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Transplantation of Human Fetal Tissue as a Promising Method in the Treatment of Diabetes Mellitus

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Experience accumulated in Russia during the last century in the treatment of diabetes mellitus by transplantation of human fetal tissues is analyzed from the historical and geographical viewpoint. Over the last 15 years about 3000 patients have been treated using this method. Such treatment has mainly resulted in stabilization of the labile forms of insulin-dependent diabetes: in 80% of recipients the exogenous insulin requirements have been reduced by 20-85%, and in some cases a short-term insulin independence has been established. Discontinuation and partial regression of secondary diabetic complications have been observed: pain and paresthesia in the extremities have diminished or disappeared; in the case of angiopathy of the lower extremities the incidence of indications for amputation due to gangrene has been reduced; the pathological process in the fundus of the eye has been arrested and visual acuity has increased in 45-65% of patients with diabetic retinopathy. At the prenephrotic stage of diabetic nephropathy transplantation has been attended by a reduction or disappearance of proteinuria and normalization of arterial pressure in 40-50% of patients.

Key Words: *transplantation of human fetal tissue; treatment of diabetes mellitus; neuropathy; angiopathy; retinopathy; nephropathy*

The present report is devoted to achievements of researchers from Russia and from republics of the former USSR in the treatment of diabetes mellitus (DM) by the methods of fetal (human and animal) tissue transplantation (FTT).

Transplantation of human and animal fetal pancreatic islet cells (PIC) is a particular case of FTT, and studies carried out in the CIS and other former Soviet republics have contributed to the development of this method [15,26,34,39,40].

As early as in 1901 in the Dissertation "The Morphology of the Pancreas after Ligation of Its Duct in Diabetes and under Some Other Conditions" the Russian pathologist and anatomist L. V. Sobolev theoretically substantiated the value of organotherapy in DM [36]. He reached such a conclusion from his own experimental findings demonstrating that the pancreatic islets of Langer-

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hans fulfill a specific function in this organ, namely they maintain carbohydrate metabolism in the organism [36]. The Sobolev "islet" theory has been entirely confirmed by further studies. It would seem quite logical to compensate for the deficiency of islet tissue in patients with DM by transplanting similar cell material from healthy donors. However, implementation of this idea in clinical practice has taken a long time. Since Sobolev himself had suggested the use of organotherapy in combination with injections of extract of a hypothetical hormone (insulin was discovered a few decades later), researchers who had no substantial theoretical basis and no practical way of solving these problems initially attempted to use extracts from the islet tissue as a preparation for substitution treatment. Back in 1904, the Russian physiologist A. A. Kulyabko used islet tissue extract derived from some species of bony fish in the treatment of diabetes mellitus. As a matter of fact, this method adopted the techniques used by his predecessors: the endocrinologist Brown-Sequard (1889, 1892) and the Russian researcher Shifarevich (1894) [34]. Later, advocates of tissue-lysate therapy (the followers of Tushnov and Filatov) returned to this idea repeatedly. Incidentally, Doctor Krauze, one of Filatov's disciples, was the first to explain in scientific terms the advisability of using fetal tissue for tissue therapy [34].

Later, the discovery and isolation of insulin largely determined the approach to the treatment of DM. The use of insulintherapy and diettherapy in combination allowed for long-term maintenance of such patients, but, as is well known, the potentials of such an approach proved rather limited. In the 60s-70s researchers and clinicians mainly focused on the creation of artificial islets of Langerhans and on the development of effective methods of transplanting viable cells. The second approach proved to be quite difficult for a number of reasons. Theoretically, the transplantation of allogenic cells is associated with unavoidable immune rejection of histologically incompatible material. This problem can only be solved if there is an extensive bank of tissues which are strictly typed according to antigens of the major histocompatibility complex. Even in the case of complete HIA matching and in the absence of differences with respect to the minor antigens of histocompatibility, graft rejection cannot be ruled out due to the autoimmune nature of the destructive changes in PIC in type I insulin-dependent diabetes.

Researchers aiming at the successful transplantation of viable cells in DM are mainly focusing on methods of protecting the transplant from rejection and on the choice of suitable transplant material.

However, in practice transplantation of allo- or xenogeneic PIC is being successfully performed, and, judging by the results described below, future expectations for successful FTT in this disease are rather promising [19,24,31,32,47-52].

In October 1979, the first allotransplantation of PIC of human fetuses to a patient with insulin-dependent DM was performed in Russia. Cells were implanted in the splenic pulp. The operation was performed at the Research Institute of Transplantology and Artificial Organs by a group of surgeons headed by one of the leading Russian transplantologists, Academician V. I. Shumakov [48]. Subsequently, the method of DM treatment suggested by Shumakov has been widely used in Russia. An important contribution to the development and improvement of the technique of DM treatment by transplanting Langerhans cells was made by researchers and clinicians from Moscow [21,45,47], St. Petersburg [14], Kiev [38], Riga [33], Erevan [5], Lvov [12], Izhevsk, Kharkov, and other cities of the former USSR. The optimal choice of material for transplantation was a task of primary importance. First, methods of culturing PIC of human and animal fetuses were developed [9,20,45,47]. A 5-7-day culturing made it possible to markedly reduce the immunogenicity of transplanted material. Fetal cells entirely preserved their functional activity during culturing. As a rule, cells derived from several allogeneic fetuses have been used for a single injection, because the donor material had to be implanted in a therapeutically effective dosage. It is worthy of note that in the experimental model on animals the implantation of the allografts derived from multiple histologically mismatched donors (4 murine strains with different H-2 haplotypes) with experimental streptozotocin-induced DM led to successful engraftment of allogeneic islet cells (100% survival) on day 100 posttransplant. On the other hand, the transplantation of an equal number of islet cells from a single allogeneic donor was followed by graft rejection [54]. Often, islet cells were repeatedly implanted to patients. Multiple introduction of allogeneic β-cells promoted the development of immune tolerance in the experiment [55]. The technique of islet cell introduction is also an important factor. In Shumakov's department implantation to the rectus abdominis is preferred (Shumakov *et al.*, 1983). Another routine method of introducing cells is intraportal infusion. The choice of donor fetuses of the same age is a very important factor in FTT. Material derived from

18-20-week fetuses is commonly used [8-10,13,42, 44,46,50,51].

One of the most important problems in the treatment of DM is dealing with the complications associated with the main disease. Proliferative diabetic retinopathy is the most severe manifestation of diabetic microangiopathy. The growth of newly formed vessels, relapsing intraocular bleeding, fibrosis of the retina and vitreous body, retinal detachment, and secondary glaucoma result in irreversible blindness. In the opinion of many ophthalmologists, the clinical course of severe forms of proliferative diabetic retinopathy does not depend on the degree of compensation for DM [19]. It is assumed that after the process of fibrous proliferation has been triggered, the further course of the disease is determined by local intraocular factors. This makes it problematic to stabilize or reverse the process by any of the methods of DM compensation.

However, an unexpected, long-term, and marked improvement of the clinical picture of the severe preterminal stages of proliferative diabetic retinopathy was attained following intramuscular transplantation of cultured PIC from 20-24-week human fetuses [35].

In 3 out of 4 patients the fundus of the eye, which had mainly exhibited fibrous proliferation, partial hemophthalmia, and local retinal detachment, demonstrated a marked improvement, along with an increase in visual acuity. In all cases similar specific changes in the fundus involved gradual resorption of preretinal bleedings and detachment of fibrous proliferations from the retina, followed by gradual reverse development of these proliferations, namely thinning of the fibrous tissue and vessel depletion in it, plus smoothing out and reattachment of the earlier detached zones of the retina. Only one patient exhibited relapses of preretinal bleeding, the growth of fibrous tissue, aggravation of vitreoretinal tractions resulting in total retinal detachment, and a reduction of visual acuity. The positive effect of treatment in 3 out of 4 patients could not have been due to a spontaneous improvement in the clinical picture, since the likelihood of such an event in proliferative diabetic retinopathy is less than 10% [53].

The effect of transplantation of human fetal PIC is even more pronounced in the case of other complications of DM. For instance, many researchers have noted the stable absence or a marked reduction of pain symptoms in patients with diabetic polyneuropathy [5,17,51].

In patients with I-II degree diabetic glomerulosclerosis proteinuria disappeared or was markedly reduced in the majority of cases, and the arterial pressure for manifest arterial hypertension normalized [37].

The cited reports demonstrate unique potentials of the method of transplantation of human fetal PIC to treat the most severe complications of DM.

In this connection, the growing international interest in the original techniques of DM treatment, widely used in Russia is understandable. Prof. Shumakov was the first to report pursuasive evidence in favor of the novel treatment at the Eleventh International Congress of Transplantologists (Helsinki, 1986). The results of 168 intramuscular transplantations of cultured PIC performed at the Research Institute of Transplantology and Artificial Organs, including 97 allografts of cultured human fetal PIC, 53 xenografts of swine fetal PIC, and 18 xenografts of bovine fetal PIC, were presented to the scientific community. Results were reported for a one-year (till 12.30.85) follow-up of 69 recipients in whom allografts of cultured PIC had been performed. From the follow-up of patients over one year and longer the conclusion was drawn that clinical intramuscular transplantation of cultured fetal IC can be regarded as an effective method of correction of the course of labile forms of DM and as a means of preventing the development of diabetic complications [52].

Studies aimed at optimizing the methods of transplantation of fetal islet cells [1-4,16] and at raising the efficacy of screening during treatment [1,25,34] are increasingly being performed in Russia and in the republics of the former USSR.

As significant advances are made by FTT in the treatment of DM, the geographical area of the use of this method is expanding. A method of autotransplantation of a pancreatic tissue suspension to patients who have undergone routine subtotal pancreatomy has been developed in Russia at the Department of Surgery of the First Medical Institute (St. Petersburg), and positive results have been obtained for allotransplantation of cultured human fetal PIC to such patients [14].

Since 1982, transplantation of allo- and xenogeneic PIC has been widely used in clinical practice at the Research Institute of Endocrinology and Metabolism (Kiev) [6]. This research clinical department has priority in xenotransplantation of cultured PIC of neonatal pigs and is the only department in the world with experience in the effective use of such xenografts in the treatment of children with Mauriac and Nobecour's syndromes [7]. Researchers from the same institute studied the effect of transplantation of cultured PIC on the course of DM and diabetic angioneuropathies

(Skrobanskaya *et al.*, 1989). The main indications for transplantation were labile insulin-dependent DM with a tendency toward hypoglycemic states and diabetic angioneuropathy in young patients. The appraisal of the results of transplantation pointed to graft rejection in some patients within the first 3 weeks. In the majority of patients during the first 3 weeks the course of DM stabilized after an uncomplicated postoperative period, with the disappearance or a marked reduction of symptoms of hypoglycemia. A marked improvement in patient condition was noted in 82% of cases. This effect was preserved for up to 6 months, and in some patients it was prolonged to 12-18 months. Reduced requirements for exogenous insulin (by 15-53% of the initial dose) were achieved in 82% of patients. In the majority of patients with diabetic angiopathies (74%) stabilization of hemodynamic and microcirculatory disturbances was noted. Regression was observed in 18% of patients, while in just 8% disturbances progressed. An improvement in the course of diabetic retinopathy was observed in 59% of patients, and the process stabilized in 24%. The researchers did not discover any differences between the therapeutic effect of allogeneic (human fetal PIC) and xenogeneic (PIC of neonatal pigs) cells.

At the Research Institute of Clinical and Experimental Surgery (Kiev) xenotransplantation of swine fetal PIC was performed in patients with chronic pancreatitis associated with DM [41]. All patients were operated on for chronic pancreatitis. The blood sugar level normalized in 4 out of 8 patients in the first 48 h after xenotransplantation and on days 3-4 posttransplant in 2 patients. In one patient, who had been receiving 40 IU insulin daily before surgery, requirements for exogenous insulin were absent for 6 months, while in 3 patients the daily dose of insulin was reduced from 80 to 20 IU for one year. These data attest to the suitability of transplanting cultured PIC to patients with disturbed carbohydrate metabolism after surgical management of chronic pancreatitis.

Allotransplantation of cultured PIC in the complex treatment of surgical patients with DM was analyzed from the clinical standpoint by researchers from the Lvov Medical Institute [11,12, 22-24]. The use of intravasal and intraportal transplantation of cultured PIC in the complex treatment of patients with acute and chronic cholecystitis against the background of DM has made it possible to correct the disturbed metabolic processes, to reduce or to abolish hyperglycemia, to lower the dose of insulin by 37-100%, to broaden indications for surgery, to reduce the incidence of postoperative complications from 41 to 8.5%, to improve the short- and long-term results, and to shorten the hospitalization period considerably. Recommendations were established for allotransplantation of cultured fetal PIC in patients with DM for eliminating the "mutual aggravation" syndrome following surgical intervention [11,12,22,23].

The Kharkov Medical Institute has developed a method of transplanting cultured PIC of neonatal pigs to pregnant women suffering from DM. This is an effective means of preventing diabetic fetopathy. Transplantation of PIC has a favorable effect on the maternal organism during pregnancy and after birth [14].

The Riga Transplantation Center has wide experience in repeated xenotransplantations of cultured PIC of intrauterine swine fetuses. Latvian researchers were the first to consider transplantation of cultured PIC as a method of correcting the metabolic state in patients admitted for routine surgery [27-30,33]. In 1983-1986, 118 grafts of PIC to 89 patients with DM were performed in Riga. Clinical improvement occurred within 3 months. The disappearance or rapid decline of manifestations of hypoglycemia was observed in 91.7% of patients without detriment to compensation. Myasthenia and proteinuria were markedly reduced. The incidence of polyneuropathies decreased. The blood levels of sugar and glycosylated hemoglobin dropped. The indexes of lipid metabolism stabilized, which is important evidence of metabolic compensation for the disease. A reduction of neuropathy and of leg pains during walking was attributed to this [32]. The same researchers noted a positive effect of transplantation of cultured PIC in the treatment of surgical septic complications in patients with DM. Rozental' and other researchers [37] pointed to a stable increase in the blood level of peptide C after transplantation of PIC. According to data of Latvian researchers, in the case of treatment of type I insulin-dependent DM, the decrease in the requirements for exogenous insulin reached 10-20% in the majority of patients, 30% in some patients, and 50% in a few patients. Such a state of relative insulin-independence was maintained for 4 months, after which it was necessary to raise the doses of insulin to the pretransplantation level [31,32]. Allogeneic cultured human fetal PIC were transplanted to 65 patients with DM at the Erevan Branch of the All-Union Center of Surgery (Academy of Medical Sciences). The clinical improvement, along with normalization of the level of hormones and of immunological parameters, was temporary due to the specific choice of patients (patients with mod-

erately severe and severe forms of diabetes predominating in this group). The researchers concluded that transplantation of cultured PIC is most appropriate at the earlier stages of disease [17,18]. However, even in this group of patients the severity of the pathological processes associated with the main disease, such as retinopathy and polyneuropathy, decreased. Stable compensation for DM was noted in 9 patients.

This geographic excursus clearly demonstrates that the new method of treatment of DM is firmly entrenched in the former USSR. Close scientific and practical communications are maintained among the majority of the above-mentioned research and clinical departments.

In summary, unique experience in the treatment of DM by transplanting cultured fetal PIC has been accumulated in Russia. From October 1979 to May 1993 more than 1100 clinical transplantations, including 412 allogeneic (from human fetuses) and about 690 xenogeneic (from swine and bovine fetuses and neonatal pigs and rabbits) transplants have been performed in Russia. As for other regions of the former USSR, more than 500 transplants, including 30 allografts, have been performed in Kiev, 140 allografts in Lvov, 200 xenografts in Zaporozh'e, 60 allografts in Erevan, and 200 xenografts in Riga (estimated data after 1990 are from personal communications). In Russia the majority of transplantations have been performed at the Research Institute of Transplantology and Artificial Organs (Moscow): 220 allografts and some 400 xenografts (predominantly from neonatal rabbits).

To sum up, the major results of allo- and xenotransplantation of PIC are as follows. First, there is the stabilization of the labile forms of insulin-dependent diabetes. In 80% of patients the requirements for exogenous insulin have dropped 20-85%. In some cases a short-term (1-4-week) insulin-independence has been established. Most importantly, treatment has resulted in the arrest and partial regression of secondary complications. For instance, pain and paresthesia in the extremities diminish or disappear, and the severity of other associated symptoms is reduced in cases of diabetic neuropathy. The therapeutic effect manifests itself in 80% of patients. The incidence of indications for amputations due to gangrene has been reduced 3-fold in the case of angiopathy of the lower extremities. Advances have also been made in the treatment of diabetic retinopathy. Arrest and regression of the pathological process in the fundus, as well as an increase in visual acuity, have been noted in 45-65% of patients. In the case of diabetic nephropathy transplantation of PIC has been followed by the reduction or disappearance of proteinuria and by normalization of the arterial pressure in 40-50% of patients in the prenephrotic stage.

A new method of transplantation, whereby a mixture of cultured human fetal islet cells and neonatal rabbit islet cells is injected to the patient, is now being successfully used. The Research Institute of Transplantology and Artificial Organs and the International Institute of Biological Medicine are involved in the development of this approach.

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