Improved Insulin Secretion Following Intrapancreatic UCB Transplantation in Patients With T2DM

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**Context:** Transplantation with stem cells has been reported as a potential treatment for diabetes. However, there are few reports examining transplantation with umbilical cord blood (UCB) in type 2 diabetes (T2DM).

**Objective:** The aim of the study was to evaluate the efficacy of intrapancreatic UCB transplantation in patients with T2DM.

**Design and Setting:** Three patients were enrolled in the study, which was performed in a hospital setting from 2010 to 2012, and the duration of follow-up was approximately 6 months.

**Patients and Interventions:** UCB cells were infused by microcatheter into the dorsal pancreatic artery in 3 T2DM patients with different diabetic histories.

**Main Outcome Measures:** Blood glucose (including 72-h continuous blood glucose), C-peptide, hemoglobin A1c, the requirement for insulin, and transplant complications were monitored before and after transplantation.

**Results:** After the transplantation, C-peptide levels had increased in all of the patients. In addition, the 72-hour continuous blood glucose monitoring results obtained after transplantation revealed that levels were more stable than before transplantation for all of the patients ($P < .05$). In addition, the requirements of insulin were reduced in all patients after transplantation.

**Conclusion:** UCB transplantation may be an approach that could somewhat improve C-peptide levels in patients with T2DM. (*J Clin Endocrinol Metab* 98: E1501–E1504, 2013)
of type 2 diabetes (T2DM). In this study, UCB transplantation was performed in 3 T2DM patients by intrapancreatic infusion, and the efficacy of the treatment was evaluated.

**Patients and Methods**

Three male patients with different histories of T2DM were included in the study. All of the patients had previously received hypoglycemic agents. Despite this treatment, their blood glucose and hemoglobin A1c (HbA1c) levels were poorly controlled, and insulin secretion was relatively insufficient under the condition of insulin resistance before transplantation. In all patients, blood glucose (including 72-h continuous blood glucose), C-peptide, HbA1c, and the requirement for insulin were monitored before and after transplantation. In addition, transplant complications were recorded after the procedure (Table 1). Clinical characteristics such as body mass index, duration of T2DM, and diabetic complications were also recorded (Supplemental Table 1, published on The Endocrine Society’s Journals Online web site at http://jcem.endojournals.org). A 2-year follow-up was performed for patient 3, but the duration of follow-up for the other 2 patients was less than 2 years after transplantation.

Before transplantation, all patients were required to sign informed consent forms. The study protocol was evaluated and approved by the Ethics Committee of Xinqiao Hospital and registered in the Chinese Clinical Trial Registry under the number ChiCTR-TRC-11001219. For the transplantation, 80−100 mL of UCB was collected from the umbilical vein of an immediate family member of each patient immediately after birth, and human leukocyte antigen typing was performed. Cell isolation was performed using a cord blood cell processing kit (Ningxia Zhonglianda Biotech Co Ltd), and an aliquot of cells was analyzed for CD34, CD45, and CD105 percentage by flow cytometry. Man leukocyte antigen typing was performed. Cell isolation was performed using a cord blood cell processing kit (Ningxia Zhonglianda Biotech Co Ltd), and an aliquot of cells was analyzed for CD34, CD45, and CD105 percentage by flow cytometry. Zhonglianda Biotech Co Ltd), and an aliquot of cells was analyzed for CD34, CD45, and CD105 percentage by flow cytometry (9). The median number of nucleated cells was 5.29 × 10⁶ (range, 4.23 × 10⁶ to 7.13 × 10⁶). The amounts of CD34⁺, CD45⁺, and CD105⁺ cells were 2.96 × 10⁶, 2.30 × 10⁶, and 3.38 × 10⁶ per kilogram of body weight for patients 1, 2, and 3, respectively.

Before transplantation, computed tomography angiography was applied to the position dorsal pancreatic artery. During transplantation, angiography of the celiac trunk and splenic artery was performed to accurately locate the dorsal pancreatic artery. Subsequently, the UCB cells were infused into the dorsal pancreatic artery by a microcatheter. The representative angiography images are shown in Figure 1, H and I.

Four months after transplantation, 72 hours of continuous blood glucose monitoring were carried out in all of the patients, and the results were compared with those collected before the transplantation (Figure 1, A−G). Three and 6 months after transplantation, all of the patients were followed up to measure their fasting and 2-hour C-peptide levels. The areas under the curve (AUCs) of C-peptide during the 2-hour oral glucose tolerance test were then calculated using the following formula: AUC = 0.25 × (fasting value) + 0.5 × (half-hour value) + 0.75 × (1-h value) + 0.5 × (2-h value) (10). The oral glucose tolerance test was administered after an 8- to 14-hour fast using a standard 75-g glucose load, and blood samples were collected at 0, 0.5, 1, and 2 hours after the test load. C-peptide was measured by electrochemiluminescence immunoassay using the kit purchased from Roche Diagnostics. Results of continuous blood glucose monitoring are expressed as mean ± SD. Statistical tests were performed using SAS statistical software (SAS Institute Inc). Paired Student’s t test was used to compare the means of two groups, and P < .05 was considered to be significant.

### Results and Discussion

Although complexity and heterogeneity exist in the pathogenesis of T2DM, the disease is characterized by progressive and inexorable β-cell dysfunction (11). Because of this, C-peptide levels are considered to be a critical indicator of the efficacy of new therapies for T2DM (12). As

<table>
<thead>
<tr>
<th>Variable</th>
<th>Blood Glucose (mmol/L)</th>
<th>C-Peptide (ng/mL)</th>
<th>Dose of Oral Hypoglycemic Agents</th>
<th>Dose of Insulin (U/kg/d)</th>
<th>Transplant Complications</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>Fasting</td>
<td>2 h</td>
<td>Fasting</td>
<td>2 h</td>
<td>AUC</td>
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<tr>
<td>Patient 1</td>
<td></td>
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<tr>
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<td>14.47</td>
<td>1.58</td>
<td>7.53</td>
<td>9.85</td>
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<tr>
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<td>11.79</td>
<td>2.06</td>
<td>8.50</td>
<td>11.40</td>
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<tr>
<td>6 mo</td>
<td>6.20</td>
<td>9.60</td>
<td>3.23</td>
<td>9.90</td>
<td>13.18</td>
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<tr>
<td>Patient 2</td>
<td></td>
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<tr>
<td>Baseline</td>
<td>6.30</td>
<td>15.32</td>
<td>1.38</td>
<td>3.94</td>
<td>5.11</td>
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<tr>
<td>3 mo</td>
<td>4.80</td>
<td>10.97</td>
<td>2.08</td>
<td>6.71</td>
<td>9.12</td>
</tr>
<tr>
<td>6 mo</td>
<td>5.20</td>
<td>8.60</td>
<td>1.27</td>
<td>3.61</td>
<td>5.04</td>
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<tr>
<td>Patient 3</td>
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<tr>
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<td>28.94</td>
<td>0.95</td>
<td>1.82</td>
<td>3.04</td>
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<tr>
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<td>25.09</td>
<td>1.73</td>
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<td>2 y</td>
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<td>10.70</td>
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<td>8.22</td>
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Abbreviations: Met, metformin; Glim, glimepiride; bid, twice a day; tid, three times a day. The therapeutic regimens for the patients were performed before they were hospitalized.
the first study of UCB-based therapy in T2DM, the most important observation in our study is that C-peptide levels (fasting, 2-h, and C-peptide AUC) increased in all of the patients by the third month after transplantation. Two years after the transplantation, the C-peptide levels of patient 3 remained considerably improved (Table 1). In addition, the 72-hour continuous blood glucose monitoring results obtained 4 months after the transplantation were more stable than those observed before transplantation in all patients \((P < .05)\) (Figure 1, A–G). We also found that the requirement for insulin and oral hypoglycemic agents was reduced in all 3 patients after UCB transplantation (Table 1). Together, these findings suggest that UCB transplantation is beneficial for the restoration of \(\beta\)-cell function in T2DM. To eliminate the impact of intensive insulin therapy on endogenous insulin secretion in the patients, the same type of hypoglycemic agents were administered before and after the transplantation.

During the follow-up period, C-peptide levels in patient 2 were found to notably increase during the third month after transplantation, whereas these levels decreased by the sixth month (Table 1). Previous studies have demonstrated that the differentiation and survival of stem cells is mainly regulated by their microenvironment (13). In patient 2, the long diabetic history and increased complications may indicate the presence of a less conducive microenvironment for the transplanted cells, leading to the short-term recovery of \(\beta\)-cell function, followed by a rapid exacerbation (Supplemental Table 1).

T1DM is characterized by direct immune injury to \(\beta\)-cells. Based on the potential of stem cells to modulate immune function, T1DM is also a possible candidate for stem cell therapy. However, in the studies by Esmatjes et al (5) and Haller et al (9), stem cell transplantation failed to increase C-peptide levels in patients with T1DM. This suggests that the transplanted cells failed to restore proper immune regulation and suffered persistent immune injury due to the T1DM. In the study presented here, C-peptide levels were improved in T2DM patients, possibly due to a less serious immune injury and a better microenvironment for the transplanted cells in T2DM.

In our study, UCB was administered to 3 patients by intrapancreatic infusion through the dorsal pancreatic artery. Conversely, in the study performed by Haller et al (9), UCB was administered by systemic iv perfusion. This difference in the method of UCB perfusion may also explain why the levels of C-peptide did not increase in Haller’s study because animal data have shown that high concentrations of cells could be observed in the lung and liver after systemic iv perfusion, but not in the pancreas (14). In support of this hypothesis, Bhansali et al (15) used intrapancreatic infusion to perform bone marrow-derived stem cell transplantation, and they achieved positive results. In addition, intrapancreatic delivery of human UCB in mice resulted in the engraftment of a number of infused cells, leading to islet regeneration and increased insulin release (16). Because of variability in the anatomical position of the dorsal pancreatic artery (17, 18), it is necessary to apply computed tomography angiography before transplantation and angiography during transplantation to accurately position the dorsal pancreatic artery.

![Figure 1. Results of continuous glucose blood monitoring and representative angiography images. A–F, Results of continuous blood glucose monitoring before and after transplantation (A, C, and E show the results before transplantation in patients 1–3, respectively; B, D, and F present the results after transplantation in patients 1–3, respectively). G, Statistical analysis results of 72-hour continuous blood glucose. Data are expressed as mean \(\pm SD\) \((n = 288)\). *, \(P < .05\) compared with pretransplantation. H and I, Representative angiography images during transplantation (the arrow in H indicates the splenic artery; the arrow in I indicates the dorsal pancreatic artery).](https://academic.oup.com/jcem/article/98/9/E1501/2833042)
Although we observed positive effects of UCB therapy in all patients, the effects are somewhat varied. For example, patient 2 had an initial improvement in fasting and 2-hour C-peptide, but levels returned to baseline after 6 months, whereas patient 3 regained essentially normal glucose tolerance after treatment. However, the 3 patients enrolled in this study were heterogeneous, with dramatically differing duration of disease, levels of glucotoxicity, and treatment regimens, making it difficult to draw definitive conclusions about how these factors impact treatment efficiency. A future study with a larger, less heterogeneous patient population will therefore provide critical information regarding the efficacy of UCB therapy.

Stem cell transplantation can cause a series of complications, including infection, tumors, and graft-vs-host disease. In our study, no complications were observed in the 3 patients. This is in agreement with the study performed by Haller et al (9), where the results of the 2-year follow-up also suggested that transplantation with UCB may be a safe approach. However, further observations of possible transplant complications are still needed.

In summary, the present study provides evidence that UCB transplantation may be an approach that could partially improve C-peptide levels of patients with T2DM. Furthermore, the efficacy of this treatment may be associated with the duration of disease, the severity of complications, the microenvironment conditions, and the perfusion approach used to administer the transplanted cells. Further studies with more cases and longer follow-up periods will characterize the efficacy and safety of UCB transplantation in the treatment of T2DM.

Acknowledgments

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References