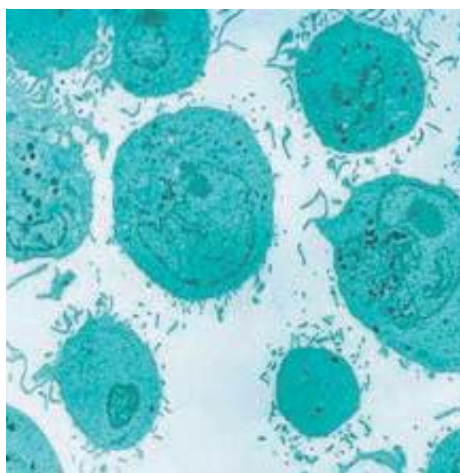


Diabetes therapy with adult stem cells

by Dr. Peter Nitsche (MD, PhD)

The utilization of insulin in the conventional treatment of diabetes mellitus – for both the dysfunctional secretion of insulin and insulin production with the objective of normalizing blood glucose levels is still common practice. However, this is a symptomatic approach and curing diabetes involves a great deal more.



In a chronic course of hyperglycaemia micro or macroangiopathic sequelae successful medical recovery is extremely rare. The targeted application of adult autogenetic stem cells which have the potential to renew the malfunctioning insulin producing β -cells of the pancreas, on the other hand, represents a causal approach to healing the overall metabolic syndrome. Stem cell therapy has long been a focus of public debate. However, this debate overshadows the possibilities and

successes of stem cell therapy, which is evident in the two classic types of diabetes mellitus.

Cologne-based XCell-Center, at the Institute for Regenerative Medicine in Eduardus Hospital, practises diabetes therapy with adult autogenetic stem cells using a method that has been officially certified by the competent government authorities. The first step of the treatment involves checking the patient's therapy tolerance. This is contingent upon patient anamnesis and constitution (see information overview on Page 3) as well as the quantity and quality of autologous stem cells. If all parameters are met, approx. 150 to 200 ml of bone marrow are biopsied from the patient's hip bone under local anaesthesia.

The preparation of the harvested bone marrow in the laboratory must be performed within 48 hours of its removal.

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 Blood plasma, erythrocytes, leukocytes and stem cells are isolated in a clean room environment. The stem cells undergo quantitative and qualitative testing. Using a special method of centrifugation, the stem cells are concentrated so that about one tenth of the originally harvested marrow contains 90 % of the stem cells. During processing, the results are analyzed and recorded in a report; the outcome is considered positive if more than 2 million stem cells (CD34+) remain and have a survival capacity of more than 80 %.

If the result is positive, the isolated stem cells are stored under sterile conditions at -196°C in liquid nitrogen. The XCell-Center has patented its method of stem cell preparation. The product also referred to as "stem cell concentrate" is considered to be a drug pursuant to German law and is therefore subject to the strict provisions of the German Pharmaceuticals Act.

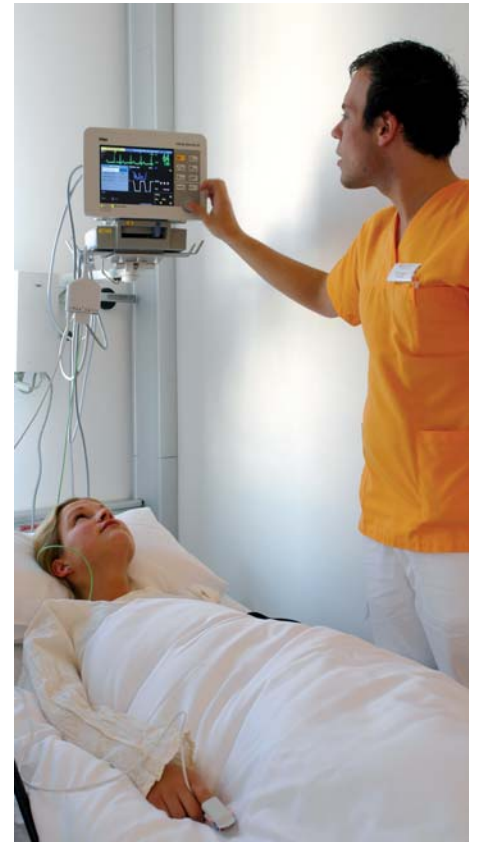
The bone marrow biopsy, its preparation and reinjection are all compliant with Good Manufacturing Practices (GMP), i. e. qualified and certified manufacturing processes.

During the further course of treatment, a pancreas MRT is routinely generated. A catheter is pushed from the femoral artery into the pancreas artery under angiographic monitoring. Then the prepared stem cells are implanted into the pancreas tissue. To treat complications of diabetes,

e. g. the diabetic foot, stem cells can be locally injected into the damaged area. This may, among other things, foster the healing of ulcers. The entire procedure, i. e. from stem cell biopsy to re-injection of the prepared stem cells normally takes 3 to 4 days. The patient can be discharged from the clinic within a few hours of bone marrow collection and stem cell re-injection.

The success rate of the diabetes treatment with stem cells at the XCell-Center is reassuring. A decrease in the daily dose of insulin required within three months of treatment is observed in the majority of patients – ideally, they can completely forego the use of insulin. The significant success rates and the low risk are both good reasons for considering treatment with adult stem cells.

Given that the prepared stem cells are autogenetic tissue, they are not rejected



by the body and all other risks are no higher than the risks associated with any intervention performed under hygienic conditions. <



Dr. med. Peter Nitsche is a physician specializing in internal medicine and diabetes. He is an expert in providing adult stem cell therapy for diabetes mellitus at the XCell-Center's Institute for Regenerative Medicine.

Before joining the X-Cell Center team, Nitsche practiced at hospitals in Herford, Bad Hersfeld and Kassel as a senior physician for several years. For the past 12 years, he has been a partner in a medical group specializing in the treatment of the diabetic foot in Münster. <

WHO SHOULD CONSIDER ADULT STEM CELL THERAPY?

Stem cell therapy is an option for any diabetes patient whose condition will not improve as a result of lifestyle changes. It is most suitable for patients who do not respond positively to standard therapies and whose blood glucose levels can only be adjusted marginally despite all efforts made. Patients suffering from diabetes-related complications, such as diabetic foot, will also benefit from the treatment with endogenous stem cells.

Cave! Stem cell therapy is not suitable for patients who have been treated for tumors over the past 15 years. Patients with blood coagulation disorders, heart failure (phase 4 and 5) or proliferating retinopathy

and kidney failure are currently also excluded from the stem cell therapy. <



How adult stem cells are supposed to function

Further research is still necessary into the contribution of bone marrow stem cells to organ regeneration. For a long time, the assumption was that the positive effects of stem cells are driven primarily by their replacement of damaged cells in the affected organs.

It is practically impossible to establish whether adult stem cells actually do integrate themselves into tissue, i.e. convert themselves into functional β -cells, or replace damaged endothelium cells in humans. Animal testing has shown that this process takes place and that the applied stem cells can mutate into local parenchyma cells. However, this only occurs on a very small scale and contradicts the earlier assumptions.

Today, scientists believe that stem cells do not replace damaged cells but stimulate extant cells in the organs to regenerate themselves. Bone marrow stem cells seem to stimulate anti apoptotic, anti inflammatory and proangiogene processes and others that influence the endogenous ability to regenerate with a parakrine secretion of growth factors. <



CASE REPORT

Case report

In 2002, Sven Fisher*, who was 34 years old at the time, was diagnosed with type 1 diabetes. He was initially treated with Levemir® (2x9 IE/day) and Novo-Rapid® (a total of approx. 20 IE per day). Although the patient monitored his blood glucose levels very diligently, he began to develop increasing symptoms of poly-neuropathy in his arms and legs over time, which manifested as tingling in the extremities, numbness and weakness. The patient also observed a considerable loss of concentrative powers. Sven F., who had been an active athlete until the onset of diabetes, felt that the disease was having a serious adverse impact on his quality of life. Consequently, he began searching for alternative treatment options for his disease and ultimately made an appointment with the XCell-Center in Cologne. A preparatory examination determined that he was a good candidate for the treatment with his own body's stem cells.

The stem cells were transplanted in May 2007. With the support of an angiographic process, the concentrated stem cells were directly injected into the pancreas via a catheter in the groin area. To harness the immune reaction, the patient was administered cortisone (Prednisolon) for the first few days after the transplant. The side effects of the transplant – a slight pain in the groin

area as a result of the catheter insertion and pressure in the abdomen caused by the cortisone – disappeared completely within three weeks of the procedure.

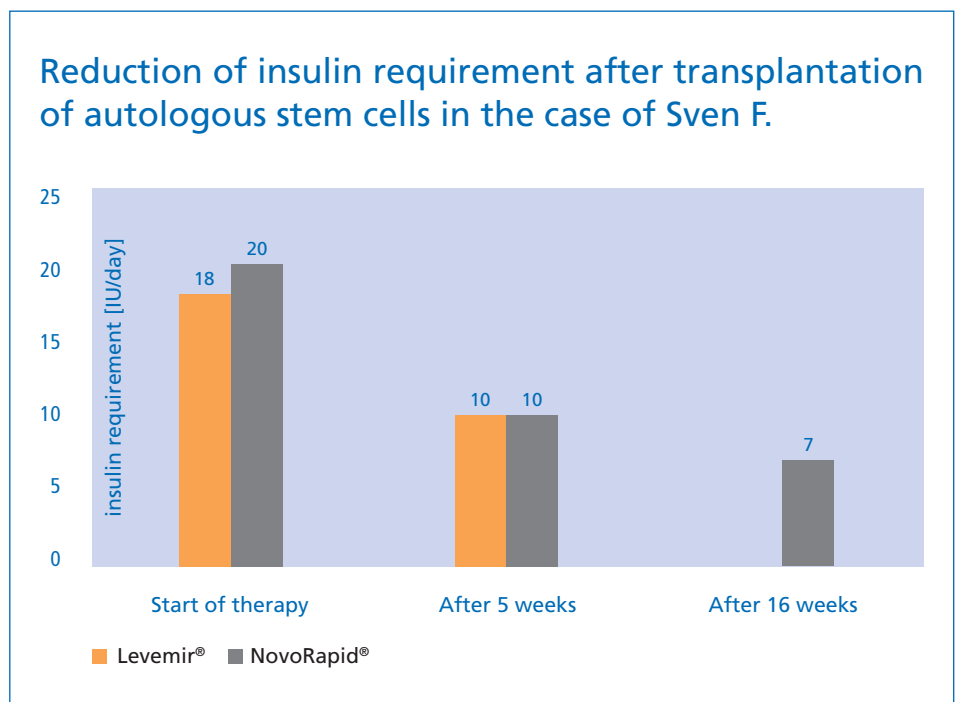
The discomfort in his arms and legs had also improved by this time, and he was able to start moderate jogging four weeks after the treatment.

From the fifth week onwards, his arm and leg problems had disappeared almost completely and the patient noticed that his concentrative powers were beginning to improve, while his need for insulin dropped. He was able to reduce the dose of long-term insulin to 2x5 IE per

day and cut down the short-term meal-accompanying insulin to only half of the original dose.

Three months after the transplant, Sven Fisher was able to go out for extended runs that even included short and long sprints. Today, about four months later, he does not need any long-term insulin and is able to maintain a relatively stable blood glucose level of 85-110 mg/dl using 5-9 IE NovoRapid® on a daily basis. <

*name changed



Interview with Sven Fisher

You have been suffering from type 1 diabetes for the past five years. What motivated you to seek out other treatment options?

I was devastated when I started to have problems so soon after beginning insulin therapy. My feet and hands tingled a lot and felt numb. It got so bad that I could hardly do any sports. I didn't want to live with these kinds of restrictions permanently, especially since I'm a passionate jogger. My doctor told me I could try blood circulation stimulating medication, but that other than that I had no further options.

What did you decide to do next?

I didn't want to give up, so I started to search hard for other treatment options. For instance, I got information about organ and island cell transplants. But both of these options would have meant me having to swallow pills for the rest of my life to suppress my body's rejection of the transplants. It was by pure chance that I saw a television report on the XCell-Center. I checked out the clinic on the internet and the information that I found made me very optimistic that maybe something could be done for me after all.

Why did you opt for the treatment with autologous adult stem cells?

Rejection isn't an issue with this new

therapy, which is why I first wanted to try it out. I assumed that – apart from the normal risks of any surgical intervention – I wouldn't have to deal with any serious side effects.

How did the XCell-Center inspire hope in you?

They were very cautious about making promises. Up to now, the XCell-Center has gained most of its experience from the treatment of type 2 diabetes. I was one of the first type 1 diabetics willing to try this therapy. There was justified hope that the treatment would be successful, but no verified data. The XCell-Center told me these facts quite bluntly.

How time-consuming was the treatment? Did you have to go to the XCell-Center a lot?

Actually, the treatment proved not to be time-consuming at all. I only had to go in twice: the first time for the bone marrow biopsy and the second time to have the concentrated stem cells injected.

When did you first feel that the transplant had been successful?

About three weeks afterwards my feet felt completely normal – the numbness was gone. It took a while longer for me to realize that I needed less insulin. Initially, I was able to reduce the dose of long-term insulin by half and finally I could stop taking it completely. My glucose



levels are still in the normal range. When I eat a meal, I still take insulin, but I'm needing less and less of it.

How did your diabetologist react?

He is very interested in the treatment since he had never heard of this therapy before. He is now monitoring my treatment intensively.

How do you rate the therapy from today's perspective?

Obviously, it would be absolutely great if the treatment resulted in me not having to take insulin at all. On the other hand, I am very satisfied as things stand – as my quality of life has improved significantly since I had the treatment. Now that I don't need to take long-term insulin any more, I can do sport whenever I feel like it without having to worry about possible diabetes-related problems. I can basically do most of the things I've always enjoyed. <

RESEARCH NEWS

Successes in the treatment of type 1 and 2 diabetes mellitus patients

The first results of the clinical studies involving the treatment of type 1 and 2 diabetes mellitus patients with adult stem cells are very promising. Although it is still not entirely clear how the mechanism works, these trials indicate that insulin consumption of diabetes patients can be reduced significantly when they are treated with adult stem cells. Some patients were even able to forego insulin completely after just a few months (Voltarelli, 2007; Li Chen, in print). Further research will have to determine whether this effect can be sustained so that these patients could be considered fully recovered.



Initial results lead to the conclusion that therapy with adult stem cells can yield lasting effects. Voltarelli et al. demonstrated in a small group of young patients suffering from type 1 diabetes that the combination of immune suppression and the application of haematopoietic stem cells led to long-term **insulin independence** in 14 of 15 patients. The therapy allowed one patient to give up insulin completely for more than 35 months and four other patients did not need insulin injections for at least 21 months. Seven patients remained insulin independent for six months and the other two patients were insulin independent for between one and five months. The endogenous

synthesis of insulin significantly improved and remained at a constant high level, which indicates a sustainable effect of stem cell therapy (Voltarelli, 2007).



The chart on page 7 shows the successes of a recently completed post-authorization trial involving type 2 diabetics. Oral insulin and anti-diabetic medication requirements declined in all 25 subjects after the transplantation of adult stem cells. Approx. 25 % of the patients did not need insulin after one treatment. Over the course of the trial significant progress was evident in relevant diabetes parameters. The fasting glucose in the plasma sank along with the concentration of glycosides haemoglobin (HbA1c), which dropped by a significant amount. The C-peptide level increased, indicating a cumulative insulin synthesis. <

XCell-Center starts SCIDIM 1 and 2

The XCell-Center is in the process of rolling out two clinical trials that examine the therapeutic effect of adult stem cell therapy in type 1 and 2 diabetes mellitus patients.

Within the next two years, 80 patients will be included in each of the two SCIDIM studies (Stem Cells in Diabetes Mellitus). They will be monitored over a period of one year, during which patients will attend 9 appointments: the initial medical examination one month before the study starts (during which a bone marrow biopsy will be performed), another examination at the time when the trial begins (including administration of the

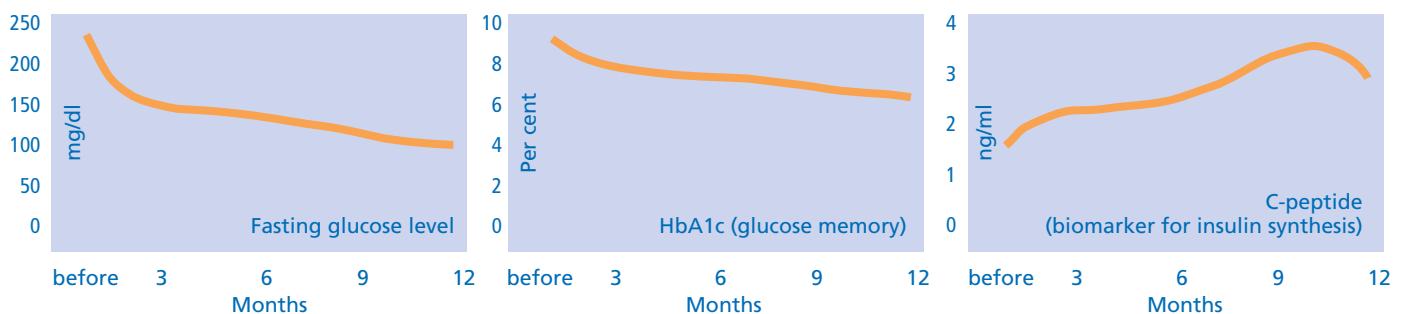
adult stem cells) and a series of follow-up examinations after 7, 14, 30, 60, 120, 180 and 360 days.

All patients will be treated with their regular diabetes medication throughout the entire period. Additional therapy with the adult stem cells will be administered. Half of the patients will be given stem cell therapy right from the beginning and the other half after six months.

The objective of the study is to record the effects of stem cell therapy on diabetes medication. The effect of the therapy will also be investigated in terms of a wide range of derivative variables. Other effects being tracked are fasting glucose, HbA1c level, renal function and patient quality of life. A first interim result will be determined as soon as 40 patients have completed the study.

Patients who wish to take part in one of the two first studies are encouraged to contact the Institute for Regenerative Medicine in Cologne directly. <

Results of diabetes therapy with adult stem cells



- Treatment resulted in a reduction of insulin and/or oral anti diabetics use in the majority of patients^{1, 2, 3}
- Approximately 25 % of the patients established complete insulin independence after one treatment^{1, 2}
- The treatment was safe and well tolerated^{1, 2}

Note: ¹Own data; ²Li Chen a.o., "Autologous Transplantation of Bone Marrow Mononuclear Cells in Treating Patients with Diabetes"; ³Voltarelli a.o., "Autologous Nonmyeloablative Hematopoietic Stem Cell Transplantation in Newly Diagnosed Type 1 Diabetes Mellitus", 297 (14): 1568, 2007 JAMA.

DISCUSSION FORUM

Talking point: Stem cells between the need for more research and already available therapy options

By Dr. Cornelius Kleinbloesem

Stem cell therapy is a polarized topic of public debate. Is it progressive treatment that has the potential to cure many diseases or are stem cells something from the dark side of genetic experimentation alongside cloning – a sadistic method that requires the killing of embryos? The world is plagued by quacks who peddle stem cell miracle cures and scientists who falsify trial results on a grand scale and bring the scientific community into disrepute.

One of the issues preventing public enlightenment is the fact that stem cells are still a topic of controversial debate even among many medical expert groups. The medical fraternity, which strives to give its patients competent advice, is being confronted with a question of principle: is stem cell therapy ready for practical applications or will it take another ten to twenty years of research?

The XCell-Center/Institute for Regenerative Medicine in Cologne answers this question with facts. Since January, it has been treating primarily diabetes and stroke patients with autogenous adult stem cells and has achieved remarkable suc-

cesses. Initial individual case reports of patients suffering from spinal injuries, multiple sclerosis, Parkinson's and Alzheimer's disease show that an attempt at therapy may yield beneficial results.

To do the one thing does not mean not doing something else. Consequently, the XCell-Center does perform accompanying trials that examine the effectiveness of stem cell therapies and will complete our understanding of the exact regenerative processes in the affected organs. Even if not all of the interactions have been conclusively researched to date, the status of the current medical insights has indeed reached a level that allows the non-

hazardous treatment with adult stem cells and puts medical professionals in a position to assume responsibility for its use.

Given the proven treatment success of regenerative medicine, the question of whether more research is needed prior to therapeutic use has already been answered. Those who nevertheless demand stem cell therapy be postponed until we know more about it are taking away patients' rights to make their own decisions as they search for medical solutions – for the kind of help stem cell therapy does offer.

Dr. Kleinbloesem is the Managing Director of the XCell-Center.

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