Upsala J Med Sci 109: 57–68, 2004

Changes in Graft Blood Flow early after Syngeneic Rat Pancreas-Duodenum Transplantation

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ABSTRACT

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Organ transplantation is associated with changes in graft blood flow, both acutely caused by reperfusion associated phenomena, and chronically due to e.g. denervation. The aim of the study was to investigate regional blood flow early after implantation of a syngeneic pancreas-duodenum transplant in rats, *i.e.* during reperfusion. Warm ischemia time was 1–2 min and cold ischemia 90 min. Blood flow values were measured with coloured microspheres both 10 and 30 min after implantation in transplanted rats, and at one time point in control rats. A marked decrease in the blood perfusion of the transplanted duodenum compared to the endogenous intestine was seen at both 10 and 30 min. Total graft pancreatic blood flow was increased both 10 and 30 min after implantation, whilst islet blood flow remained unchanged compared to the endogenous gland. We conclude that the blood perfusion of the graft is markedly changed in the immediate post-transplantation period, presumably due to reperfusion. However, islet blood perfusion remains constant, suggesting that islet vasculature is less sensitive to changes induced by the implantation.

INTRODUCTION

Procurement of organs for subsequent transplantation usually necessitates the use of preservation solutions (1, 2). In combination with hypothermia the electrolyte composition of these solutions allows for survival and preservation of function after implantation. There is nevertheless hypoxia in the organs during preservation, and when blood flow is re-established a reperfusion syndrome of varying magnitude will occur (2). This syndrome is, among other things, characterized by the increased formation of reactive oxygen species (ROS), which are known to affect the microcirculation in different organs (3). Thus, ROS will affect the bioavailability and gen-

Received 13 September 2004
Accepted 21 October 2004

Key words: Pancreatic islets, Organ Transplantation, Microspheres

eration of several vasoactive mediators, such as nitric oxide, and also serve as modulators of vascular smooth muscle function (3).

The pancreas contains both exocrine and endocrine parts, with different capabilities to cope with reperfusion injury after implantation of the whole organ. We have previously shown that the blood perfusion of a transplanted pancreas-duodenum preparation in rats is associated with a slightly increased blood perfusion from the second post-implantation week and onwards, presumably due to the absence of neural modulation of the vascular smooth muscle in the blood vessels (4, 5).

The nervous system seems to be of particular importance in the regulation of pancreatic islet blood flow (6). However, previous studies have demonstrated that islet blood flow is also regulated by a complex interplay between substances derived from the islet metabolism per se (7, 8), as well as endothelium-derived factors, such as nitric oxide (9). We have previously demonstrated that alloxan, a substance exerting a major part of its diabetogenic effect through ROS (10), has a marked influence on pancreatic islet blood flow, and is one of the most powerful potentiators of islet blood perfusion seen (11).

In view of these considerations we performed the present study where we examined the blood perfusion in a transplanted pancreas-duodenum preparation both 10 and 30 min after re-establishing the blood flow. Since the endogenous pancreas is intact in the grafted animals, the preparation allows us to simultaneously study the effect of the reperfusion in a denervated, transplanted pancreas and duodenum and compare it to the innervated endogenous organs not exposed to reperfusion.

METHODS

Animals

Male, inbred Wistar-Furth rats weighing 325 g, were purchased from B&K Universal (Sollentuna, Sweden). All animals had free access to tap water and pelleted rat food throughout the experiments. Principles of laboratory animal care (NIH publication No. 23, revised 1985) were followed. All experiments were approved by the local animal ethics committee at Uppsala University.

Pancreas-duodenum transplantations

This procedure has been described in detail elsewhere (4). Briefly, the donor was anaesthetised with an intraperitoneal injection of ekviticine (chloral hydrate and pentobarbital; Apoteksbolaget, Umeå, Sweden), and placed on a heated operating table. The whole pancreas, together with approximately 5 cm (1 g) of the duodenum, was dissected free from surrounding tissues. Through a catheter in the abdominal aorta the preparation was flushed with 5–7 ml of cold (4°C) UW-solution (ViaSpan™; Du Pont Pharmaceuticals Inc., Wilmington, DE, USA) at a pressure of approximately 100 cm H_2O. The warm ischemia time was less than 2 min. The graft was then removed from the animal, together with approximately 1 cm of the aorta

which contained the two pancreatic arterial blood vessels, and stored at 4°C for 1.5–2 h (cold ischemia time) before being implanted into the recipient.

The recipients were anaesthetised with an intraperitoneal injection of thiobutabarbital sodium (120 mg/kg; Inactin™; Research Biochemicals International, Natick, MA, USA) and placed on a heated operating table to maintain body temperature at 38°C. Polyethylene catheters, filled with heparinized saline (100 U/ml) were inserted into the ascending aorta, via the right carotid artery, and into the left femoral artery. The former catheter was connected to a pressure transducer (PDCR 75/1; Druck Ltd., Groby, UK), and the mean arterial blood pressure was continuously monitored throughout the experiments. The abdominal cavity was opened and the left kidney was removed, and the pancreas-duodenum graft was anastomosed to the renal blood vessels by a non-suturing cuff technique as previously described (12). The secretions from the graft duodenum were diverted from the abdomen through a drain inserted into the distal end of the graft.

Blood flow measurements with microspheres

The arterial blood perfusion of the whole pancreas, islets, duodenum, colon, adrenal glands, kidneys, lungs and liver was measured with a microsphere technique (13). These experiments were performed in non-transplanted, untreated control rats as well as in transplanted animals. Briefly, a total of $1.5–2.0 \times 10^5$ non-radioactive microspheres (EZ-Trac™; Triton Microspheres, San Diego, CA, USA), with a diameter of 10 mm, were injected via the catheter with its tip in the ascending aorta during 10 sec. Starting 5 sec before the microsphere injection, and continuing for a total of 60 sec, an arterial blood sample was collected by free flow from the catheter in the femoral artery at a rate of approximately 0.4 ml/min. The exact withdrawal rate was confirmed in each experiment by weighing the sample. One injection, with black microspheres, was made 10 min after re-establishing the blood perfusion to the graft. A second injection, with the same amount of green microspheres, was made 30 min after revascularization of the graft. Reference samples were collected during both these injections. In non-transplanted control rats, only one microsphere injection (green) was made after approximately the same time as required to perform the second measurement in the transplanted rats.

Arterial blood was collected from the carotid catheter for determination of blood glucose (at both microsphere injections) and serum insulin concentrations (only after the last injection) as given below. The animals were then killed, and the endogenous and transplanted pancreas were removed *in toto*, blotted, weighed and treated with a freeze-thawing technique, which visualised the pancreatic islets and microspheres (14). Approximately 100 mg each of the colon (descending part) left kidney (thin section through the middle, encompassing both cortex and medulla), middle lobe of the left lung, median lobe of the liver and both the endogenous and transplanted duodenum (around the papilla), were removed and treated in the same way. The microspheres in the organs were then counted in a microscope equipped with both bright and dark field illumination (Wild M3Z; Wild Heerbrugg Ltd., Heerbrugg, Switzerland). This enabled us to separate the green and black micros-

Table 1. Body weight, organ weights and hematocrit in untreated control Wistar-Furth rats or 30 min after syngeneic pancreas-duodenum transplantation.

Treatment	None	Transplantation
No of animals	7	7
Body weight donor (g)	NA	331 ± 5
Body weight recipient (g)	308 ± 2	325 ± 5
Pancreas weight (mg)		
Endogenous	928 ± 27	930 ± 30
Transplanted	NA	981 ± 28
Weight transplanted duodenum (mg)	NA	410 ± 23
Hematocrit	44.7 ± 0.7	41.4 ± 1.0*

Values are means ± SEM for 7 experiments. NA denotes not applicable. * denotes P<0.05 when compared to the control rats.

pheres, thereby making it possible to perform two blood flow measurements in the same animal. The blood flow values were calculated according to the formula $Q_{org} = Q_{ref} \times N_{org}/N_{ref}$ where Q_{org} is organ blood flow (ml/min), Q_{ref} is withdrawal rate of the reference sample, N_{org} is number of microspheres present in the organ and N_{ref} is number of microspheres in the reference sample.

The number of microspheres in the arterial reference samples were determined by sonicating the blood, transferring samples to glass microfibre filters (pore size <0.2 μm), and then counting the number of microspheres in the microscope referred to above.

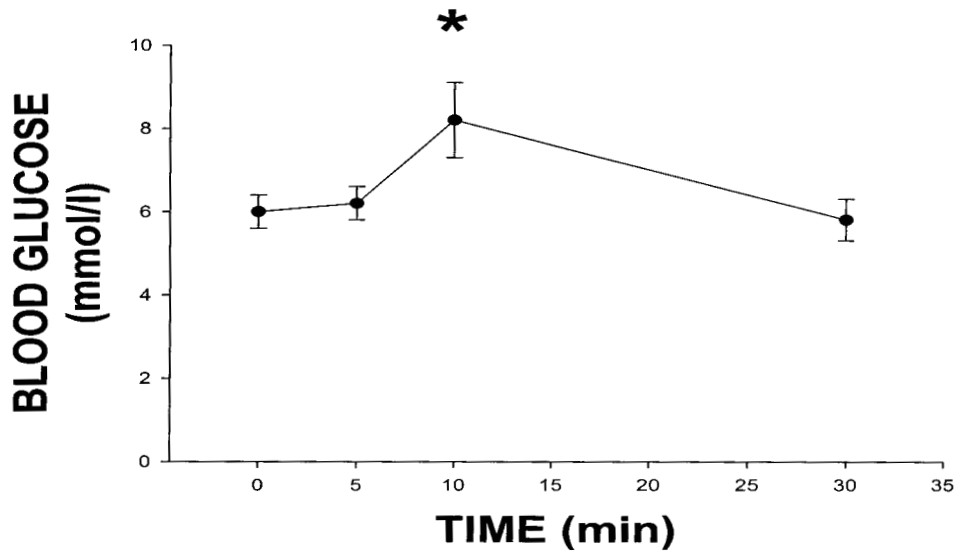

Fig 1. Blood glucose concentrations immediately after implantation of a syngeneic pancreas-duodenum transplant in Wistar-Furth rats. The value at time 0 is before opening of the abdominal cavity of the rat. Values are means ± SEM for 7 experiments. * denotes P<0.05 when compared to the values at time 0 and 30 min)ANOVA).

Measurements of blood glucose and serum insulin concentrations

Blood glucose concentrations were determined with test reagent strips (Medisense™; Medisense Sweden, Stockholm, Sweden) before and 5, 10 and 30 min after the transplantation. Serum insulin concentrations were measured with ELISA (Rat Insulin ELISA; Mercodia AB, Uppsala, Sweden) in samples taken before and 30 min after pancreas-duodenum transplantation.

Statistical calculations

All values are given as means ± SEM. Probabilities (P) of chance differences were calculated with Students paired *t*-test or analysis of variance (ANOVA; Sigmastat; SSPD, Erfart, Germany) with Bonferroni's *post-hoc* test. A value of $P<0.05$ was considered to be statistically significant.

RESULTS

All animals tolerated the surgical procedures without any signs of adverse reactions. Mean arterial blood pressure was similar in control animals (105 ± 8 mm Hg) and

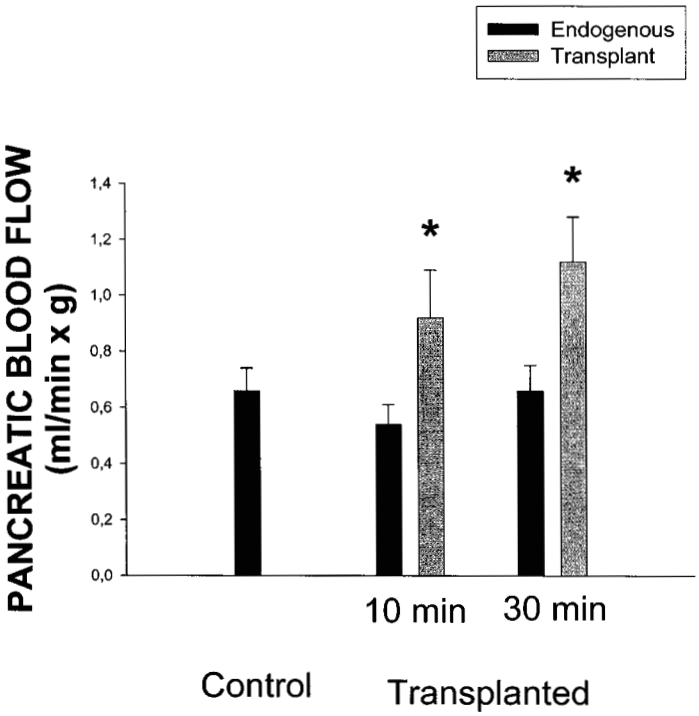

Fig. 2. Total pancreatic blood flow in untreated control Wistar-Furth rats and rats receiving a syngeneic pancreas-duodenum transplant. Measurements were performed both 10 and 30 min after implantation in the transplanted rats. Values are means ± SEM for 7 experiments. * denotes $P<0.05$ compared to the value in the endogenous gland at the same time point (Student's paired t-test).

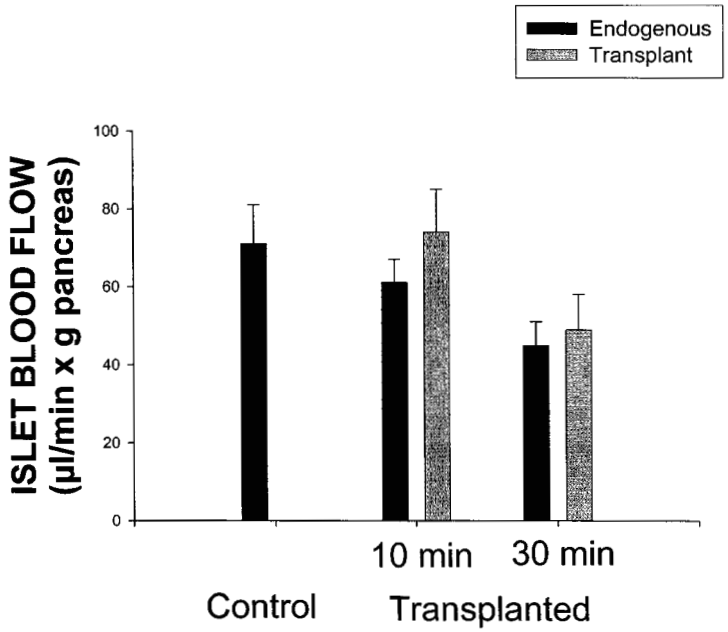

Fig 3. Pancreatic islet blood flow in untreated control Wistar-Furth rats and rats receiving a syngeneic pancreas-duodenum transplant. Measurements were performed both 10 and 30 min after implantation in the transplanted rats. Values are means ± SEM for 7 experiments.

transplanted animals (110 ± 7 mm Hg) before re-establishing graft circulation. When the vascular anastomosis were made and blood flow through the graft was re-established an immediate approximately 20–25% decrease in mean arterial blood pressure was seen, and the value remained lower during the course of the study, *i.e.* 30 min. Non-transplanted control rats deviated <5% during the course of the experiments. The hematocrit was lower in the transplanted rats when compared to control animals (see Table 1).

Table 2. Blood flow measurements were made in untreated control Wistar-Furth rat or 10 and 30 min after syngeneic pancreas-duodenum transplantation.

		Transplantation	
Treatment	None	10 min	30 min
Colonic blood flow (ml/min × g)	0.61 ± 0.23	0.73 ± 0.13	0.89 ± 0.10
Arterial hepatic blood flow (ml/min × g)	0.17 ± 0.04	0.14 ± 0.03	0.21 ± 0.12
Renal blood flow (ml/min × g)	2.93 ± 0.45	2.47 ± 0.27	3.82 ± 0.56*
Pulmonary blood flow (ml/min × g)	0.16 ± 0.06	0.17 ± 0.10	0.14 ± 0.06

Values are means ± SEM for 7 experiments. NA denotes not applicable. * denotes P<0.05 when compared to the control rats.

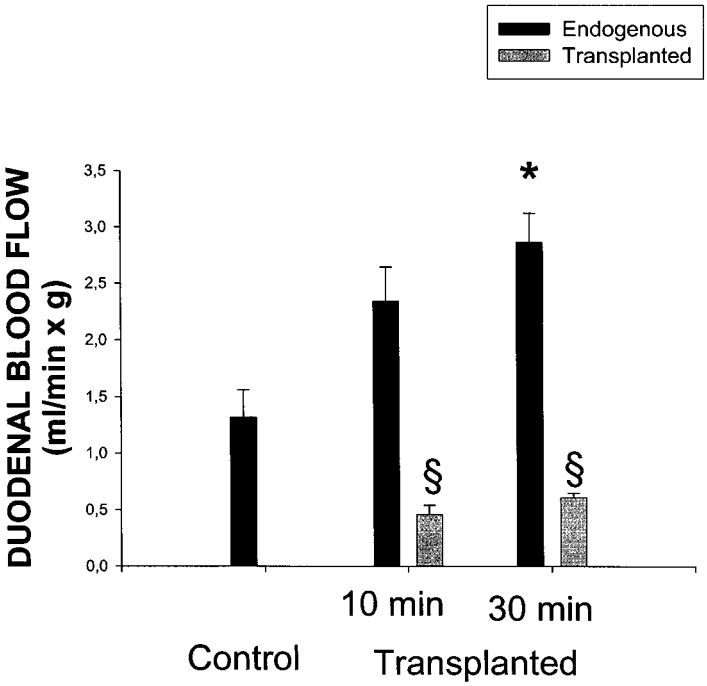

Figure 4: Duodenal blood flow in untreated control Wistar-Furth rats and rats receiving a syngeneic pancreas-duodenum transplant. Measurements were performed both 10 and 30 min after implantation in the transplanted rats. Values are means ± SEM for 7 experiments. * denotes $P<0.05$ compared to the value in the control animals (ANOVA). § denotes $P<0.001$ when compared to the corresponding value in the endogenous duodenum (Student's paired t-test).

The blood glucose concentration was increased 10 min after reperfusion of the graft, but was similar to the control value after 5 and 30 min (Figure 1). Glucose concentrations remained stable during the experimental procedures in the non-transplanted control rats (data not shown). Serum insulin concentrations in the transplanted rats were 3.15 ± 0.43 ng/ml before and 6.10 ± 0.75 ng/ml 30 min after reperfusion (n=7; $P<0.01$ with Student's paired t-test). In non-transplanted control rats the values were 3.66 ± 0.39 ng/ml (n=7) at the end of the experiments.

Total pancreatic blood flow was higher in the transplanted pancreas when compared to the endogenous gland in the same animal both 10 and 30 min after reperfusion (Figure 2). No changes in islet blood flow were seen (Figure 3). Both total pancreatic and islet blood flow were similar in non-transplanted control rats when compared to the values in the endogenous pancreas in the implanted rats (Figures 2 and 3).

The duodenal blood flow was markedly decreased in the transplanted intestine both at 10 and 30 min post-transplantation when compared to the value in the endogenous intestine in the same animals (Figure 4). Blood flow to the duodenum in non-transplanted control rats was lower than the value seen in the endogenous

duodenum 30 min after implantation (Figure 4). There were no changes in colonic, arterial liver or pulmonary blood flow either at 10 and 30 min after transplantation (Table 2). Renal blood flow was higher 30 min than 10 min post-transplantation, but did not differ from the value in non-transplanted control rats (Table 2).

DISCUSSION

In several instances previous studies have demonstrated changes in the blood perfusion of newly transplanted organs. Thus, total pancreatic blood flow increased 90 min after reperfusion in pig pancreas transplants (15). However, measurements with tissue oximetry revealed that most of this increase was not nutritive, but rather shunt blood flow (15). After several hours total flow decreased below normal levels, but shunt flow still accounted for 50% of total flow. This means that tissue pO_2 decreased after reperfusion despite a blood flow increase in this model. In another study on 11 patients undergoing simultaneous pancreas-kidney transplantation a decreased post-transplantation pO_2 was also seen (16), whereas blood flow and venous haemoglobin saturation were normal. An immediate decrease in tissue pO_2 is seen also after transplantation of livers (17).

In a study on pancreas-duodenum grafts in pigs graft blood flow was measured with Doppler flow probes over duodenum, tail and head of the pancreas 30 and 90 min after reperfusion (18). Duodenal flow was <50% in duodenum grafts when compared to the value in donor duodenum, whereas that in the pancreas was decreased by approximately 30–40% [26]. It should be noted that an endothelin-A receptor antagonist exerted a protective effect against graft pancreatitis in this model (18), and the preservation solution Celsior induced increased staining for endothelin-1 in pancreas-transplanted minipigs (19). Blood flow was also markedly reduced in the transplanted lung baseline and 3 h after reperfusion in dogs (20). Since hypoxic vasoconstriction was unlikely to occur it was speculated that this was due to increased endothelin secretion, decreased NO production or altered angiotensin II metabolism (21). In view of these studies it can be speculated that preservation may change the local production of endothelium-derived factors thereby influencing graft vascular function.

In the present study total graft pancreatic blood flow was increased both 10 and 30 min after implantation, whereas duodenal blood flow was markedly decreased. It should be noted that graft handling was optimized with regard to ischemia times and that only a very limited graft pancreatitis occurs during these settings (4). It is also unlikely that transcription of any endothelium-derived factors occurs during the short time span before vascular anastomosis (21). The unchanged islet blood flow argues against any effects of endothelium-derived factors, since islet blood perfusion is much more sensitive to both vasodilatation (7) and vasoconstriction (9) induced by such substances than blood vessels in the exocrine parenchyma (6).

Both warm ischemia (1–2 min) and cold ischemia times (60–90 min) were low in the present study, thereby minimizing the degree of reperfusion injury. Furthermore,

we used UW solution, which originally was developed to minimize organ damage during pancreas preservation (22). Nevertheless, even this brief period of ischemia will inevitably lead to accumulation of e.g. ROS and other vasoactive substances within the grafts (1, 2). Indeed, ischemia-reperfusion injuries have been thought to be causative in the development of graft pancreatitis, suggesting that the mediators produced during preservation-induced ischemia are of importance for graft function (23).

We therefore deem it likely that the formation of ROS in the grafted organs after commencing reperfusion may affect graft vasculature. We have previously seen that the scavenging enzyme superoxide dismutase affects pancreatic blood flow in rats (24), and that the radical generating substance alloxan profoundly influences islet blood perfusion (25). Furthermore, intestines are very sensitive to ROS, as well as to decreased ATP-concentrations (26). It may well be that such substances can induce the observed changes in pancreatic and intestinal blood flow, but this notion awaits further experimental confirmation.

An interesting observation was that the islet blood perfusion remains unaffected in the immediate post-transplantation period. This is in line with the consistent findings that the endocrine function of a transplanted whole pancreas is able to immediately reverse hyperglycaemia (4). The reason for the slight increase in blood glucose concentrations seen after 10 min, which is back to normal again after 30 min, is likely to represent a stress reaction to the reperfusion. The hyperinsulinaemia seen after implantation of the pancreas is most likely explained by the fact that the islet mass was doubled by the transplantation. A peripheral insulin resistance due to the surgery in itself is also likely to occur. Furthermore, it cannot be excluded that some β-cells in the transplanted pancreas have become injured and passively leak insulin.

Despite the pronounced effects noted in the grafts, no or only minor effects on the blood flow to other organs were seen, with the exception of the endogenous duodenum and kidney. The blood perfusion in these organs was increased 30 min, but not 10 min, after recommencement of the circulation. The reasons are unknown. Local secretion of the proinflammatory cytokine tumour necrosis factor α (TNF-α) may affect remote organs (lungs) after release from liver during reperfusion (27), and the concentration of this substance peaks during the first half hour after reperfusion (28). It seems, however, remarkable if only the duodenum and kidneys would be affected by a TNF-α release from the graft. Furthermore, extended cold ischemia time during liver transplantation upregulates the chemokines macrophage inflammatory protein-2 and cytokine-induced neutrophil chemoattractant, which through leukocyte activation may affect blood flow (29). In grafted islets chemokines are also upregulated (30). However, since the preservation period was limited in the present study the latter is unlikely to have occurred. However, this issue with effects of increased cytokines/chemokines in the immediate post-implantation period is worthy of further studies.

The major finding in the present study was that re-establishment of the blood flow to a pancreas-duodenum graft leads to immediate and organ-specific changes in graft blood perfusion when compared to the corresponding endogenous organs.

Thus, total pancreatic blood flow increased, duodenal blood flow decreased, whereas islet blood flow remained unchanged.

ACKNOWLEDGEMENTS

The skilled technical assistance of Astrid Nordin is gratefully acknowledged. Financial support was received from the Swedish Research Council (72X-109, 72XD-15043), the Swedish Diabetes Association, the Juvenile Diabetes Research Foundation, the EFSD/Novo Nordisk for Type 2 Diabetes Research Grant, the NOVO Nordic Research Fund, Åke Wibergs Stiftelse, Magnus Bergvalls Stiftelse, Barndiabetesfonden, Anérs Stiftelse, Groschinskys Minnesfond, Svenska Läkaresällskapet and the Family Ernfors Fund.

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