the pathogenesis of brain-death-related donor hyperglycaemia [1], for which there is currently a paucity of relevant and robust data [3]. We totally agree with their suggestion of a potential role of circulating microRNA and cell-free DNA to clarify the respective impact of irreversible beta cell death and reversible insulin resistance (stress hyperglycaemia) on donor pancreas function. Whilst we have previously reported the potential application of cell-free DNA data to pancreas transplantation [4] and have publicly presented some of our microRNA [5] data in relation to this, we look forward to sharing our complete biomarker data with the academic community in the near future.

Ventura-Aguiar et al raised concerns about our definition of graft function [1], which was 'a return to exogenous insulin therapy within 3 months post-transplantation' [2]. Ours is the first analysis of the relationship between donor insulin use and clinical outcomes after pancreas transplantation, and in our paper we have acknowledged the limitations of using the available retrospective registry data. Whilst we are confident in our findings, it would be helpful for future research studies in this area to collect data that would enable better characterisation of beta cell function as outlined by the International Pancreas and Islet Transplantation Association (IPITA) and the European Pancreas and Islet Transplantation Association (EPITA) consensus [6] and, ideally, for these data to be collected prospectively in national registries.

Attention was drawn to the relationship between BMI and islet graft failure [1]. We would like to highlight that donor insulin use remained significantly related to islet graft failure after adjusting for donor BMI (see Table 4 in our publication [2]). Recipient BMI was not a significant predictor ($p = 0.1$) of isolated islet failure in the reported data and thus was not eligible for inclusion in the multivariable analysis at a threshold of $p < 0.1$. Using regional data from over 7600 peri-transplant glucose values in 123 pancreas transplant recipients, we have previously shown that peri-transplant hyperglycaemia (defined as mean daily glucose ≥7 mmol/l over the first 5 days post-transplant) predicts graft survival independently of recipient BMI [7]. Consequently, we are reassured that the exclusion of recipient BMI from the multi-variate analysis of national data was appropriate.

Ventura-Aguiar et al highlight that our follow-up was limited to 3 months [1]. Our main justification for doing this is that we previously published our data in islet transplantation, which demonstrated a relationship between donor insulin use and poorer islet function at 3 months [8]. Given the significance of this risk factor in islet transplantation and its potential impact on donor selection, we were interested in providing outcome data at the same time-point to enable a direct comparison between pancreas and islet transplantation. The donor pancreas pool is a single and scarce resource that is shared between two

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different modalities of beta cell replacement therapy. Optimal allocation and donor selection from this single source is therefore important. However, it will be important that future studies extend the duration of follow-up.

In their conclusion, Ventura-Aguiar et al suggest that our study 'highlights the importance … of stress hyperglycaemia on long-term pancreas graft outcomes' [1] but we respectfully disagree with this statement. Our study focused on the relationship between donor insulin use and early outcomes after pancreas transplantation [2]. The pathophysiological mechanisms underlying these relationships require further research and, in particular, we need to clarify the roles of beta cell death and insulin resistance (stress hyperglycaemia) in these relationships.

We agree with Ventura-Aguiar et al that donor hyperglycaemia should not be the sole criteria to exclude a potential pancreas transplant donor [1], and we would go further to state that there should be no immediate clinical implications of our work. Further research is needed to validate our findings and to understand how to best use information on donor insulin use, along with other clinical and biomarker data, to optimise the selection of donor pancreases for islet or pancreas transplantation.

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