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REVIEW ARTICLE

Human Umbilical Cord Blood Therapy for Diabetes Mellitus : A Review

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Abstract

Stem cell therapy for patients with diabetes mellitus is receiving great attention among scientists and clinicians. Although bone marrow is considered one of the rich sources of stem cells, its limited availability of donors precludes its use for all the suitable patients. Human umbilical cord blood mononuclear cells or its-derived mesenchymal cells are being increasingly used as an alternative source of stem cells for cell-based therapy for malignant and nonmalignant diseases. Human umbilical cord blood cells have low potential for graft-versus-host disease and tumorigenicity. Also, no immunosuppression is required. Experimental evidence has shown that human umbilical cord blood -derived stem cells can differentiate into insulin-secreting β-cells. Transplantation of Human umbilical cord blood cells has been shown to improve blood glucose levels, and ameliorate kidney as well as neuropathic complications in diabetic animal models. Although the first use of autologous Human umbilical cord blood transfusion in type 1 diabetic children had a short-term beneficial effect in reducing the daily requirement of insulin dose and the maintenance of near normoglycemia, subsequent studies have failed to show this beneficial effect. In this review, we will provide both experimental and clinical evidence in favor and against the beneficial effect of human umbilical cord blood cells and cord blood-derived mesenchymal cells in the management of diabetes mellitus.

Keywords: Diabetes mellitus, human umbilical cord blood, mesenchymal cells, stem cells, Tregs, blood glucose, C-peptide

Introduction

In 2021, the estimated prevalence of diabetes in adults (20-79 years) worldwide was 537 million[1]. This represents 1 in 10 individuals. It is predicted that this number may increase to 643 million and 783 million by years 2030 and 2045, respectively. This increase in the prevalence of diabetes may impose great burden not only on the cost but also on the quality of life. Despite the availability of several oral hypoglycemic agents and a variety of insulin preparations, the treatment of both type 1 and type 2 diabetes is less than adequate in view of prevention of both microvascular and macrovascular complications. In 2021, diabetes was responsible for 6.7 million deaths worldwide, representing 1 every 5 seconds (1). Besides the availability of large number of oral hypoglycemic agents and insulin preparations, stem cell therapy is being extensively investigated in both diabetic animals and human subjects[2-11]. The stem cell therapy aims at restoring the endogenous production of insulin and maintenance of possible euglycemia without insulin treatment. The stem cells that were used include bone marrow mesenchymal stem cells, bone marrow hematopoietic stem cells, adipose tissue stem cells, human umbilical cord blood cells, Human umbilical cord blood mesenchymal cells, Wharton's jelly mesenchymal cells, and mesenchymal precursor cells. Studies with these stem cells showed varying degrees of success in both animal models and human subjects. In this review, we will focus on the studies of human umbilical cord blood cells in the treatment of both type 1 and type 2 diabetes mellitus.

Human umbilical cord blood

The human umbilical cord supplies oxygen and nutrients from mother to the fetus. The cord blood is obtained from the umbilical cord after birth for preservation and subsequent use. In the past, the human umbilical cord blood was discarded; however, recent studies have shown that it is a rich source of stem cells that are therapeutically useful in many disease conditions. Thus, human umbilical cord blood mononuclear cells and its-derived mesenchymal cells remain an alternative source of stem cell therapy for type 1 and type 2 diabetes mellitus.

Availability and dosage of human umbilical cord blood

There were 134 million human births in 2021 worldwide. This indicates that there is an abundant supply of cord blood. In our Initial studies, it was observed that cord blood has 8-18 stem cells/ml that are capable of producing replatable blast cell colonies with few recognition antigens, which are probably similar to embryonic stem cells derived from the fetus or embryos[12]. These cells were named 'Berashis' or 'beginning' cells. It is estimated that 1 unit of cord blood may have 0.8-1.0 billion mononuclear cells. It is our opinion and recommendation that intravenous transfusion of a total of 3 units of fresh cord blood consecutively supply adequate number of mononuclear cells in

addition to red blood cells for persistent therapeutic effect. It was observed that cord blood transfusions are much safer than adult blood transfusions[12].

Human umbilical cord blood -derived stem cells

Although bone marrow is a rich source of hematopoietic progenitor cells that can differentiate into a variety of cells, including insulin-producing β-cells, its limited availability and painful sampling make it less attractive than human umbilical cord blood. It was shown that human umbilical cord blood is also a rich source of hematopoietic progenitor cells that can give rise not only to erythroid, myeloid and lymphoid cells but also nonhematopoietic cells such as epithelial, endothelial and mesenchymal progenitor cells[13-21]. Human umbilical cord blood-derived lymphocytes are immunologically naïve and produce only a few activating cytokines. In addition, the cord blood has many $CD4^+CD25^+$ regulated T (Treg) cells with fewer natural killer cells[22,22a]. Treg cells play an important role in immune regulation as they can effectively suppress the activity of effector T cells reactive to both self- and non-self antigens. Therefore, the absence of Tregs or impairment of their function can lead to autoimmune diseases, such as type 1 diabetes. Kögler et al.[19] described a CD45-negative cell population, which they termed unrestricted somatic stem cells in the human umbilical cord blood. These unrestricted somatic stem cells have the potential to differentiate into osteoblasts, chondroblasts, adipocytes, hematopoietic and neural cells including astrocytes and neurons that express neurofilament, sodium channel protein, and various neurotransmitter phenotypes. These unrestricted somatic stem cells were also found to differentiate into albumin-producing hepatocytes and cardiomyocytes when transplanted into fetal sheep. Zhao et al.[20] isolated stem cells from the human umbilical cord blood, which they designated cord blood-stem cells. These cells displayed embryonic stem cell characteristics such as transcription factors (OCT-4 and Nanog), stage-specific embryonic antigen (SSEA)-3 and SSEA-4 as well as hematopoietic cell antigens (CD9, CD45 and CD117). These cord blood-stem cells could be stimulated to differentiate into endothelial-like (mesodermal) and neuronal-like (ectodermal) cells. Also, they could give rise in vivo to insulin-secreting (endodermal) islet cells. Other studies have shown differentiation of human umbilical cord blood cells into endothelial progenitors[19-21], mesenchymal cells[23,24], keratinocytes[25], and muscle cells[26]. Also, human umbilical cord blood cells can differentiate into insulin-secreting β-cells[27-31]. More recently, Romonov et al.[32] measured the concentrations of cytokines and growth factors in human umbilical cord blood serum and plasma, and found significantly higher concentrations of IL-4, 5, 6, 7, 10 and 15, MCP-1 (monocyte chemoattractant protein-1), and SDF-1 (stromal derived factor -1 alpha), as well as growth factors such as granulocyte-colony-stimulating factor, hepatocyte growth factor, platelet derived growth factor BB, and vascular endothelial growth factor that are involved in the processes of regeneration. Besides human

umbilical cord blood -derived mesenchymal cells, cord blood plasma and serum are a rich source of cytokines and growth factors that possess antiinflammatory, antiapoptotic, and angiogenic properties, and thus, can be used not only in the treatment of diabetes but other fields of regenerative medicine as well.

Advantages and disadvantages of human umbilical cord blood transplantation

As shown in Table 1, there are several advantages and disadvantages of human umbilical cord blood transplantation. The most important advantages are the unlimited and rapid availability with no risk to the donor, successful transplantation with a higher degree of mismatch compared to bone marrow from unrelated donor, low potential for transmission of viral infections, tumorigenicity and graft-versus-host disease. Also, production of noninflammatory cytokines such as IL-10 and angiogenic is an added advantage of human umbilical cord blood transplantation. In addition, cord blood plasma and serum contain several cytokines and growth factors that possess antiinflammatory, antiapoptotic, and angiogenic potential Several ethical concerns have been raised for the use of either embryonic or other stem cell applications in human subjects; however, use of human umbilical cord blood avoids many of these concerns surrounding this delicate issue. The disadvantage is probably insufficient stem cell supply in one autologous cord blood infusion that may not be sufficient to have a long-lasting beneficial effect, but this can successfully be achieved by multiple transfusions from mixed donors. However. the major disadvantage is the unavailability of the same donor blood for transplant in case of disease relapse in the recipient.

Table 1. Advantages and disadvantages of human umbilical cord blood

Advantages	Disadvantages
• Abundant supply • Low risk to the mother or infant • Risk of transmitting viral infections such as cytomegalovirus, Epstein-Barr virus is low • Tumorigenic potential of cord blood cells is low • Incidence of graft-versus-host disease is low, and no immunosuppression is required • Cord blood can be transfused to individuals with a higher degree of HLA mismatch • Cord blood can secrete noninflammatory cytokines • Transfusion of cord blood can avoid many ethical issues concerning stem cell therapies • Cord blood plasma or serum contains several antiinflammatory, antiapoptotic, and angiogenic factors	• Requires transfusion of at least 3 units because of low cell dose per unit • Unavailability of the same donor blood for transplant in case of disease relapse in the recipient • Slow hematopoietic cell (neutrophil and platelet numbers) recovery and requirement for blood and platelet transfusions • Prolonged length of hospital stay

Effect of human umbilical cord blood and its stem cells on blood glucose levels

Animal studies

Our group was the first to examine the effect of human umbilical cord blood cells in diabetic mice[33-35]. In the first study, we reported that administration of human umbilical cord blood mononuclear cells to nonobese diabetic mice with type 1 diabetes lowered blood glucose levels[33]. Subsequently, we demonstrated that lowering of blood glucose levels is dose-dependent, and injection of 200 x10^6 cells had a greater effect than injection of 100 x 10^6 cells. This improvement in blood glucose levels was related to a reduction in insulitis caused by human umbilical cord blood cells. Thus, abolition of insulitis seems responsible for better glucose control in mice that received the highest dose of human umbilical cord blood cells. Also, the lifespan of the mice with the highest dose of cells was prolonged much more than untreated or low-dose-treated mice. We extended the study to type 2 diabetic mice[35]. These mice received 200 x 10^6 human umbilical cord blood cells, and they were followed for approximately 400 days. Both blood glucose and survival of the treated mice were improved as compared with untreated mice.

Subsequent studies confirmed our observations. Zhao and associates[20] reported improvement in hyperglycemia in streptozotocin-induced diabetic mice. These investigators injected 5 million cord blood stem cells intraperitoneally into streptozotocin Balb/c nude mice and intraperitoneal glucose tolerance test (IPGTT) was performed 7 days later. Not only IPGTT but also blood glucose levels were normalized in these mice as compared with control diabetic mice. This improvement in glucose disposal seems to be related to new generation of C-peptide titers which were increased by two-fold after glucose challenge. This study clearly demonstrates in vivo production of insulin in cord blood stem cells-treated mice.

Zhang and associates[36] also observed blood glucose-lowering effect of human umbilical cord blood mononuclear cells in streptozotocin-induced diabetic mice, but this effect was transient. In this study, serum insulin levels were elevated. The short-lived beneficial effect in glucose and insulin in diabetic mice seems to be related to low dose (2 x 10^6) of human umbilical cord blood cells.

Type 1 diabetes is a cell-mediated autoimmune disease, and it is assumed that control of autoimmunity can improve blood glucose. The studies of Zhao et al.[37] confirmed this assumption. These investigators co-cultured autologous $CD4^+CD62L^+$ Tregs with CB stem cells (CB-SC) and called them modified CD4CD62L Tregs. These modified CD4CD62L Tregs were injected intraperitoneally into nonobese diabetic (NOD) mice, and blood glucose levels were monitored every 2 days for 45 days. IPGTT was done 3 weeks after injection of cells. Both blood glucose and IPGTT were normalized in treated mice compared to control mice that received CD4CD62L Tregs only. Insulin levels were significantly elevated in modified CD4CD62L Treg-treated mice. Also,

histologic evaluation of pancreas showed reduction in insulitis and apoptosis of infiltrated leukocytes in pancreatic islets. Thus, the results suggest that cord blood stem cells play an important role in modulating autoimmunity in type 1 diabetic NOD mice.

Several other studies also observed blood glucose lowering effect of cord blood stem cells in diabetic animals. Hasein et al.[38] reported that intravenous injection of $CD34^+$ cells into streptozotocin diabetic mice lowered blood glucose levels (278 mg/dl) significantly compared to untreated diabetic mice (530 mg/dl). Also, immunohistochemistry analysis demonstrated the presence of insulin-producing cells in pancreas of $CD34^+$-treated mice. Tsai et al.[39] were able to induce cord blood mesenchymal cells to differentiate into insulin-producing cells and transplanted them into the liver of streptozotocin diabetic rats through portal vein. Weekly blood sugar levels were found to be lower, Also, human nuclei and C-peptide were detected in the rat liver by immunohistochemistry. In another study, co-administration of cord blood-derived mesenchymal cells and cord blood cells to type 1 diabetic mice improved hyperglycemia. Also, the presence of donor-derived cells was observed in the recipient's pancreas and kidney[40]. Similarly, blood glucose-lowering effect of card blood mononuclear cells was observed in streptozotocin diabetic rats by El-Mesallamy and associates[41].

Human studies

Most of the studies with umbilical cord blood mononuclear cells and umbilical cord-derived mesenchymal cells were performed in diabetic animals than in diabetic human subjects. Human studies with cord blood cells were initially conducted by Haller and associates[42,43] in type 1 diabetic children. They reported their preliminary data in 8 subjects after 6 months of autologous transplantation of human umbilical cord blood cells[42]. Their mean age, duration of diabetes and HbA1c at time of infusion were 5.29 ± 1.8 (range: 2.4-7.3) years, 0.84 ± 0.8 years and 6.3 ± 0.7%, respectively. The number of infused mononuclear cells per kilogram was 1.9×10^7 and the cell viability was 96%. The patients did not receive any immunosuppression. The controls included a group of randomly selected type 1 diabetic children with similar age and duration of diabetes with good glycemia. Total daily insulin requirement and HbA1c were compared between human umbilical cord blood-treated and insulin alone-treated controls. Children who received human umbilical cord blood cells had significantly lowered average daily insulin requirements (0.45 ± 0.23 versus 0.69 ± 0.24; $P<0.0001$) as well as lowered HbA1c (7 ± 1.77 % versus 8.04 ± 0.8%; $P<0.0031$). Also, mixed meal stimulated C-peptide values that were determined prior to infusion, 3 months and 6 months after infusion of human umbilical cord blood cells were higher at 3 months with a gradual decline at 6 months. No infusion-related adverse events were observed. Thus, human umbilical cord blood cell transfusion lowered daily insulin requirements, improved HbA1c levels and preserved C-peptide levels in type 1 diabetic children for 6 months.

In a subsequent study, the same authors reported their results in 15 patients 1 year after infusion of autologous human umbilical cord blood cells, and found no changes in autoantibody titer, Tregs, CD4 to CD8 ratio, or other T-cell phenotypes[44,45]. Also, cord blood cells failed to improve C-peptide, insulin requirements and HbA1c levels. When the study was extended for 2 years with 24 children, a single infusion of autologous human umbilical cord blood cells failed to preserve C-peptide[46].

In another study[47], the same group evaluated the effect of a single autologous human umbilical cord blood infusion followed by 1 year of oral docosahexaenoic acid (DHA) and vitamin D supplementation for C-peptide preservation in 10 children with type 1 diabetes. Five diabetic children served as controls, and both groups received intensive treatment for diabetes. Both DHA and vitamin D have immunomodulatory effects, and vitamin D has been shown to increase the percentage of Tregs[22a]. After 1 year of follow-up, the treatment with HUCB cells, DHA, and vitamin D failed to preserve C-peptide, although the absolute rate of C-peptide decline was slower in treated (0.23 pmol/ml per 120 min) versus control subjects (0.33 pmol/ml per 120 min). However, this differences in did not reach significance at 1 year (P = .29). The authors attributed this nonsignificance to the small number of subjects.

Giannopoulou et al.[48] examined the effect of a single autologous cord blood infusion in 7 newly diagnosed type 1 diabetic and 10 control diabetic children in a non-randomized, controlled, open label intervention trial. Determinations of area under the curve and peak C-peptide, HbA1c, insulin use, and immune outcome (islet autoantibody titer and T-cell response) were performed at 1 year of infusion. They found no significant difference among metabolic and immune outcomes between infused children and controls. However, there were no transfusion-related adverse events.

Further studies were conducted by Zhao and colleagues[49] in both type 1 and type 2 diabetic subjects, using a procedure called Stem Cell Educator therapy. In this procedure, a patient's blood was circulated through a closed-loop system that separated lymphocytes, and these lymphocytes were co-cultured with adherent cord blood stem cells before returning them to the patient's circulation. These autologous lymphocytes that entered the circulation after being treated with cord blood stem cells were termed the Stem Cell Educator. In an open-label, phase1/phase 2 study, 15 type 1 diabetic patients received one treatment with the Stem Cell Educator. This therapy markedly increased both basal and glucose-stimulated C-peptide levels over a period of 40 weeks. Also, an improvement in HbA1c with less insulin requirement was observed. In addition, increased numbers of $CD4^+CD25^+F0xp3^+$ Tregs and restoration of Th1/Th2/Th3 cytokine balance were observed. Thus, Stem Cell Educator therapy was well tolerated, and produces long-lasting glucose control in type 1 diabetic patients.

This Stem Cell Education therapy was also applied to type 2 diabetic patients[50]. In this

study, a total of 36 patients on oral medications only received a single Stem Cell Educator therapy. Of these 36 patients, 7 had impaired β-cell function. This therapy reduced median HbA1c from 8.61% to 7.25% at 12 weeks and to 7.33% at 1 year. It was suggested that the improvement in HbA1c was due to increased insulin sensitivity. The 7 patients with impaired β-cell function benefitted the most, as these patients recovered their β-cell function by restoring their C-peptide levels. Thus, Stem Cell Educator therapy seems to improve insulin resistance in type 2 diabetic patients.

Li et al.[24] followed 15 type 2 diabetic patients before and after injection of human umbilical cord blood mesenchymal stem cells into the quadriceps muscle. Blood glucose and insulin requirements were evaluated 1, 2, 4, 8, and 12 months after transplantation. Both were significantly reduced in all 15 patients.

A long follow-up of blood glucose levels and HbA1c, C-peptide levels, and insulin requirements in 3 type 2 diabetic patients following intrapancreatic injections of human umbilical cord blood nucleated cells was reported by Tong and colleagues[51]. Two patients were on insulin in addition to oral hypoglycemic agents. At 3 and 6 months, 2-h glucose levels and HbA1c were much lower compared to baseline values. Two-hour C-peptide levels following oral glucose tolerance test were also much higher than baseline levels. In addition, the requirement of insulin decreased in those 2 patients. In one patient, the improvement in metabolic panel and insulin requirement was maintained even after 2 years follow-up, No complications of transplantation were noted in any one of the patients. This study is unique in terms of long follow-up compared to other studies in type 2 diabetic patients.

Although infusion of human umbilical cord blood mononuclear cells or cord blood-derived mesenchymal cells seems to lower blood glucose levels in diabetic animals, their infusion has not improved C-peptide level in type 1 diabetic children. However, their infusion in type 2 diabetic patients appears to improve both the glucose and C-peptide levels. As we suggested before, it is our impression that one autologous infusion of human umbilical cord blood mononuclear cells may not be sufficient to improve glycemia and C-peptide levels, and allogenic transfusion of at least 3 units of cord blood mononuclear cells is needed. Until such studies are performed, the usefulness of human umbilical cord blood and diabetes cannot be ruled out.

Effect of human umbilical cord blood on diabetic kidney disease

Diabetic kidney disease is a serious complication in both type 1 and type 2 diabetic patients. Although good glycemic and blood pressure control has been shown to improve kidney disease, the effect of human umbilical cord blood on albuminuria, glomerular filtration rate, and pathology of the kidney has not been studied that well. In a study of type 2 diabetic mice, we reported glomerular hypertrophy and tubular dilatation, and both changes improved following infusion of human umbilical cord

blood cells. This improvement in kidney structural changes may be related to good glycemic control in these type 2 diabetic mice[35].

Masoad et al.[52] examined the effect of umbilical cord blood mononuclear cells on kidney functional and histologic changes in streptozotocin diabetic rats. Each diabetic rat received a single dose of 150 × 10^6 mononuclear cells. At the end of 8 weeks, diabetic control rats had elevated blood pressure, creatinine, blood urea nitrogen, and albumin/creatinine ratio. Histologic changes of the kidney showed hyalanosis, hypertrophy and distortion of glomeruli, dilated tubules and thick basement membranes, with significant elevation in mean histopathologic score (increased extracellular matrix). All of these changes were ameliorated by treatment with umbilical cord blood mononuclear cells. It is interesting to note that the amelioration of these parameters were more pronounced in rats treated with mononuclear cells than the rats treated with pioglitazone, an oral hypoglycemic agent.

Although the study of Park et al.[53] was unable to observe reversal of kidney and glomerular hypertrophy in streptozotocin diabetic rats by human umbilical cord blood - derived mesenchymal cells (5 x 10^5 cells per rat) injected through the tail vein, however, they reported improvement in proteinuria, fractional mesangial area, and TGF-β1-extracellular matrix upregulation. Also, blood glucose levels were not improved. The mesenchymal cells were injected 2 days after induction of diabetes. The same authors also reported improvement in established proteinuria and mesangial matrix expansion even when these cells were infused 4 weeks after induction of diabetes. This improvement occurred without lowering glucose levels[54]. Thus, both studies suggest that kidney injury is prevented via paracrine mechanisms rather than blood glucose control.

A recent extensive study by Chen and colleagues[55] in streptozotocin diabetic rats confirmed reversal of glomerular hypertrophy, total proteinuria, albuminuria, and glomerular histologic changes following injection of umbilical cord blood-derived mesenchymal cells. After 6 weeks of established diabetes, umbilical cord blood-derived mesenchymal cells (2 × 10^6 cells) were injected via a tail vein once a week for consecutive 2 weeks. The rats were sacrificed after 2 weeks of injection. Untreated diabetic rats had abnormal glomerular hypertrophy and extracellular mesangial matrix, vacuolation of tubular epithelial cells, and cylinder as well as apoptosis of nephrocytes. Severe tubulointerstitial fibrosis was also observed in these diabetic rats. These kidney function abnormalities and kidney histologic changes were reversed in rats that received umbilical cord blood-derived mesenchymal cells. The authors suggest that the antiapoptotic effect of umbilical cord blood-derived mesenchymal cells may be mediated by inhibiting thioredoxin-interacting protein upregulation, downregulation of thioredoxin 1, and activation of apoptosis signal-regulating kinase 1 and P38 MAPK in the kidney of diabetic rats.

In another recent study by Xiang et al.[56], amelioration of kidney function abnormalities

and kidney histologic changes was observed in streptozotocin diabetic rats following tail vein injection of 2 × 10^6 umbilical cord mesenchymal cells. Also, transplantation of umbilical cord mesenchymal cells reduced the levels of pro-inflammatory cytokines (IL-6, IL-1β, and TNF-α) and pro-fibrotic transforming growth factor-β1 in the kidney and blood of diabetic rats. These beneficial effects occurred without improvement in blood glucose level.

A study in type 2 diabetic patients, transfusion of allogeneic human umbilical cord blood improved microalbuminuria[57]. Although blood glucose levels were not reported after transfusion, this interesting observation needs further evaluation and confirmation.

Effect of human umbilical cord blood on neuropathy

Besides diabetic kidney disease, diabetic neuropathy was also found to be improved by human umbilical cord blood cell therapy. Naruse et al.[58] injected endothelial progenitor cells from cord blood mononuclear cells intramuscularly into the hindlimb skeletal muscle of streptozotocin-induced diabetic nude rats. endothelial progenitor cell transplantation reversed sciatic motor nerve conduction velocity and sciatic endoneurial nutritive blood flow without lowering blood glucose levels in these diabetic rats. This increase in blood flow appears to be related to an increase in the number of blood vessels (microvessels) in the endothelial progenitor cell-injected side of the hindlimb skeletal muscle, as compared with the saline-injected side of the hindlimb. There was no effect of endothelial progenitor cells in normal rats. Thus, the endothelial progenitor cells from cord blood cells may be a useful treatment for diabetic neuropathy.

In this connection, it is worthwhile to mention a case report of a 37-year-old nondiabetic woman who recovered her sensation and hip as well as thigh movement 41 days later after intrathecal injection of 1 million human umbilical cord blood cells each for two times[59]. To our knowledge, such case reports have not been reported in human subjects but a large number of animal studies have shown improvement in spinal cord injuries following transplantation of human umbilical cord blood -derived cells[60].

Conclusions

Human umbilical cord blood is a rich source of stem cells and they can differentiate into pancreatic β-cells. It is available at short notice and is safe with low potential for graft-versus-host disease and tumorigenicity. Also, donor matching requires only blood group rather than HLA matching. Furthermore, the cord blood contains Tregs which may prevent destruction of β-cell mass[22,61]. Studies to improve glycemia and preservation of C-peptide levels in diabetic models with human umbilical cord blood mononuclear cells or mesenchymal cells derived from cord blood cells are uniformely successful. Also, amelioration of diabatic kidney and neurological complications was observed with cord blood cells or its mesenchymal cell transplantation. Although the initial studies of Haller et al.[42-44] showed promise in type 1

diabetic children, further studies showed failure to preserve C-peptide levels [46,47]. Similar observations by Giannopoulou and colleagues[48] in type 1 diabetic children confirmed that one autologous transfusion of human umbilical cord blood cells is not sufficient to maintain glycemia and C-peptide levels in these children. However, the observations of Zhao and colleagues[49,50], using Stem Cell Educator therapy, are of particular importance in the management of type 1 and type 2 diabetes. It is the hope of the authors of this review that more clinical trials should follow that of Haller and Giannopoulou and their associates[46-48], using both related and unrelated donor cord blood cells, to study the efficacy of human umbilical cord blood without immunosuppression in diabetic subjects to improve their diabetes care and associated complications.

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