CORONAVIRUSES AND PANCREATIC INVOLVEMENT

Various studies have investigated the diabetogenic potential of coronaviruses. Yang et al[14] localized ACE2 expression in the pancreatic endocrine part and suggested SARS-CoV-1 entry into islets via ACE2, leading to islet damage and acute diabetes. Limited case reports have elucidated diabetes development in COVID-19 infection.[15] Although the information about pancreatitis occurrence with SARS-CoV-1 infection is sparse, multiple case reports and case series have described the development of acute pancreatitis in patients with COVID-19 infection.[4–7]

The autopsy reports of 4 SARS patients detected SARS-CoV in the pancreatic samples.[16] However, autopsy data on COVID-19 patients are limited. Pancreatic autopsy samples of 3 patients from China revealed a small number of islet cell degeneration without apparent exocrine involvement or SARS-CoV-2 virus detection in pancreatic tissue.[17]

To conclude, we believe that the avid pancreatic expression of ACE2 makes the pancreas particularly susceptible to injury in COVID-19 patients. Additional histopathological and clinical data in the future are likely to establish the proposed association.

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Long-term Stability of β-Cell Graft Function After Total Pancreatectomy and Islet Autotransplantation

To the Editor:

We read the article entitled "Change in Functional Beta Cell Capacity With Time Following Autologous Islet Transplantation" by Ali et al[1] published in May/June 2019 with great interest. The authors described a decline in the function of autologous islet grafts in a longitudinal study of 31 patients after total pancreatectomy and islet autotransplantation (TPIAT) based on BETA-2 scores and mixed meal tolerance testing. Interestingly, this is reported as the first use of BETA-2 for the assessment of islet graft function in the setting of autotransplantation.

However, we would like to respectfully point out that we have previously validated and used the BETA-2 score as a reliable tool to monitor islet graft function in the setting of islet autotransplantation in a report published in November 2018.[2] Subsequently, we reported a longitudinal study, which demonstrated stable long-term islet graft function after allotransplantation was made possible with engraftment of an optimal islet mass.[3] All patients with long-term insulin independence had BETA-2 scores consistently above 17, despite fluctuations in individual scores above this cutoff. This fluctuation of the BETA-2 score, in the setting of stable optimal islet graft function, is related to transient changes in basal insulin requirement and fasting c-peptide serum levels, which, in turn, are due to changes in insulin sensitivity (resistance) resulting from body weight increase, infection, physical activity, or other factors. For example, when a patient is subjected to a transient stress, insulin resistance increases and prompts islets to secrete more insulin to maintain optimal glucose control. This results in a higher fasting c-peptide serum concentration and ultimately translates into a higher BETA-2 score. After the stressor subsides, less insulin is required and a lower serum c-peptide value results in a reduced calculated BETA-2 score. Thus, fluctuation of a BETA-2 score above 17 does not, ipso facto, reflect a decline of islet graft function.

Intrigued by the findings reported by Ali et al,[1] we performed additional analysis of BETA-2 scores over time in our cohort of 22 patients after TPIAT performed for chronic pancreatitis with at least 2-year follow-up. We retrospectively divided patients into 3 groups depending on insulin use

and functional graft status according to Igls classification, which we adjusted for autotransplantation[2]: group 1 — 9 insulin independent patients with optimal Igls outcome; group 2 — 4 patients with good Igls outcome and requiring only long acting insulin or only minimal insulin supplementation with meals; and group 4 — 9 patients with good and marginal Igls outcome and requiring full insulin supplementation in multiple daily doses.[2,4] Figure 1A presents BETA-2 scores in group 1 over time. BETA-2 scores fluctuated for each individual patient as in allotransplant patients, but in the range above 15, similar to our previous studies in TPIAT patients.[2,3]

In addition, we found stable islet graft function in 4 patients who required only minimal insulin supplementation (group 2) (Fig. 1B). Again, BETA-2 scores also fluctuated over time but remained consistently elevated, reflecting stable islet graft function. The remaining patients requiring full insulin supplementation (group 3) had low BETA-2 scores (ie, below 10). Nevertheless, these patients never completely lost their serum c-peptide despite follow-up times as long as 6 years. BETA-2 scores in the low range reflect blood glucose control mostly related to insulin dose adjustments rather than to β-cell function itself. Therefore, a BETA-2 score might be not the best estimate of β-cell functional capacity in such cases.

Lastly, an unfortunate discrepancy in the precise BETA-2 formula exists in the literature. The original article in which Forbes et al[5] derive the BETA-2 score was first published in the Wiley Online Library with an erroneous version of the formula. We have recently notified the publisher of the discrepancy between the online and print versions. Unfortunately, it appears that Ali et al[1] cited the online version of the article and used the erroneous formula. The correct BETA-2 score formula is the following:

$$\text{BETA-2 score} = \left(\frac{\sqrt{\text{fasting C-peptide[nmol/L]}} \times (1 - \text{insulin dose [units/kg]})}{\text{fasting plasma glucose [mmol/L]} \times \text{HbA1c [\%]}}\right) \times 1000.$$

Fortunately, despite using the erroneous formula, the general interpretation of the results presented by Ali et al[1] remains unchanged. Overall, the individual BETA-2 scores are lowered on average by 1 point and thus do not affect the general direction of the trend or the outcomes.

In summary, our work suggests more stable islet graft function in contrast to the experience reported by Ali et al.[1] A possible explanation for the conflicting results is that Ali et al[1] analyzed mean BETA-2 scores for all patients combined at each time point (see Fig. 2 in Ali et al[1]), rather than analyzing trends for each patient separately. Furthermore, it seems that many patients did not have BETA-2 scores at each time point (eg, n = 40 at 6 months vs less than n = 17 at subsequent time points), which makes the analysis less reliable.

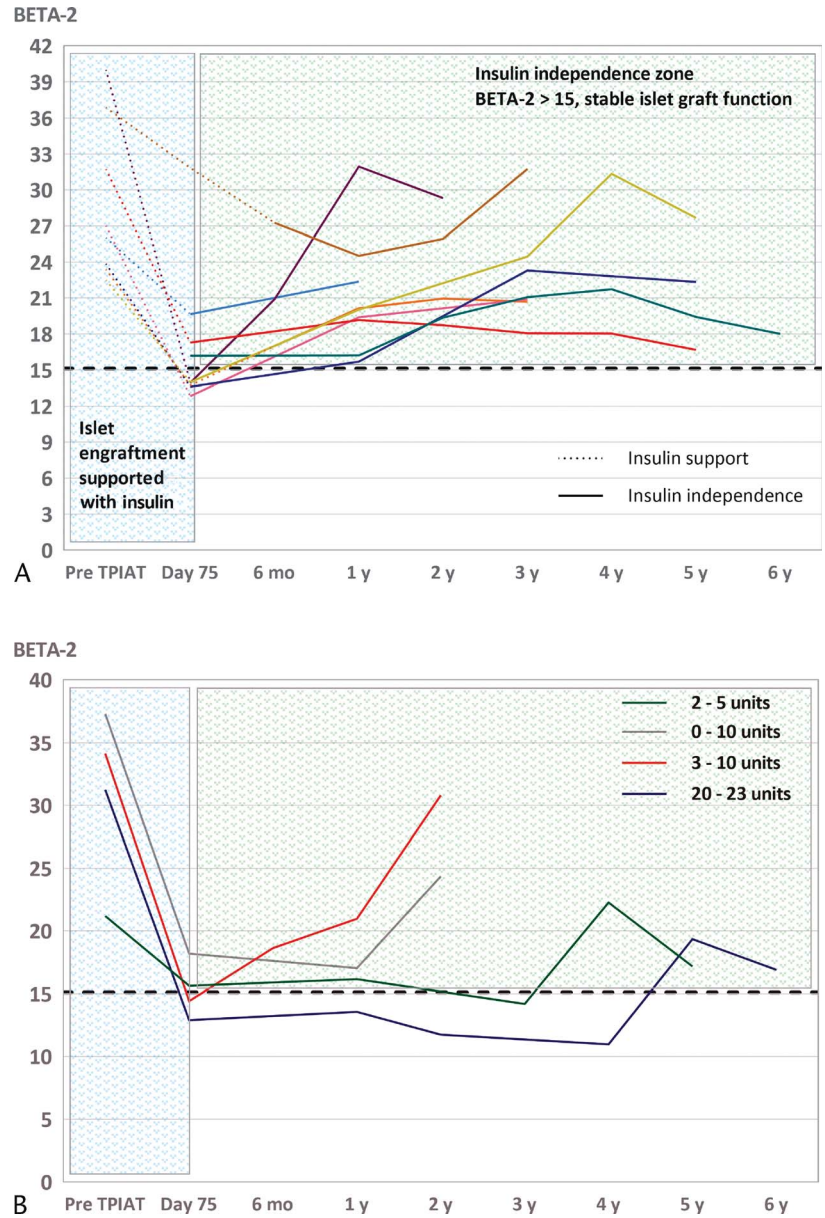

FIGURE 1. Trends of BETA-2 in patients after TPIAT due to chronic pancreatitis and intractable pain. A, Trends of BETA-2 in group 1 (n = 9) in patients with long-term insulin independence. Patients were supported initially with exogenous insulin (dotted line) to support islet function and optimize conditions for islet engraftment. Afterward, insulin was successfully weaned off maintaining optimal glucose control (continuous line represents insulin independence). In insulin-independent patients, the BETA-2 scores remain above 15 (dashed line) and thus reflect stable islet graft function. Nevertheless, the scores are noted to fluctuate. B, Trends of BETA-2 in group 2 (n = 4) in patients with partial islet graft function and good functional outcomes based on Igls classification.[2,4] Patients required minimal insulin support once a day with long-acting insulin or only small doses during their meals. In those patients, BETA-2 scores also remained stable and fluctuated in a range above 10 (dashed line), reflecting stable islet graft function. The legend shows decreasing doses of insulin supplementation for individual patients corresponding to lines with different colors.

Of note, we suspect that a slightly higher BETA-2 cutoff for insulin independence after allotransplantation (BETA-2 >17), when compared with autotransplantation (BETA-2 >15),

might be related to higher insulin resistance due to immunosuppression.[3] The resulting fasting c-peptide serum levels would be higher and would translate into higher BETA-2 scores in allotransplant patients.

In light of these reservations and based on our own findings, we posit that β-cell function may remain stable after islet autotransplantation and plays a very important long-term role in improved glucose control and patient quality of life.[6]

The authors declare no conflict of interest.

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Reply:

We read with great interest the letter to the editor submitted by Bachul et al regarding our recent article titled "Change in Functional Beta Cell Capacity With Time Following Autologous Islet Transplantation."[1] We reported our observations of a cohort of 31 subjects undergoing total pancreatectomy and islet autotransplantation (TPIAT), detailing the change in beta cell functionality after transplantation.[1] We specifically reported a steeper decline in beta cell functionality in the first 6 months after TPIAT, with a slower and steadier rate of decline, thereafter. Our assessment of beta cell functionality was done via the novel BETA-2 scoring assessment along with the classic mixed-meal tolerance testing. Our findings were initially presented at the Endocrine Society's Annual Meeting in Chicago, Ill in March 2018 as noted in our original manuscript.[1,2] In a rapidly evolving scientific field, such as that of islet cell biology, clinical research groups across the nation have been uniformly and simultaneously invested in the new and novel for the advancement of islet cell outcomes, often inspired by each other's works. The work of Bachul and others on the novel BETA-2 scoring assessment in late 2018 along with their many other valuable contributions support this noble and committed pursuit toward improving the science of islet cell transplantation.

We specifically read with great interest the work of Bachul et al on the BETA-2 analysis of 22 subjects undergoing TPIAT. The authors described 3 groups of patients: group 1 (n = 9) characterized by optimal glycemic outcomes and independence of insulin therapy; group 2 (n = 4) harboring partial islet graft function, requiring only long-acting insulin therapy; and group 3 (n = 9) requiring full insulin supplementation with multi-daily insulin dosing.[3] The authors published trends of BETA-2 scores for individual patients in groups 1 and 2, from baseline (pre-TPIAT) and up to 6 years of follow-up. We note that nearly all subjects in groups 1 and 2 had shown a steep decline in BETA-2 scores in the first 6 months of follow-up, particularly in the initial 75 days, with the least individual BETA-2 score decline registering at a 6-point loss. In our analysis, we observed similar trends in BETA-2 scores, though less steeper, in the first 6 months after TPIAT. We, therefore, believe that both articles[1,3] have demonstrated the inevitable decline in beta cell functionality occurring within the initial 6 months after TPIAT, but with varying degrees of absolute decline. Additionally, the steep decline can now perhaps be further narrowed down to the initial 75 days after TPIAT, as demonstrated by our colleagues.[3]

After the 6-month timepoint, we observed a statistically significant and steady decline in BETA-2 scores, whereas Bachul et al reported fluctuations in individual BETA-2 scores after the 6-month mark. We fully agree with Bachul et al in that the 2 distinct methods of analyses (intraindividual vs interindividual BETA-2 scores analysis) could explain the differing trends in BETA-2 scores after the 6-month timepoint. We have previously noted this as a limitation to our study.[1]

As for the erroneous BETA-2 scoring formula, we thank Bachul and his team for the astute observation and correction of a critical formula, and agree in that the overall trend of our BETA-2 scores will remain largely unchanged.

The authors declare no conflict of interest.

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