Whole Organ Transplantation and Glucose Regulation

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Abstract:

Pancreas transplantation has gained clinical acceptance since its initial application more than 30 years ago. A constellation of surgical, pharmacologic, and metabolic alterations occur with transplantation, particularly if pancreatic transplantation is performed in addition to renal transplantation in a uremic diabetic. Increasingly sophisticated studies have allowed analysis of the performance of the transplanted organ and have enhanced our basic understanding of insulin's complex interplay in peripheral glucoregulatory processes.

Article:

Clinical experience with pancreas transplantation was not overwhelmingly successful during the late 1960s and early 1970s [1]. Over the next 20 years a period of constant reevaluation and reassessment of early clinical failures resulted in the development of animal models of transplantation. These models ultimately led to advances in surgical techniques and immunosuppression therapy and provided a better understanding of the impact of surgically induced alterations to the pancreas on carbohydrate metabolism. As pancreas transplantation enjoyed an increasing success rate and longer patient survival, posttransplant graft physiology and the metabolic response to the new insulin source became an interesting area of research.

EARLY MODELS OF TRANSPLANTATION

Surgical alterations of the pancreas that occur during transplantation include (1) reduction of the beta cell mass (by resection, immunologic loss, or preservation ischemic loss); (2) systemic venous drainage versus portal venous drainage of the pancreatic venous effluent; and (3) denervation. Surgical alterations per se should lead to an altered insulin source. What effect, if any, might this have on peripheral levels of insulin or insulin's glucoregulatory properties? Would it ultimately affect the function of the transplanted pancreas? To address these questions and attempt to delineate the role of surgical alterations of the pancreas on longterm glucose homeostasis in transplanted patients, studies were performed using primarily dog or rat models.

Reduction of Beta Cell Mass

The complex interplay between insulin secretion and insulin action was suggested nearly 50 years ago by Dragstedt et al.'s observation that the amount of insulin required to control glucosuria after partial pancreatectomy exceeded the amount needed after complete pancreatectomy [2]. Subsequently, it became evident that surgical models of partial pancreatectomy might result in alterations of alpha and beta cell ratios, which could explain earlier observations. Studies evaluating a dog model of 60% to 80% partial pancreatectomy showed that these animals have a reduced insulin response to the intravenous glucose tolerance test (IVGTT) and altered potassium values, indicating altered glucose metabolism [3]. It was suggested that

pancreatectomy led to a postoperative state of hyperglycemia, which results in depleted beta cell insulin stores and reduced insulin responses to glucose and non-glucose stimulation [4]. Others suggested that resection might result in lowered peripheral levels of insulin, with concomitant *enhanced* peripheral sensitivity [5]. There was, however, no uniform agreement to the latter concept.

Systemic Drainage

The complete diversion of pancreatic venous flow from the portal to the systemic venous circuit would have particular anatomic relevance to transplantation and, perhaps, specific metabolic consequences. The importance of insulin's major glucoregulatory properties and its relation to glucagon have been well studied. Cherrington et al. described 35% suppression of hepatic glucose output by insulin during somatostatin-suppressed glucagon deficiency [6]. This report and others have underscored the importance of the presence of insulin in the portal circulation to modulate these effects [7]. However, other reports have stated that *peripheral* rather than portal levels of insulin were more important for optimal glucose handling [8].

Despite the controversy about portal versus systemic release of insulin, few reports evaluated *endogenous* systemic venous insulin release. Florack et al. reported that basal amounts of insulin continue to exist in the portal vein after complete systemic diversion, and additionally, decreased peripheral insulin levels occur after systemic diversion of a reduced beta cell mass. They concluded that systemic drainage itself had little effect in dog models of transplantation [3].

Transplantation (Denervation)

Pancreas transplantation combines the effects of anatomic reduction of the beta cell mass with systemic drainage and, additionally, denervation. Some reports suggest that vagotomy had no effect on insulin release after oral or intravenous glucose challenge [9]. The pancreas transplant model allows in vivo evaluation of denervation. Early studies of pancreatic autograft and allograft models suggested that fasting and stimulated insulin release was enhanced or at least that elevated peripheral levels of insulin were attributed to a combination of denervation and systemic venous drainage [10]. Other studies did not universally corroborate enhanced insulin release in the dog autotransplant model. Florack et al. showed lowered serum insulin levels in segmental pancreas transplants [3]. Munda et al. [11] reported normal fasting but enhanced arginine-stimulated insulin levels, and Cutfield et al. [12] reported fasting hyperinsulinemia with a lowered integrated insulin response to intravenous glucose stimulation.

CLINICAL STUDIES OF PANCREAS TRANSPLANTATION

By the early 1980s, largely through the diligence and persistence of Sollinger at the University of Wisconsin and Sutherland at the University of Minnesota, pancreas transplantation enjoyed acceptable success especially in a select group of type I diabetes patients with significant, progressive complications. The use of simultaneous renal transplantation in patients with predictably progressive diabetic nephropathy appeared to have the best patient and graft survival [13]. During this same period, as a result of earlier animal studies, there was increasing knowledge of the peripheral action of insulin and increased understanding of insulinotropic hormones, such as glucose-dependent insulinotropic peptide (GIP) and glucagon-like peptide (GLP), and the role of pancreatic polypeptide and somatostatin in the regulation of insulin release. This information allowed more sophisticated studies of pancreas transplantation. The standard IVGTT and oral glucose tolerance test (OGTT) were replaced by computer-controlled

hyperglycemic or hyperinsulinemic challenges ("Clamp") that allowed a steady-state challenge to the pancreas allowing us to measure insulin release or to peripheral target organs allowing quantitative analysis of hepatic glucose production or peripheral glucose disappearance [14].

Initial Experience at the University of Virginia

Clamp Studies. In 1990 initial studies employing the Andres hyperglycemic clamp on 11 pancreas/kidney transplant recipients, 7 kidney transplant recipients, and 7 normal controls were completed [15]. Each patient underwent a 120 minute stable hyperglycemic clamp challenge, and multiple parameters of glucose homeostasis were measured including hormone levels and insulin action on hepatic glucose production and peripheral glucose disposal. The pancreas/renal transplant group had significantly elevated (fourfold) basal and glucose-stimulated insulin levels compared to the renal transplant and normal control groups (Fig. 1).

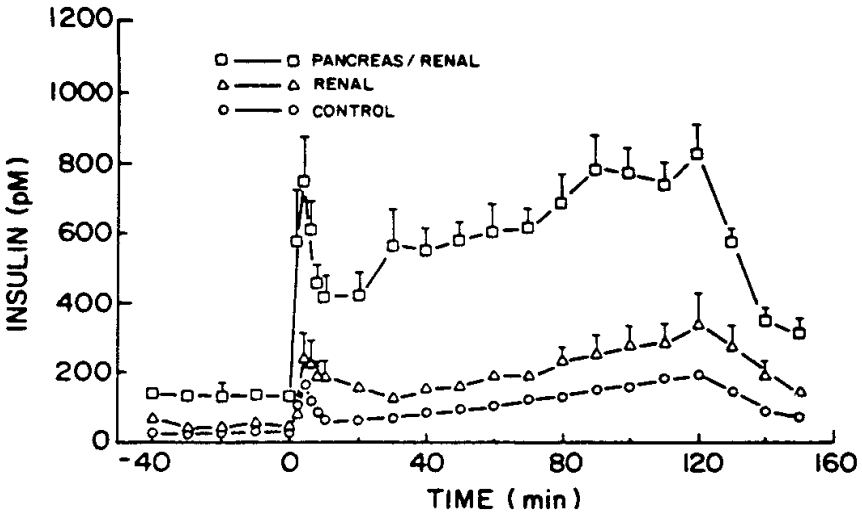

Fig. 1. Plasma insulin levels in response to a square wave hyperglycemic challenge (clamp) in pancreas renal (n = 11), renal (n = 9), and normal control (n = 7) subjects. Data are the means ± SE. (From Elahi et al. [15] with permission.)

This was mirrored in associated C-peptide and glucagon levels but was not appreciated in pancreatic polypeptide levels. We found that, despite marked systemic hyperinsulinemia in the pancreas/ kidney group, hepatic glucose production was normal in the basal and glucose-stimulated states. We thought that these data showed that portal vein insulin was *not* essential for normal control of the hepatic glucose production and peripheral glucose disposal.

Portal Drainage of Pancreas Allograft. Because of significant hyperinsulinemia and the possibility of long-term metabolic consequences and perhaps atherogenesis, a model of pancreas transplantation employing portal drained anatomy has been described [16]. The recipient splenic vein is anastomosed to the donor portal vein and in a fashion that would allow complete portal venous release of all transplant venous effluent. We studied three such portal vein drainage patients and compared them to 18 preoperative diabetic patients and 18 systemic drainage patients [17]. Employing an OGTT, we were intrigued that the peripheral glucose levels were identical in response to orally ingested glucose in the systemic and portal vein drainage groups. Hyperinsulinemia persisted in the portal vein drainage group, although it was significantly lower

than that in the systemically drained group. These studies confirmed what was previously hinted at in previous studies; that is, varying endogenous levels of insulin after transplantation seemed to have little effect on glucose homeostasis in the periphery. Portal venous drainage resulted in partial normalization of peripheral plasma insulin levels.

Longitudinal Analysis of Pancreas Transplantation. Our group proceeded on a longitudinal study of graft function after pancreas transplantation whereby the hyperglycemic clamps were repeated at 1-year intervals [18]. We were intrigued that the hyperinsulinemic response to the clamp persisted, although it was decreased approximately 30% from the previous year. We thought that the lower insulin concentrations in the follow-up studies were not attributable to the decreased clearance of insulin, as the rates of decline and disappearance of plasma insulin after determination of the glucose infusion between the two studies were similar. We also thought that causes could include an evolving reduction in viable beta cell number, a deficit in beta cell function, or increased peripheral insulin sensitivity. The data suggest a time-related decrease in insulin secretion, and this was confirmed by analysis of the C-peptide responses during the hyperglycemia. Follow-up studies measuring hepatic glucose output during the basal and hyperglycemic portions of the clamp demonstrated little difference from initial studies compared to repeat studies 1 year later. Measurement of peripheral glucose disappearance showed little difference from normal controls or changes over a 12-month period.

PANCREAS TRANSPLANTATION AND GLUCOSE REGULATION

Increasing success with the clinical application of pancreas transplantation in addition to improved clamp methodology have allowed more sophisticated analysis of posttransplant alterations in carbohydrate metabolism at many centers around the world. The literature has confirmed some of the earlier findings in the animal models and has provided further insight into the complex interplay of insulin's glucoregulatory properties.

Hyperinsulinemia and Altered Metabolism. The most apparent change in transplantation is that a new insulin source is supplying a different amount of insulin into a different circuit in the recipient (for those undergoing systemic drainage). Luzi et al. [19] evaluated glucose and free fatty acid metabolism in uremic diabetic patients after systemically drained pancreas transplantation with simultaneous renal transplantation. This group confirmed the previous findings of hyperinsulinemia and additionally reported that these patients had normal basal free fatty acid (FFA) turnover and that the new insulin source resulted in normal inhibition of FFA turnover and oxidation. Using the insulin clamp, however, the group showed that suppression of hepatic glucose production was defective in transplant patients compared to that in normal controls.

Christiansen's group also evaluated hyperinsulinemia on whole- body glucose metabolism. These authors reported that during acute hyperinsulinemia ("clamp") nonoxidative glucose metabolism was impaired in the pancreas transplant group compared to that in normal controls [20]. This finding was similar to that of Luzi et al. [19] and further identified that defective skeletal muscle glycogen synthetase activity could partially explain the defect. The report suggests that this defect could explain the resulting chronic peripheral hyperinsulinemia.

Kendall et al. [21] addressed the important question of the effect of posttransplant hyperinsulinemia on counterregulatory processes. This group used graded hyperinsulinemia increases to establish graded hypoglycemia and evaluated epinephrine and nonepinephrine responses. The epinephrine response to maximal hypoglycemia was improved compared to that in type I diabetics; however, the pancreas transplant group response was still significantly lower than that in normal controls and a kidney transplant control group. Interestingly, cognitive recognition of hypoglycemic symptoms improved dramatically in this group and approached that of normal controls.

The question of systemic versus portal delivery of insulin as a cause of hyperinsulinemia has led to altering techniques to avoid significantly increased insulin levels. Our group has attempted to do this, with improvement but not complete normalization of insulin values, as addressed earlier. More recently, Gaber's group has reported preliminary data showing that, in response to oral glucose and nutrient solutions, basal and stimulated insulin levels may approach normal values for portal-drained whole pancreas transplantation [22].

Other intriguing explanations for significant posttransplant hyperinsulinemia were suggested by two groups. Luzi et al. studied insulin-induced hypoglycemia in pancreas transplant patients and hypothesized that feedback inhibition of insulin is normally under neural control [23]. After transplantation (with denervation) insulin inhibition is only partially restored, most likely due to catecholamine release. The blunted feedback inhibition might well cause, or partially explain, the peripheral hyperinsulinemia.

Altered Insulin Secretion and Sensitivity. The use of high-dose immunosuppression including steroids and cyclosporine may well affect insulin sensitivity. Additionally, the reduced secretory capability of the transplanted B (beta) cell mass has been studied. Teuscher et al. reported that the acute maximal insulin response to arginine stimulation was significantly reduced in whole gland cadaveric transplant patients and even more so in segmental gland transplant at the University of Minnesota, one of the few centers that employs the latter procedure [24].

Insulin secretion and peripheral sensitivity were studied extensively by Christiansen et al. [25]. They compared two sets of patients who had had cadaveric segmental pancreas transplants combined with renal grafts: one with "normal glucose tolerance according to WHO criteria" and four other patients with "abnormal" glucose tolerance. These two groups were compared to kidney transplant recipients and normal controls. This study demonstrates a number of interesting points. First, immunosuppression results in increased insulin secretion in response to an oral glucose load, raising the question of decreased peripheral sensitivity. Second, peripheral glucose disappearance is comparable for normal kidney recipients and "normal" functioning pancreatic grafts. The second group of pancreatic grafts had parameters of failure that suggest impaired first-wave insulin secretion, reduced B cell responsiveness, and impaired nonoxidative glucose metabolism. This latter group of patients also had impaired early inhibition of glucagon secretion.

Cottrell addressed the issue of insulin sensitivity after pancreas transplantation and how it might change over time [26]. That study addressed the fact that immunosuppressive drug doses are often significantly decreased after the first 12 months. It evaluated whole pancreas and kidney

recipients sequentially from immediately after surgery (3–6 months) to 48 months. Stable euglycemia was documented over the whole period. Peripheral sensitivity was diminished during the early phase, for which compensatory hyperinsulinemia and enhanced peripheral glucose disappearance occurred. At 12 to 24 months insulin sensitivity appeared to improve, although residual hyperinsulinemia persisted. Cottrell thought that the decreasing insulin response to glucose change over this time was *not* due to diminished B cell capacity but to changing (and improving) peripheral sensitivity most likely affected by decreased immunosuppressive drug therapy.

Rooney and Robertson investigated insulin sensitivity in more depth by evaluating insulin action on the liver after pancreas transplantation [27]. This group evaluated 10 pancreas transplant recipients (two solitary and eight simultaneous renal transplants) and compared them to normal controls and renal transplant patients using a hyperinsulinemic clamp study. The clamp protocol included an additional 90 minutes of glucagon stimulation after a 120 minute euglycemic hyperinsulinemic challenge. Several intriguing findings were reported. First, exogenous insulin sup pressed hepatic glucose production (HGP) in all three groups, yet HGP transplantation should allow significant improvements in knowledge about carbohydrate and lipid metabolism (Fig. 2).

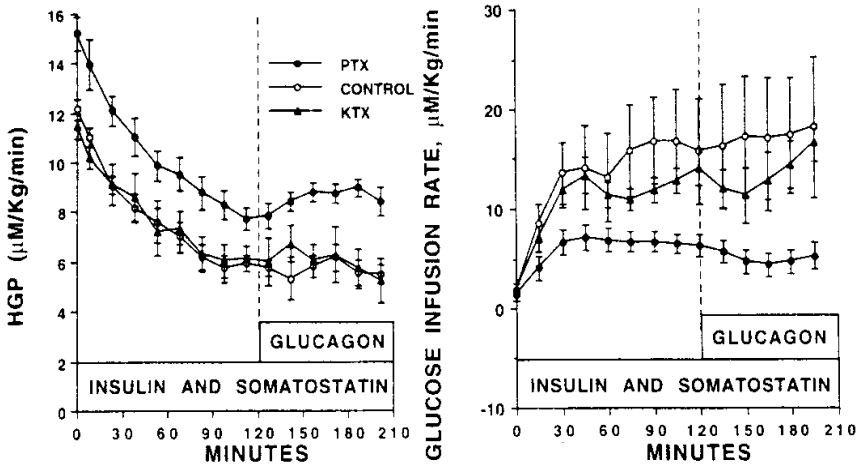

Fig. 2. Hepatic glucose production (HGP) and exogenous glucose infusion rates during stage 1 (insulin infusion) and stage 2 (combined insulin–glycogen infusion) of pancreas transplant (PTX), control, and kidney transplant (KTX) patients. (From Rooney and Robertson [27], with permission.)

An intrinsic alteration in insulin action in the liver and in the periphery appears to be taking place after pancreas transplantation. Whether placing grafts in the portal circulation can ameliorate the effect must be studied.

AREAS OF FUTURE RESEARCH

Posttransplant Improvement in Exercise Tolerance

Exercise in normal, healthy individuals results in a decrease in insulin and an increase in glucagon so normal glucose levels can be maintained. Catecholamines work in a "feed-forward"

system to increase hepatic glucose production by suppressing insulin action, and this suppression is proportional to the intensity of the exercise. Denervation of the pancreas due to transplantation results in a loss of normal neural input to the pancreas islets during exercise and may result in a decline of blood glucose levels during exercise [28]. Alternatively, it has been hypothesized that during stress abnormal sensitivity to circulating catecholamine levels could result in hyperglycemia due to impaired insulin secretion [29]. The only study investigating the effects of exercise on glucose regulation in pancreas transplant patients was completed by Redmond et al. [28]. Glucose, insulin, and glucagon concentrations were monitored during 1 hour of exercise (40% of each individual's VO_2 peak) in normal, healthy individuals and systemically drained pancreas transplant patients matched for age, height, weight, and exercise training status. Glucose levels declined after the onset of exercise in both groups. The insulin and C-peptide levels decreased significantly and glucagon levels rose significantly in the normal subjects. Similar trends were observed in the pancreas transplant patients, but the changes were not significant and were somewhat delayed. This delay, or "lag," in the response of the glucose homeostasis system with exercise should be expected in systemically drained pancreas transplant patients, as normal neural connections to the pancreas are missing and blood from the pancreas misses the "first pass" through the liver. This group concluded that although subtle alterations in insulin and glucagon secretion may occur during exercise they do not result in clinically significant changes in blood glucose. These data indicate that the lack of neural innervation in pancreas transplant patients does not affect their ability to maintain normal blood glucose levels during 1 hour of exercise at 40% VO_2 peak. These subtle, insignificant changes may be more profound during higher intensity exercise when stress to the system is greater, and the delay in the response may have greater effects on overall glucose homeostasis. Alternatively, it can be postulated that the catecholamine "feed-forward" system is so efficient at stimulating hepatic glucose production the changes in blood flow and lack of neural input are of minimal consequences regardless of the intensity of exercise.

Additionally, the time since transplantation for the pancreas transplant patients in the Redmond study was relatively short (less than 2 years), and it is difficult to predict the outcome of this study in a group of pancreas transplant patients who had received an allograft more than 5 years previously. The effects of long-term hyperinsulinemia in pancreas transplant patients is not known, and its effect on exercise tolerance in this group has not been studied. Clearly, more studies of exercise tolerance in pancreas transplant patients are warranted, because this information is crucial as the role of long-term hyperinsulinemia in pancreas transplant patients is more completely understood.

Posttransplant Hyperinsulinemia, Alterations in Lipid Metabolism, and Risk of Coronary Heart Disease

The clustering of certain physiologic disorders (e.g., hypertension, obesity, dyslipidemia, hyperinsulinemia) in a single individual (the deadly quartet, the metabolic syndrome, syndrome X) and the increased risk for coronary heart disease (CHD) has been described. In type II diabetics hyperinsulinemia has been thought to be due to peripheral resistance; and in these individuals altered lipid metabolism, hypertension, and enhanced coronary and peripheral vessel atherosclerosis occurs [30]. It has been suggested that hyperinsulinemia plays a central role in the development of these physiologic disorders, and a strong argument has been made that elevations in insulin concentration *precede* the development of numerous metabolic disorders [31]. Intriguingly, however, we have found little to suggest the consequences of dyslipidemia or

hypertension in posttransplant patients with surgically created hyperinsulinemia in our studies or in others. Scattered reports have attempted to evaluate altered lipid levels and have shown normal or nearly normal lipid and lipoprotein levels. Peripheral hyperinsulinemia up-regulates lipoprotein lipase (LPL) activity, especially in fatty tissues, leading to low postprandial lipemia and some favorable changes in lipid profiles [32]. However, studies investigating the influence of hyperinsulinemia on lipoproteins after pancreas transplantation have observed unfavorable changes in the *surface composition* of plasma lipoproteins, but the clinical importance remains questionable because it is accompanied by lower postprandial lipemia [33]. Additionally, the specific up- regulation of LPL in the abdominal visceral area of pancreas transplant patients and its effects on intraabdominal visceral fat accumulation in these individuals is currently unknown. Of critical importance is the fact that hyperinsulinemia in the "normal" scenario rarely occurs without other metabolic aberrations, such as dyslipidemia, obesity, or hypertension. In pancreas transplant patients it is rare to find clustering of these metabolic problems, as is commonly found in the "metabolic syndrome" or "syndrome X." Although hyperinsulinemia has been shown to precede other metabolic aberrations in nontransplant patients [30], it is impossible to know the effect of hyperinsulinemia when it is isolated, specifically without the effect of obesity. Therefore despite post- transplantation hyperinsulinemia, the "metabolic syndrome," for whatever reason, does *not* seem to be occurring—yet few of these studies is longer than 2 years and no in-depth longitudinal studies can be found. On the other hand, there is extensive literature about the effects of chronic hyperinsulinemia in other clinical circumstances, such as type II diabetes.

The alterations in metabolism as a result of hyperinsulinemia are predictable and severe, leading to the question of the possible long-term effects of this state with pancreas transplantation. Improvement in transplantation techniques and immunosuppressive therapy have increased the long-term survival of pancreas transplant patients. Currently, two studies have investigated long-term survival and cause of death in pancreas transplant patients [34, 35].

Wilson et al. [34] observed a decreased graft survival rate in obese pancreas/kidney recipients with a body mass index of less than 27. Despite the decreased graft survival rate for both the kidney and pancreas in the obese group, the incidence of hypertension or lipid abnormalities did not differ in the two groups. Graft function and immunosuppressive exposure were similar; and although posttransplant complications tended to be more common in obese patients, the difference was not statistically significant. Interestingly, the most common cause of death was cardiac complications, and the 5-year patient survival rate had a downward trend in the obese group (68% vs. 85%). Although this was not statistically significant, a difference of 17% in the survival rate is large and should be noted.

More recently, Sollinger et al. [35] reported their experience with 500 simultaneous pancreas/kidney transplants. The data show that this is a highly successful transplant procedure with 76.3% patient survival after 10 years. Similar to the Wilson et al. study [34], the most common cause of death was cardiac complications (38%). In this group, 12 of 20 patients died of myocardial infarction. Mortality statistics from these two studies clearly indicate that coronary complications are likely to occur in posttransplant patients and the possible role of hyperinsulinemia for increased risk of coronary heart disease (CHD) should not be overlooked.

Intraabdominal Visceral Fat

As early as 1963, Randle et al. [36] proposed that increased FFA levels were associated with preferential FFA oxidation, which then interfered with other processes such as insulin action and glucose oxidation and storage. The authors elaborated on this glucose-fatty acid concept and suggested that elevated FFA levels would have a mechanistic role in the development of certain metabolic disorders, including type II diabetes. Perhaps more importantly, it has been shown that the regional distribution of body fat is related to lipolytic activity [37]. Intraabdominal visceral fat shows the highest lipolytic activity, whereas peripheral fat depots such as gluteofemoral adipose tissue has blunted lipolytic activity. This has led to the suggestion that these regional differences in lipolytic activity of fat stores are related to metabolic complications, with increased levels of intraabdominal visceral fat being related to the highest risk of metabolic complications [38]. Portal adipose tissue (omental and mesenteric) has been shown to be highly sensitive for mobilization of FFAs with increased a-adrenergic receptors and reduced a-adrenergic inhibition [38]. Therefore in individuals with elevated levels of intraabdominal visceral fat there is a greater flux of FFAs to the liver through the portal circulation [38].

It has been shown that increased intraabdominal visceral fat (AVF) results in increased risk of CHD in the normal population Therefore it is highly possible that hyperinsulinemia in pancreas transplant patients may lead to increased risk of CHD not by affecting lipid levels directly but, rather, by increasing the accumulation of AVF. Unfortunately, no studies investigating AVF levels have been completed in pancreas transplant patients. It would be interesting to see how AVF levels in these patients compare to those in normal healthy individuals, obese individuals, and CHD patients. Although AVF levels in pancreas transplant patients may be similar or even lower than those observed in these higher risk groups, it is also important to consider the change in AVF that occurs from before transplantation to afterward. In the pancreas transplant patient, small amounts of AVF may lead to an increased chance of metabolic change and possibly CHD, as the effect of rerouting the blood flow systemically and the effect of altering organs and fat as a result of transplantation are unknown. Considering the link between increased AVF and the increased risk of CHD in the normal population, it would be interesting to assess the survival rate based on AVF in a group of pancreas transplant patients. The observations concerning hyperinsulinemia, AVF, and CHD post interesting and paramount questions about the influence of systemic versus portal delivery of insulin.

Peripheral Glucose Transporters

In peripheral tissues, especially skeletal muscle cells, glucose is not freely permeable across the cell membrane. It appears that specific protein transporters effect passive transport down a concentration gradient. Several transporter proteins encoded at different gene sites have been recently identified and characterized [40]. Under normal circumstances, adipose and skeletal muscle cells respond to increasing levels of insulin by increased glucose transport via translocation of the transporter protein across the cell membrane. In skeletal muscle the GLUT-4 transporter protein is the most important physiologically [41].

Recently, skeletal muscle transporter activity has been studied in several disease states. Interestingly, consistent evidence fails to find altered levels of the transporter protein in insulin-resistant states, either with decreased insulin secretion in type I diabetes or hyperinsulinemic states such as type II diabetes [42]. Because of the failure to find altered levels of the transporter protein in insulin-resistant states, including obesity, it has been hypothesized that the pathology

resided in altered function of the transporter or perhaps initiation of the insulin receptor–transporter protein interaction. We were therefore intrigued to find a significant (45%) reduction in GLUT 4 protein in skeletal muscle (vastus lateralis) of pancreas/renal transplants in our studies of pancreas transplant patients [18]. These data represented one of the first reports and possibly the only time that significant down-regulation of a peripheral glucose transporter protein has been shown as a possible explanation for what appears to be "normal" glycemic control in the face of the hyperinsulinemia after pancreas transplantation. Clearly, longitudinal studies of changes in GLUT 4 protein content in pancreas transplant patients are necessary.

It is well established that pancreas transplant patients have peripheral hyperinsulinemia, regardless of whether the allograft is systemically or portally drained. Both short-term (7 days) [43] and long-term (14 weeks) [44] exercise training have been shown to increase muscle GLUT 4 protein content by two- to threefold. One would expect that exercise training of pancreas transplant patients after surgery would also result in increased GLUT 4 protein content and improved insulin sensitivity. We do not know of any exercise training studies in pancreas transplant patients that have systematically addressed the issue of changes in GLUT 4 protein content in skeletal muscle. Data from Redmond et al. [28] tend to indicate that although the pancreas transplant patients have increased insulin levels, they maintain near-normal glucose levels during exercise. It is possible that because increases in GLUT 4 transporter activity can be achieved through "insulin- independent" mechanisms during exercise (stimulated by contraction and Ca^{2+}) the pancreas transplant patients have developed a peripheral adaptation in the GLUT 4 transporter that is independent of insulin levels and functions to maintain normal levels of the GLUT 4 transporter despite hyperinsulinemia. Studies investigating exercise training-induced changes in GLUT 4 protein content in pancreas transplant patients are necessary to understand the role they play in maintaining glucose homeostasis during physical activity in the pancreas transplant patients.

Pulsatile Insulin Release

There has been increasing evidence that the pulsatile release of various hormones, especially those from the hypothalamus, has much to do with their peripheral efficacy. There is suggestive evidence that altered patterns of pulsatile insulin release may be an early marker for type II diabetes [45]. The extent to which and the type of defects in the wave-like pattern of insulin release might contribute to frank diabetes or minimal alterations in peripheral glucose metabolism is unknown. Increasing knowledge is describing such defects, however. Recent studies in dogs have studied the pulsatile and nonpulsatile insulin appearance in the portal system and systemically. Porksen's group has used methods to quantitate the pulsatile parameters of insulin's actions and has calculated that as much as two-thirds of the mass of insulin secreted is in pulsatile form [46]. They hypothesized that alterations in waveform delivery could affect peripheral efficiency. Studies evaluating altered pulsatility in transplant patients have begun to emerge, testing the hypothesis that autonomic interruption may affect insulin action by altering the patterns of release. Sonnenberg et al. evaluated six patients who had received simultaneous whole pancreas and kidney grafts during basal and enteric stimulated time periods [47]. The high frequency waveform in patients with transplants was identical to that in normal controls; a low frequency waveform was maintained, but the amplitude was diminished. Further studies with the development of pulsatility analysis should allow sophisticated analysis of the importance of the

characteristics of insulin release, which may be more important than peripheral levels or the mass of insulin secreted.

CONCLUSIONS

Robertson et al. correctly pointed out that pancreas transplantation is "here to stay" [1]. In addition to supplying a new endogenous source of insulin in cases of complicated diabetes, the transplant results in altered glucose metabolism. Whether serious long-term consequences of such alteration will affect the overall success of transplantation is unknown. Careful and increasingly sophisticated studies of patients with transplants and animal models evaluating the surgical alterations of pancreas transplantations should allow significant improvements in our knowledge of carbohydrate and lipid metabolism.

RÉSUMÉ

La transplantation du pancréas a acquis une place dans la pratique clinique depuis son début il y a 30 ans. On assiste à une constellation de modifications chirurgicales, pharmacologiques et métaboliques en rapport avec la transplantation, particulièrement si elle est pratiquée en même temps que la transplantation rénale chez un diabétique urémique. Il existe de plus en plus d'études sophistiquèes pour permettre une analyse de la performance des organes transplantés, ainsi qu'une meilleure compréhensin du rôle complexe de l'insuline dans le processus de la régulation glucidique périphèrique.

RESUMEN

El trasplante de páncreas ha ganado aceptación clínica desde su aplicación inicial hace más de 30 aiios. Luego del trasplante sobreviene una constelación de alteraciones guirúrgicas, farmacológicas y metabólicas, especialmente si el trasplante de páncreas se hace adicional a un trasplante renal en pacientes con uremia diabética. Nuevos y sofisticados estudios han permitido el análisis del comportamiento del órgano trasplantado, e incrementado el conocimiento básico de la compleja interrelación de la insulina en los procesos glucoregulatorios periféricos.

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