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Review

Impact of pancreas transplantation on diabetic secondary complications and quality of life

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Rationale for pancreas transplantation

Diabetes mellitus is a growing worldwide health problem often leading to medical and psychosocial disasters including blindness, amputations, coronary artery disease, stroke and kidney failure among others [1]. Although the possibilities of training and treating, particularly young, motivated insulin-dependent diabetic (IDDM) patients are numerous and sophisticated, none are able to normalise the metabolism of people who have been diabetes for years or even decades [2, 3] even though this is a prerequisite for the prevention of secondary diabetic complications. In addition, modern therapy of IDDM is laborious and troublesome for the patient and a formidable task for the physician. Even if the patient and his/her doctors do their best, they are rarely rewarded by a stable metabolic state without hypoglycaemia and without the appearance of severe complications. Therefore, much research effort has been undertaken to develop a patient-controlled endogenous source of insulin and other islet cell hormones in order to improve quality of life and to prevent, stabilise or reverse secondary complications. There are three directions for possible therapeutic interventions:

1. human vascularised pancreatic transplantation [4];
2. transplantation of adult islets or fetal pancreatic tissue from humans or other species (xenotransplantation) as free grafts or separated by an immune barrier [5, 6];
3. implantation of an artificial mechanical device which should be able to imitate at least some functions of the islet, namely glucose sensing and insulin delivery [7].

Since the first report on implantation of sheep pancreas into an IDDM patient in 1894 [8] much research has been performed to provide the patient with an endogenous source of insulin and other islet cell hormones. So far, only pancreatic grafting is able to restore normal metabolism for long periods [9]. Pancreatic transplantation started in many centres in the early 1980s when cyclosporin entered the therapeutic field of organ transplantation and steadily increased to reach more than 6800 pancreas transplant recipients according to the International Pancreas Transplant Registry [10]. Also the success rates of grafting increased impressively: the 10-year pancreas graft survival rate is 76% and that of the patients is 90% [10]. Long-term metabolic control in patients after successful pancreatic grafting is impressive as judged by daily blood glucose levels, glycated haemoglobin values and glucose tolerance tests [11–13] and is superior to intensified insulin treatment [2, 3, 14]. Most important, optimal glucose control can be achieved without the danger of acute metabolic derangements such as severe and recurrent hypoglycaemia.

The natural course of development of diabetes-specific complications is depicted in Figure 1. After 5 to 8 years diabetic complications appear and 20 to 25 years after onset of the disease many patients suffer from severe problems. In recently published prospective studies in IDDM patients [2, 3, 15] intensified insulin treatment was started mostly much earlier. In contrast pancreatic grafting is performed almost exclusively in patients undergoing chronic dialysis together with a kidney transplantation, which is on average 22 years after onset of diabetes.

In recent years the number of thoroughly investigated pancreas graft recipients has increased considerably. However, the data from the different centres

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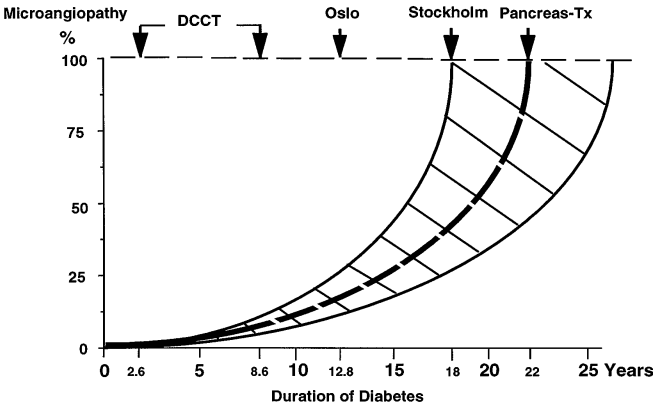

Fig. 1. Illustration of the natural time course of the development of diabetic microangiopathy. Primary and secondary intervention with intensified insulin therapy started early at a mean of 2.6 and 8.6 years after diagnosis in the DCCT study [2], 12.6 in the Oslo [72] and 18 years after manifestation of diabetes in the Stockholm study [33]. In contrast pancreas transplantation with subsequent normalization of glucose metabolism is performed at a mean duration of diabetes of 22 years

are often not easy to compare, mainly due to the lack of universally accepted study protocols, inhomogeneous patient groups especially concerning renal function, metabolic control and the degree of multimorbidity as well as the number of cases investigated.

It is the purpose of this review to analyse in detail the impact of pancreatic grafting on secondary complications and on quality of life.

However, it is out of the scope of this work to discuss the intermediary metabolism after pancreatic grafting.

Retinopathy

After the first report of a favourable effect of pancreatic grafting on diabetic retinopathy [16], conflicting results have been published. For example, in the study by Ramsay and colleagues [17], no significant difference between the groups (pancreas/kidney vs kidney only) in the course of retinopathy and visual acuity was reported at least with a mean follow-up period of 24 months. Despite physiological control of blood glucose over a minimum of 12 months, progression of retinopathy and deterioration of visual acuity could be observed. No marked difference in the rate of progression was found between the study and the control group (kidney only group) whether retinopathy was mild or advanced. The results suggested however that pancreatic grafting has late beneficial effects which became obvious after 36 months post-transplant [17].

In a recent long-term study with a mean observation time of 40 months, retinopathy regressed in 9 % (4 out of 45 eyes), stabilized in 73 % and progressed in 18 % of pancreas recipients while in the control group 34 % (14 out of 26 eyes) stabilized and 46 % deteriorated ($p < 0.03$) [18]. In the two patients of the study group showing a clear improvement, the grade of retinopathy was mild indicating that amelioration can only be expected at early stages of retinopathy.

In other studies with shorter observation times and smaller numbers of patients, pancreatic transplantation led to a stabilization [19, 20] or a progression of diabetic retinopathy [21]. The influence of combined kidney/pancreas grafting on the progression of diabetic retinopathy has been thoroughly studied in a large series of patients ($n = 51$ pancreas/kidney and $n = 21$ kidney only recipients). Unfortunately, data were analysed only after a 1-year follow-up period [22], which is certainly too short to see an amelioration. The authors found no evidence that normalization of glucose metabolism had any influence on the progression or regression of advanced retinopathy: changes in combined transplanted vs kidney transplanted patients when considering the overall retinopathy score were: 34 vs 25 % regression, 44 vs 45 % no change, 22 vs 30 % progression ($p = 0.7$).

The most extensive prospective study on retinopathy after pancreatic transplantation was performed in 30 pancreas/kidney recipients with 15 kidney recipients as control subjects [23]. In 27 of the study group and 13 of the control group the follow-up period was longer than 30 months (mean 52 months). In both groups retinopathy remained stable; a closer look at the few patients who did not receive laser treatment prior to transplantation (14 study and 6 control eyes) revealed that 4 control eyes significantly deteriorated with a retinopathy score of 2.8 points while the mean retinopathy score remained stable in the pancreas transplant recipients despite the fact that glycosylated haemoglobin was clearly below 10 % in the control group (mean HbA_1 8.4 %, normal < 8 %), which seems to be of great importance for the development and progression of retinopathy [24–26].

In conclusion, while chronic hyperglycaemia is the most important risk factor for the development and progression of retinopathy [2], these data suggest that advanced diabetic retinopathy might not benefit from pancreatic grafting. However, one has to keep in mind that almost all studies except one had a short observation time and that at least 80 % of the patients [23] had received panretinal laser coagulation prior to transplantation, which has been amply demonstrated to lead to a low but stable function of the retina and make interpretation of any therapeutic intervention very difficult.

Nephropathy

Diabetic nephropathy is one of the most severe life-threatening complications in IDDM patients. Good metabolic control can prevent or reverse diabetic renal lesions in animals [27–31] and in humans [2, 32,

Table 1. Morphometric analysis of renal biopsies in pancreas plus kidney vs kidney recipients [42]

Patients	Mean glomerular volume ($\times 10^6$ μm^3)	Mesangial volume fraction ($\mu m^3/\mu m^3$)	Mesangial vol./glomerulus ($\times 10^6$ μm^3)	BMT thickness (nm)
Pancreas plus kidney recipients				
	1.80 ± 0.55	0.19 ± 0.07	0.34 ± 0.14	499 ± 124
	(1.06–3.02)	(0.09–0.31)	(0.13–0.54)	(310–790)
Kidney only recipients				
	2.47 ± 0.73	0.31 ± 0.10	0.80 ± 0.33	545 ± 116
	(1.63–4.44)	(0.15–0.46)	(0.36–1.55)	(359–800)
p value	0.02	0.004	0.001	0.17

Data are mean ± SD (and range)

33] and the impact of improved diabetes care has led to a marked reduction in the incidence of diabetic nephropathy in young IDDM patients [34]. Normal kidneys transplanted into diabetic individuals can develop structural abnormalities such as mesangial enlargement and basement membrane thickening 2 to 4 years post-transplant [35–38]. Although the degree of light microscopical changes correlated with the serum creatinine of the patients, it is likely that recurrent nephropathy will be of major clinical significance only in those patients who will have a very long renal graft survival. The effects of pancreatic grafting on prevention or reversal of diabetic nephropathy have been evaluated in two centres. The Stockholm Group first presented preliminary evidence that basement membrane thickness (BMT) in biopsies from diabetic recipients of combined kidney and pancreas transplants was within the normal range (291 to 434 nm 12 to 48 months post-transplant) while it was significantly increased in diabetic recipients of kidney transplants ranging from 309 to 1017 nm 13 to 105 months after transplantation [36, 39, 40]. Recently these results were confirmed in a larger series of patients (number of patients/biopsies: 20/36 pancreas and kidney recipients, 30/36 kidney only recipients). When biopsies were taken one to 6,8 years after transplantation there was a significant difference in BMT [41]. In the pancreas/kidney group 91.7 % had BMT values within 2 SD of normal while in the kidney only group 35.3 % had a normal BMT. In a semiquantitative score from 0 to 9 including light microscopical parameters 6.7 % in the combined group but 45.8 % in the kidney group had a score of greater than 3. The relative mesangial volume was normal in 75 % (< 2.5 years post-transplant) and 82 % (> 2.5 years post-transplant) in patients after simultaneous pancreas/kidney transplantation. In contrast to diabetic kidney recipients the relative volume of the mesangium was normal only in 11 % and 12 % of biopsies (< 2.5 and > 2.5 years after transplantation respectively). From these data it was concluded that pancreatic grafting with subsequent long-term normalization of blood glucose can prevent or reduce typical signs of diabetic nephropathy in kidney allografts.

The Minneapolis group performed a kidney biopsy study in 12 IDDM patients 1 to 7 years after renal transplantation and repeated the biopsies 23 months to 10 years after pancreas transplantation. The data were compared with specimens of renal biopsies in 13 kidney recipients under conventional insulin therapy [42]. In Table 1 the main morphological findings of this study are summarized. After pancreas grafting no progression was detected in any structural measure of the glomerulus. In addition, glomerulopathy was significantly less in kidneys after pancreas transplantation supporting the notion that normoglycaemia can prevent the progression of diabetic nephropathy. In contrast to Wilczek et al. [41], however, there was no significant difference in the BMT between both groups of patients suggesting different pathogenetic mechanisms in the two types of glomerular lesions.

In a second study renal biopsies were taken before and 5 years after successful pancreas transplantation from 13 non-uraemic IDDM patients with micro- and macroalbuminuria and compared with baseline and 5-year-biopsy specimens from 10 IDDM patients without transplantation [43]. BMT did not significantly change in the groups (603 ± 139 vs 565 ± 111 nm in the transplant group and 594 ± 151 vs 609 ± 160 nm in the control group) nor was there a difference between the groups. Mesangial fractional volume increased significantly in both groups and there was no difference between pancreas transplant recipients and the diabetic patients. Mean glomerular volume was smaller after transplantation and the total volume of mesangium per glomerulus did not change in the pancreas recipients while it increased in the control patients. Creatinine clearance fell in the transplant recipients (102 ± 21 to 68 ± 24 ml/min per 1.73 m^2) while it remained unchanged in the control group (79.6 ± 8.8 vs 79.6 ± 17.7 ml/min per 1.73 m^2). The fall in glomerular filtration rate occurred in the first year post-transplant and remained unchanged thereafter. Since function and morphology of native or transplanted kidneys can be severely changed by cyclosporin which exerts specific nephrotoxicity [44] and by acute and chronic allograft rejection, the results of these studies have to be interpreted with

caution and have to be confirmed by a greater number of kidney biopsies and by renal function studies.

Peripheral microcirculation

Peripheral microcirculatory disturbances are important causes of nutritional and infectious complications, especially in the lower extremities of diabetic patients [45]. Non-invasive methods measuring nutritional and total skin blood flow have been used in pancreas recipients [46–49].

Transcutaneous oxygen tension ($tcpO_2$) on the foot increased significantly from 46 ± 2 to 63 ± 3 mmHg (normal values: 67 ± 7 mmHg) 3 years after pancreas and kidney transplantation [47]. In contrast, in kidney only recipients there was no significant amelioration of $tcpO_2$ (44 ± 0.3 to 41 ± 2 mmHg).

Vascular reactivity also increased markedly. When $tcpO_2$ was monitored prior to, during and after 3 min suprasystolic occlusion, reoxygenation time of the foot decreased from 224 ± 12 to 114 ± 6 s (normal value: 79 ± 2 s) in pancreas/kidney recipients, while it increased from 219 ± 7 to 244 ± 10 s in kidney only recipients [47].

Using *laser Doppler fluxmetry* to evaluate total skin microcirculation, the resting flow increased from 33 ± 12 to 67 ± 11 mm (normal 66 ± 11 min) 38 months after combined kidney/pancreas transplantation [49]. Also peak flow measurements after 1 min of arterial occlusion (= 200 mmHg) were higher post-transplant.

Videophotometric capillaroscopy of the nailfold capillaries of the fingers measuring nutritional skin microcirculation also revealed an increase both during rest and reactive hyperaemia post-transplant [49]. However, a delayed time to peak hyperaemia was found at baseline (2 months post-transplant) and was even more impaired 38 months after pancreatic grafting which is in contrast to the findings of Abendroth et al. [47] measuring vascular reactivity with $tcpO_2$. When morphometric analyses of nailfold capillaries were performed using computer-assisted fluorescence intravital microscopy [50] 1 to 12 months post-transplant the morphometric characteristics such as shape, size, configuration, tortuosity, number and density of distribution were similar and very much comparable to diabetic patients and patients pretransplant. However, 12 to 30 months later the density of distribution of the capillaries had increased although thin-walled capillaries, single-file blood cell movement and capillary tortuosity were still present.

The effects of pancreatic grafting on *skin temperature* have been measured with an electronic thermistor and with computerized telethermography. While Jörneskog et al. [49] did not see any change, Landgraf et al. [46] found a significant increase of skin temperature in pancreas/kidney recipients ($\Delta 1.92 \pm 0.07$ °C) while kidney only recipients showed no significant improvement ($\Delta 0.36 \pm 0.02$ °C) after the observation time of 9 months.

Microvascular permeability is increased in IDDM [51, 52]. Using sodium fluorescein the flow of the capillaries can be visualized under fluorescence epi-illumination and its leakage into the neighbouring intercapillary space videotaped [50]. While it took 187 ± 42 s to measure fluorescence leakage from nailfold capillaries in healthy non-diabetic control subjects, the diabetic patients pretransplant leaked at 30 ± 17 s ($p < 0.001$). The leakage time post-transplant increased significantly: 0–3 months: 30 ± 17 s; 12 months 155 ± 76 s; 12 to 30 months: 178 ± 22 s ($p < 0.001$). Whether cyclosporin adds to the reduction of microvascular permeability cannot be ruled out from this study, since it has been shown that this immunosuppressant is beneficial in nephrotic patients [53].

Neuropathy

An intra-individual follow-up as well as the inclusion of kidney graft recipients as control subjects are mandatory in order to answer the crucial question of whether pancreatic transplantation prevents, arrests or reverses neuropathy, or solely elimination of uraemia leads to improvements of neuropathy in diabetic kidney recipients.

Autonomic neuropathy

There are only a few studies examining autonomic nerve function after transplantation. Symptoms of autonomic dysfunction improved, mainly in pancreas/kidney recipients [54], but the improvements were only marginal within the observation time of 36 months.

The R-R variation of heart rate during deep breathing, mainly a measure of parasympathetic vagal function, is low prior to or immediately after transplantation. There was only a minor improvement of the autonomic index [55] after an observation time of 42 months, when comparing the results with IDDM patients awaiting transplantation or after graft failure. The difference between maximal and minimal heart rates during deep breathing (6 times per min) changed from 8.8 ± 1.6 to 10.7 ± 3.0 (NS) in the pancreas/kidney recipients while in diabetic kidney recipients it decreased from 8.4 ± 4.2 to 5.8 ± 1.6 (NS). However, there was a significant difference between both groups at the end of the study. Solders et al. [56] found an ameliorated R-R variability 4 years after transplantation, but this was true both for kidney/pancreas and renal graft recipients. The other studies [54, 57–59] could not demonstrate any significant change in beat-to-beat variation.

Small nerve fibre function (sweating and temperature discrimination) did not improve 2 years after pancreas/kidney transplantation [60].

Although there was no marked change in cardiovascular reflexes, delayed gastric liquid emptying [61] and overall gastric emptying as well as electrogastrographic recording of gastric rhythm [62, 63] improved more in patients after pancreas-kidney when compared with kidney-alone transplantation.

Despite small or no changes in autonomic nerve function, indicating that thin myelinated and unmyelinated nerve fibres recover less or at a slower rate than thick myelinated fibres after pancreatic grafting, patients with a functioning pancreas transplant had much better survival rates than patients with a failed graft and also better than IDDM patients with autonomic neuropathy but without pancreas transplantation [64].

Peripheral sensory-motor polyneuropathy

In contrast to autonomic dysfunction, peripheral sensory-motor polyneuropathy improved in most studies considering group comparisons as well as intraindividual longitudinal data.

The symptom score improved in both pancreas-kidney and in the kidney alone transplanted patients after a 2-year follow-up, but deteriorated thereafter in the diabetic kidney recipients while in the pancreas/kidney grafted patients the symptoms improved further [65]. The neurological disability score including muscle power, sensation and tendon reflexes, however, showed no significant improvements in both groups [55, 56, 65, 66].

The neurophysiological measurements demonstrated that motor and sensory nerve conduction velocities increased much more in pancreas/kidney graft recipients than in kidney transplanted diabetic patients [46, 55–57, 59, 64–67]. Early improvements of nerve conduction by elimination of uraemia in the first 2 years post-transplant [55, 56, 65] is abolished by progression of diabetic neuropathy in kidney recipients. Only the successfully pancreas grafted patients showed a significant and lasting amelioration of polyneuropathy when the observation time was extended to 3 years and more. It is therefore suggested that nerve regeneration [68] and repair after normalization of glucose metabolism seem to be much slower than the amelioration of nerve dysfunction seen after elimination of uraemia by kidney transplantation. In fact, long-term euglycaemia leads to structural improvements of the nerves as reported in a preliminary investigation [69].

Very recently Müller-Felber et al. (unpublished data) accumulated data for both pancreas/kidney and kidney only recipients over an observation time of 6 years. There was a steady increase of nerve conduction velocity in the pancreas grafted patients, while in the kidney transplanted patients nerve conduction velocity decreased although these patients had a perfect long-term metabolic control with a mean glycated haemoglobin of 6.8 % (normal < 6.0 %). Similar results have been published from the Stockholm group [70].

In two studies [55, 65] amplitudes of nerve action potentials, which correlate with the number of axons, did not increase after an observation period between 3 to 4 years. This indicates that improvement of myelin function can occur but that the axonal loss remains unchanged.

Increased nerve conduction velocities are different depending on the nerves studied. For example, median and sural sensory NCVs were insignificant [65] or less improved [55] post-transplant when compared to the corresponding motor NCVs, indicating that sensory fibres respond less to improved diabetic metabolism. This is in agreement with an earlier study, which demonstrated that intensified insulin treatment did not result in an improvement of sural NCV [71]. This is however in contrast to the data of the Oslo study [72].

Sensory median nerve conduction can be significantly influenced by a high rate of carpal tunnel syndrome pre- and especially post-transplant [73]. This might lead not only to retrograde changes of the nerve fibres in the forearm [74] but is probably also the cause of the smaller increase of median NCV compared with peroneal NCV [65]. Therefore, studies on the median nerve should not be taken as representative of diabetic polyneuropathy.

Macroangiopathy

Although cardiovascular complications are the main cause of the excess mortality in diabetic patients, the influence of pancreas transplantation on the fate of macrovascular lesions has not been investigated in detail. It is well known that there is an elevated incidence of cerebrovascular events and myocardial infarctions [75–77] as well as of thromboembolic complications [78] after kidney transplantation, and immunosuppressive therapy has been reported to increase the vascular risk profile after cardiac or renal grafting [79–84].

Recent studies however could demonstrate a favourable effect of pancreas and kidney transplantation on serum lipids [85–89]. While lipid status of subjects with IDDM and renal failure was abnormal before pancreas-kidney transplantation, cholesterol fell sharply during the immediate postoperative period (< 2 months), but increased afterward. HDL-cholesterol rose significantly in the same time frame from 1.07 ± 0.09 to 1.31 ± 0.08 mmol/l and triglycerides decreased from 5.85 ± 0.56 to 4.54 ± 0.48 mmol/l [88].

There was also a remarkably normal postprandial triglyceride clearance in pancreas recipients after an oral fat tolerance test due to a high post-heparin lipoprotein lipase activity [86]. A decrease of triglycerides and total cholesterol was also noted in another study [87], however, these lipid changes were seen both in kidney only and kidney/pancreas recipients. Similar data were found by us [90] in which the levels of triglycerides, total as well as LDL- and HDL-cholesterol, were very similar in pancreas/kidney ($n = 26$) and kidney only ($n = 23$) recipients. These data have been confirmed by a recently published extensive study showing total cholesterol and HDL- and LDL-cholesterol very comparable in diabetic patients with end-stage renal disease and in pancreas/kidney and kidney only recipients [89]. But triglycerides were significantly lower in pancreas/kidney recipients when compared to diabetic patients prior to and after kidney grafting. The same result was obtained with VLDL-cholesterol and VLDL-triglycerides as well as LDL- and HDL-triglycerides. Apoprotein B was lower and Apo A1 higher in the pancreas recipients. However, compared with a non-diabetic control population there was not a complete normalization of the lipoprotein profile, since VLDL particles and the triglyceride content of LDL- and HDL persisted after pancreas transplantation. It is suggested that insulin resistance with a higher ratio of peripheral to hepatic insulin levels is probably the cause of these lipoprotein abnormalities [89]. HDL-cholesterol was remarkably high after transplantation [91]. Elevated HDL-cholesterol levels have been reported after transplantation [79, 91] and after intensified insulin therapy [92]. The latter is probably related to higher peripheral insulin levels as in pancreas grafting leading to activation of tissue lipoprotein lipase with subsequent enhanced formation of HDL-cholesterol from VLDL particles [93].

Hypertension is more prevalent in renal transplant recipients than in healthy control subjects [94] with a persistent risk of cardiovascular mortality in these patients [95], however with a marked reduction of excess mortality in kidney recipients when compared to dialysis patients. Simultaneous pancreas/kidney transplantation was associated with an improvement of arterial hypertension [90, 96], but there is still a marked elevation of blood pressure in successfully grafted patients with antihypertensive therapy necessary in 65 % of them. Besides persisting hypertension in end-stage renal disease after successful pancreas and/or renal transplantation, blood pressure elevation is almost certainly partially related to cyclosporin therapy.

Fibrinogen is a potent predictor of cardiovascular events [97]. After pancreas transplantation there was a significant elevation of fibrinogen concentration (4.16 ± 0.75 g/l [94]) and also of $alpha_2$-macroglobulin another acute-phase protein. Both are main determinants of *plasma viscosity*. Indeed plasma viscosity was markedly increased in this group of patients [90].

Despite significant improvements in glucose and lipid metabolism there remains an elevated risk for cardiovascular events in patients after pancreas/kidney transplantation which might be attributable to hypertension, hyperfibrinogenaemia and impaired haemorheology although clear-cut clinical endpoints of cardiovascular complications like stroke, myocardial infarction and amputation have not been studied.

Quality of life

There is increasing recognition that expensive and incisive therapeutic regimens which aim to prolong or ameliorate life in chronic illnesses must be assessed in terms of their impact on quality of life (QOL) in addition to more traditional measures such as morbidity and mortality. This is especially true for medical interventions such as organ transplantation which carry a considerable risk and involve many socio-economic aspects. In recent years it has become possible to measure in detail QOL although there is some disagreement about the most suitable approach. Some workers prefer structured inpatient interviews, some an evaluation by the physician and others use self-administered questionnaires. It is important to stress that all instruments used should be disease- and treatment-specific.

There are a number of cross-sectional studies on QOL in pancreas transplant recipients. Nakache et al. [98] were the first to use the QOL index of Spitzer. They reported on the benefit of combined pancreas-kidney transplantation (group 1) in comparison to diabetic kidney only recipients (group 2). In group 1 90 % but in group 2 only 50 % had full-time occupations, the amount of lost work days decreased by 44 % in group 1 but was unchanged in group 2, also hospitalization was significantly less in group 1 than in group 2 (12 vs 25 days). In addition, pancreas-kidney recipients achieved a better QOL in the three health concepts physical well-being, sole functioning and perception of self. In an extensive analysis 131 pancreas transplant recipients who were 1 to 11 years post-transplant were studied [99]. Patients with functioning pancreas grafts ($n = 65$) expressed in comparison with non-functioning pancreas graft recipients but good kidney function ($n = 66$) more overall satisfaction with their life (68 vs 48 %), felt healthier post-transplant (89 vs 25 %) and reported that they were able to care for themselves and their daily activities (78 vs 56 %). Similar results although less convincing had been published previously [100, 101]. The most detailed study of the different aspects of QOL was performed applying a disease-specific self-administered questionnaire (217 questions and various subscales) [102]. The group of

157 patients was categorized into 6 subgroups: patients pretransplant without dialysis ($n = 29$; A), pretransplant under dialysis ($n = 44$; B), post-transplant with functioning kidney and pancreas ($n = 31$; C), post-transplant with funtioning kidney only ($n = 29$; D), post-transplant after rejection of both organs ($n = 15$; E) and post-transplant after unsuccessful single pancreas grafting and good renal function ($n = 9$; F). The results indicated a much better quality of life in C + D as compared to the other groups, especially for their satisfaction with physical capacity, leisure-time activities and overall QOL. There was no marked improvement in the vocational situation after successful grafting indicating a highly attractive social network with little force of restarting professional life after successful transplantation in the country of origin of this study (Germany). It was also interesting to note that in general all scores were highest in patients with functioning pancreas-kidney grafts but without significant differences to the patients with functioning kidney only, suggesting that elimination of uraemia with the necessity of dialysis treatment has the greatest impact on the amelioration of QOL, although the small sample size may account for the lack of significance that occurred with the various measures. Comparable conclusions have been drawn by Milde et al. [103] using a similar number of patients.

Since these promising results have been obtained by cross-sectional studies which may be influenced by sample and selection biases or time effects, prospective studies have been initiated. In a preliminary 1-year follow-up study using the Medical Outcome Study Health Survey 36-Item Short Form (SF-36) [104] and comparing pancreas-kidney, kidney only and IDDM control subjects improvement of general health perception, social function, vitality and pain was seen in both transplanted groups, but physical limitations improved only in pancreas-kidney recipients [105]. The total SF-36 score was significantly higher in the pancreas/kidney recipients when compared to the kidney only group. Using the same instrument for the measurement of QOL as for the cross-sectional analysis [102] overall QOL, financial situation, physical capacity, job situation, sexual and leisure time activities increased from pretransplant to 22 ± 4 months after pancreas/kidney transplantation. Due to the low number of patients, however, no statistical significance was observed [106]. During an observation of 6 months post-transplant using a two-group (kidney alone and kidney/pancreas) pre/post-transplant design and the Sickness Impact Profile as the instrument with 12 behavioural dimensions Hathaway et al. [107] found a higher degree of improvement in the pancreas/kidney group (80 % of the scales improved), while only 40 % were better for the kidney alone group. In the most recent study [108] life and health qualities increased significantly in both pancreas/kidney and kidney alone transplant recipients during an observation time of 6 or more months post-transplant, but there were no significant group differences suggesting that achieving one's transplantation goal, functioning organ(s), has a major impact on QOL. In a long-term study (7 years post-transplant) although with a rather low number of patients in each group (kidney/pancreas group 1 $n = 8$; kidney alone group 2 $n = 10$) physical well-being (86 vs 30 %), perception of health (71 vs 20 %), physical abilities (86 vs 10 %) and the re-integration-to-normal-living index (86 vs 40 %) were significantly higher in group 1 [109].

Conclusion

Pancreatic transplantation has improved considerably in recent years for patient and graft survival (80–90 % 1-year graft survival in the experienced centres). In contrast to the single centre retrospective analysis of mortality which showed a marked reduction in 3-year patient survival in pancreas/kidney recipients vs diabetic kidney recipients (68 vs 90 % [110]) the International Pancreas Transplant Registry clearly finds that pancreas transplantation is now a safe procedure and patient survival is between 90 and 100 % in centres specialized in the surgical procedure, in preoperative patient selection as well as in peri- and post-operative organ recipient care [4]. Therefore there is no reason not to make uraemic IDDM patients dialysis free *and* insulin-independent by simultaneous or consecutive kidney-pancreas transplantation. Kidney transplantation recipients are already obliged to undergo immunosuppression and the surgical risk for an additional pancreatic grafting is low. However, it is important to mention that early post-transplant morbidity is greater after combined pancreas/kidney grafting when compared to renal transplantation alone [111, 112].

For extremely labile, non-uraemic diabetic individuals with poor quality of life due to hypoglycaemia unawareness or fluctuating hypoglycaemia and ketoacidosis a pancreas transplant alone might be an available option especially when using immunosuppressive drugs such as mycophenolate mofetil and tacrolimus.

Careful analysis of the impact of pancreatic transplantation on secondary complications has demonstrated that even in advanced stages of diabetes, normalization of glucose metabolism has a series of vascular and neurological benefits and significantly improves many aspects of quality of life. Recently it has been argued that pancreas transplantation should be stopped, since islet transplants, transplantation of encapsulated islets (human and pig), closed-loop insulin pump devices and/or gene therapy are around the corner or are already working. We are all enthusiastically waiting for a major breakthrough in this

field, but what do we do with the increasing numbers of patients who have major diabetes problems today? After careful information and clinical investigation they should be offered a pancreas transplant!

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