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Administration of human umbilical cord blood to low birth weight infants may prevent the subsequent development of type 2 diabetes

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Summary Both epidemiological and experimental studies have shown that impaired growth in utero due to maternal malnutrition, resulting in low birth weight, is associated with a high incidence of glucose intolerance, insulin resistance, and type 2 diabetes in adult life. Maternal malnutrition is a worldwide problem and unavoidable; therefore, prevention of type 2 diabetes in low birth weight infants who reach adulthood is difficult to achieve. Administration of human umbilical cord blood (HUCB) mononuclear cells into type 1 and type 2 diabetic mice has been shown to improve both their blood glucose levels and survival. It has also been shown that the progenitor cells derived from HUCB improve not only glycemia but also other disease conditions, including systemic lupus erythematosis, amyotrophic lateral sclerosis, Alzheimer's disease, stroke, brain damage in animals and certain malignancies in humans. Transfusion of unrelated HUCB, although abundantly available, is underutilized as a therapeutic agent. Therefore, we propose the hypothesis that transfusion of HUCB to low birth weight infants be considered a therapeutic modality to prevent the development of type 2 diabetes in their adulthood.
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Introduction

A number of epidemiological and experimental studies have shown that impaired intrauterine growth, resulting in low birth weight (less than the 10th percentile), is associated with a variety of adult-onset diseases, including type 2 diabetes, hypertension, hyperlipidemia, cardiovascular disease, stroke [1—10] and kidney disease [11,12]. The common underlying mechanism for most of these disease conditions seems to be glucose intolerance and insulin resistance with hyperinsulinemia. Worldwide, maternal malnutrition, leading to poor fetal nutrition, seems to be the important cause of fetal growth retardation [8]. In this under-nourished fetus, it is hypothesized that the nutrient supply to the brain is well preserved at the expense of the other organs. For example,

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the growth of the pancreas and kidney and possibly the skeletal muscle is reduced. Rats fed a low protein diet during pregnancy results in significant reduction in pancreatic β-cell proliferation and islet cell size in the neonates [13]. In addition, apoptosis of β-cells and decreased islet vascularization was observed in 14-day-old neonates born to low protein diet mothers [14]. Thus, the reduction in β-cell mass occurs at the expense of the growth of the brain. The net result of this ''trade off'' is a decrease in insulin secretion in the low birth weight infant. Decreased insulin secretion alone is not sufficient to cause glucose intolerance, because the under-nourished infant is usually thin and may have normal insulin sensitivity. However, overfeeding during childhood with development of obesity in adulthood may cause glucose intolerance and insulin resistance, leading to type 2 diabetes later in life [7,8].

Hypothesis

Lifestyle modification with diet and appropriate caloric intake to improve insulin secretion in the offspring of malnourished pregnant mothers will help prevent the development of type 2 diabetes later in life. However, such a strict lifestyle modification in a growing child is not always feasible. Cherif et al. [15] supplemented pregnant rats on low protein diet with taurine, which stimulates the release of insulin from islet cells, and found restoration of insulin release from malnourished fetal islets. Thus, insulin release from islets can be improved even in the presence of low birth weight. However, no such studies have been done in humans. Therefore, we propose the hypothesis that administration of unrelated HUCB to low birth weight infants may prevent the development of type 2 diabetes in adulthood. This proposed hypothesis is based on the following observations. First, embryonic stem (ES) cell therapy for diabetes has received considerable attention in recent years [16–29]. These ES cells from multiple sources differentiate into insulin-producing cells and improve glycemia in animal models of diabetes. Recently, we have shown that non-obese diabetic (NOD) mice with type 1 diabetes when treated with HUCB cells, without immunosuppression or radiation, significantly lowered their blood glucose levels with an improvement in their survival, as compared with untreated mice [30]. In addition, a significant reduction in insulitis was observed in treated than in untreated mice. Similarly, a decrease in blood glucose levels was associated with an increase in lifespan in type 2 diabetic db/db mice [31]. Thus, HUCB cells function like ES cells and improve hyperglycemia. Second, transplantation of HUCB mononuclear cells into mice was also found to improve the clinical condition of mice with lupus erythematosis [32], amyotrophic lateral sclerosis [33,34], Alzheimer's disease [35] as well as stroke [36] and brain injury [37] in rats. In these studies, the pluripotential capacity of the HUCB cell or cells was not adequately identified. However, a recent study showed that the CD45-population of the HUCB cells has the potential to differentiate into osteoblasts, chondroblasts, adipocytes, and hematopoietic and neural cells including astrocytes and neurons that express neurofilament, Na^+ channel protein, and various neurotransmitter phenotypes [38]. These CD45-cells were also found to differentiate into albumin-producing hepatocytes and cardiomyocytes when transplanted into fetal sheep [38]. In another study, HUCB mononuclear cells containing CD34+ were injected in the tail vein of NOD/scid mice following experimental myocardial infarction, and these CD34+ cells were found to improve the left ventricular function by neoangiogenesis and remodeling the infarcted myocardium [39]. Furthermore, transplantation of HUCB-derived endothelial progenitor cells into hindlimb skeletal muscles of streptozoticin-induced diabetic nude rats improved neuropathy by neovascularization in these skeletal muscles [40]. Third, transplantation of HUCB, which is rich in hematopoietic progenitor/stem cells [41–46], is being evaluated as an alternative to bone marrow transplantation to treat metabolic [47] and malignant as well as non-malignant diseases [48–53]. Thus, HUCB mononuclear cells can be used as another modality of stem cell therapy to prevent a variety of disease states, including diabetes. Finally, Tse and Laughlin [52] discuss various advantages of HUCB as hematopoietic stem cells for allogenic transplantation, and conclude that HUCB from unrelated donors is a feasible alternative source of stem cells for transplantation. The most important advantage is that HUCB is abundantly available, and its application is not associated with current ethical concerns raised for the use of embryonic stem cells. Furthermore, the incidence of viral transmission and graft-vs.-host disease is rather low. In our study, both the diabetic and non-diabetic mice that received HUCB cells did not demonstrate any clinical or histologic evidence of either acute or chronic graft-vs.-host disease [30,31,53].

In conclusion, we suggest that transfusion of unrelated HUCB to low birth weight infants should be considered a feasible and easily available alternative to prevent the development of type 2 diabetes in their adulthood. Based on the evidence, it is

also proposed that transfusion of HUCB to low birth weight infants may be protective from other adult-onset diseases.

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