

Diabetics cured by stem-cell treatment

David Rose April 11, 2007 TIMESONLINE.com UK Edition

Diabetics using stem-cell therapy have been able to stop taking insulin injections for the first time, after their bodies started to produce the hormone naturally again.

In a breakthrough trial, 15 young patients with newly diagnosed type 1 diabetes were given drugs to suppress their immune systems followed by transfusions of stem cells drawn from their own blood.

The results show that insulin-dependent diabetics can be freed from reliance on needles by an injection of their own stem cells. The therapy could signal a revolution in the treatment of the condition, which affects more than 300,000 Britons.

People with type 1 diabetes have to give themselves regular injections to control blood-sugar levels, as their ability to create the hormone naturally is destroyed by an immune disorder.

All but two of the volunteers in the trial, details of which are published today in the *Journal of the American Medical Association (JAMA)*, do not need daily insulin injections up to three years after stopping their treatment regimes.

The findings were released to reporters yesterday as the future of US stem-cell research was being debated in Washington.

Stem cells are immature, unprogrammed cells that have the ability to grow into different kinds of tissue and can be sourced from people of all ages.

Previous studies have suggested that stem-cell therapies offer huge potential to treat a variety of diseases such as Alzheimer's, Parkinson's and motor neuron disease. A study by British scientists in November also reported that stem cell injections could repair organ damage in heart attack victims.

But research using the most versatile kind of stem cells — those acquired from human embryos — is currently opposed by powerful critics, including President Bush.

The *JAMA* study provides the first clinical evidence for the efficacy of stem cells in type 1 diabetes. Sufferers of the chronic condition, which normally emerges in childhood or early adulthood, have to inject themselves at least four times a day.

Type 2 diabetes, which tends to affect people later in life, is linked to lifestyle factors such as obesity. There are almost two million type 2 diabetics in Britain, most of whom control their blood-sugar levels with pills or through diet.

The new study, by a joint team of Brazilian and American scientists, found that one of the first patients to undergo the procedure has not used any supplemental synthetic insulin for three years. "Very encouraging results were obtained in a small number of patients with

early-onset disease," the authors, led by Julio Voltarelli, from the University of São Paulo in Ribeirão Preto, Brazil. write. "Ninety-three per cent of patients achieved different periods of insulin independence and treatment-related toxicity was low, with no mortality."

Type 1 diabetes occurs when the body's own immune system malfunctions and destroys the insulin-producing beta cells of the pancreas, causing a shortage in the hormone.

By the time most patients receive a clinical diagnosis, 60 to 80 per cent of their beta cells have been wiped out. The disease progresses from this point very quickly, and can result in serious long-term complications including blindness, kidney failure, heart disease and stroke.

Dr Voltarelli's team hoped that if they intervened early enough they could wipe out and then rebuild the body's immune system by using stem cells, preserving a reservoir of beta cells and allowing them to regenerate.

They enrolled Brazilian diabetics aged between 14 and 31 who had been diagnosed within the previous six weeks. After stem cells had been harvested from their blood, they then underwent a mild form of chemotherapy to eliminate the white blood cells causing damage to the pancreas. They were then given transfusions of their own stem cells to help rebuild their immune systems.

Richard Burt, a co-author of the study from Northwestern University's Feinberg School of Medicine in Chicago, said that 14 of the 15 patients were insulin-free for some time following the treatment. Eleven of those were able to dispense with supplemental insulin immediately following the infusion of stem cells and have not had recourse to synthetic insulin since then, he said. "Two other patients needed some supplemental insulin for 12 and 20 months after the procedure, but eventually both were able to wean themselves from taking daily shots, he added." One patient went 12 months without shots, but relapsed a year after treatment after suffering a viral infection, and resumed daily insulin injections. Another volunteer was eliminated from the study because of complications. The therapy, known as autologous hematopoietic stem cell transplantation, has already shown benefits to individuals with a range of auto-immune diseases such as rheumatoid arthritis, Crohn's disease and lupus.

There are still question marks about exactly how the treatment works, and further studies will be required to fully evaluate its safety and efficacy.

"As a research scientist I am always hesitant to speak of a cure, but the initial results have been good and show the importance of conducting more trials," Dr Burt said.

Given the right funding opportunities, university hospitals in London could be conducting research into the therapy within the next 12 months, he added.

"It will probably be five to eight years before we see a treatment being widely available," he said.

In an accompanying editorial in *JAMA*, Dr Jay Skyler, of the Diabetes Research Institute at the University of Miami, wrote: "Research in this field is likely to explode in the next few years and should include randomized controlled trials, as well as mechanistic studies."

Autologous Nonmyeloablative Hematopoietic Stem Cell Transplantation in Newly Diagnosed Type 1 Diabetes Mellitus

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Context Type 1 diabetes mellitus (DM) results from a cell-mediated autoimmune attack against pancreatic beta cells. Previous animal and clinical studies suggest that moderate immunosuppression in newly diagnosed type 1 DM can prevent further loss of insulin production and can reduce insulin needs.

Objective To determine the safety and metabolic effects of high-dose immunosuppression followed by autologous nonmyeloablative hematopoietic stem cell transplantation (AHST) in newly diagnosed type 1 DM.

Design, Setting, and Participants A prospective phase 1/2 study of 15 patients with type 1 DM (aged 14-31 years) diagnosed within the previous 6 weeks by clinical findings and hyperglycemia and confirmed with positive antibodies against glutamic acid decarboxylase. Enrollment was November 2003-July 2006 with observation until February 2007 at the Bone Marrow Transplantation Unit of the School of Medicine of Ribeirão Preto, Ribeirão Preto, Brazil. Patients with previous diabetic ketoacidosis were excluded after the first patient with diabetic ketoacidosis failed to benefit from AHST. Hematopoietic stem cells were mobilized with cyclophosphamide (2.0 g/m^2) and granulocyte colony-stimulating factor ($10 \text{ } \mu\text{g/kg}$ per day) and then collected from peripheral blood by leukapheresis and cryopreserved. The cells were injected intravenously after conditioning with cyclophosphamide (200 mg/kg) and rabbit antithymocyte globulin (4.5 mg/kg).

Main Outcome Measures Morbidity and mortality from transplantation and temporal changes in exogenous insulin requirements (daily dose and duration of usage). Secondary end points: serum levels of hemoglobin A_{1c}, C-peptide levels during the mixed-meal tolerance test, and anti-glutamic acid decarboxylase antibody titers measured before and at different times following AHST.

Results During a 7- to 36-month follow-up (mean 18.8), 14 patients became insulin-free (1 for 35 months, 4 for at least 21 months, 7 for at least 6 months; and 2 with late response were insulin-free for 1 and 5 months, respectively). Among those, 1 patient resumed insulin use 1 year after AHST. At 6 months after AHST, mean total area under the C-peptide response curve was significantly greater than the pretreatment values, and at 12 and 24 months it did not change. Anti-glutamic acid decarboxylase antibody levels decreased after 6 months and stabilized at 12 and 24 months. Serum levels of hemoglobin

A_{1c} were maintained at less than 7% in 13 of 14 patients. The only acute severe adverse effect was culture-negative bilateral pneumonia in 1 patient and late endocrine dysfunction (hypothyroidism or hypogonadism) in 2 others. There was no mortality.

Conclusions High-dose immunosuppression and AHST were performed with acceptable toxicity in a small number of patients with newly diagnosed type 1 DM. With AHST, beta cell function was increased in all but 1 patient and induced prolonged insulin independence in the majority of the patients.

Trial Registration [clinicaltrials.gov Identifier: NCT00315133](https://clinicaltrials.gov/ct2/show/study/NCT00315133)

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