Exercise May Still Pose a Challenge to Glucoregulation in Islet Transplant Recipients

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ABSTRACT

Islet transplantation (ITx) is effective in preventing severe hypoglycemia by restoring glucose-dependent insulin secretion in type 1 diabetes (T1D), but may not normalize glucose regulation. Studies suggest that physical activity plays a role in maintaining beta cell mass and function in individuals with type 2 diabetes and animal models of diabetes. This could indicate that physical activity plays a role in graft survival in ITx recipients. The objective of this review is to assess current knowledge related physical activity in ITx recipients. Responses to other challenges in blood glucose control (i.e. hypoglycemia), in human ITx recipients were examined to provide in depth background information. To identify studies involving exercise in ITx recipients, a systematic search was performed using PubMed, Medline and Embase revealing 277 English language publications. Publications were excluded if they did not involve ITx recipients, did not involve physical activity or hypoglycemia, or did not report on glucose, insulin, or counterregulatory hormones. During induced hypoglycemia, studies indicate normal suppression of insulin in ITx individuals compared to healthy non-T1D controls. Studies involving exercise in ITx animals have conflicting results, with time since transplantation and transplantation site (spleen, liver, kidney, peritoneal cavity) as possible confounders. No study examining blood glucose responses to physical activity in human ITx recipients was identified. A small number of induced hypoglycemia studies in humans, and exercise studies in animals, would suggest that glucoregulation is greatly improved yet still imperfect in this population and that ITx does not fully restore counterregulatory responses to challenges in blood glucose homeostasis.

KEY WORDS: islet transplant, type 1 diabetes, physical activity, exercise, hypoglycemia, beta cell

INTRODUCTION

Type 1 diabetes (T1D) is characterized by insulin deficiency resulting from the autoimmune destruction of pancreatic beta cells. People with T1D must take exogenous insulin by multiple daily injections or continuous subcutaneous insulin infusion to regulate blood glucose levels. The ability to achieve insulin independence that was maintained for up to 14.9 months in individuals with T1D by transplanting pancreatic islets was a major breakthrough (Shapiro et al. 2000). Islet transplantation (ITx) has subsequently emerged as an effective treatment option for select people with T1D at high risk for severe hypoglycemia who generally have impaired symptom awareness (Senior et al. 2012). While ITx is known to restore endogenous insulin secretion, the glucagon response to hypoglycemia may still be impaired (Kendall et al. 1997; Paty et al. 2002; Rickels et al. 2005). In theory, this would affect responses to stresses such as insulin-induced hypoglycemia and physical activity, which is normally associated with a high risk of hypoglycemia in patients with T1D.

While great progress has been made in ITx, there is still much to learn. Islet transplant recipients provide a unique experimental model to explore certain aspects of glucose homeostasis, which involves a balance between insulin and counter-regulatory hormones (including glucagon). Potential sites which could be utilized for transplantation include the kidney capsule, pancreas, liver, spleen, omentum, subcutaneous space, peritoneal cavity, gastrointestinal wall, and immune privileged sites (Bruni et al. 2014) (ex. brain (Niederkorn 2006)), with the liver being the standard site for clinical ITx. Intraportal islets secrete both insulin and glucagon which are delivered directly to the liver. Insulin inhibits glucagon release from alpha cells by a paracrine action, but intrahepatic insulin secretion may not be sufficient to normally regulate glucagon release from alpha cells in the native pancreas since this would require an endocrine action of insulin through the systemic circulation. The present review seeks to explore the existing literature related to such challenges in glucoregulation (i.e. hypoglycemia and exercise) in ITx recipients.

METHODS

A narrative review approach was used to describe the context and recent advances in ITx procedures as well as the resulting changes in counterregulation. The narrative review was supplemented by a systematic search for articles related to physical activity or exercise following ITx. The systematic search was only used for the exercise subsection because of the difficulty in identifying relevant studies and the clearly defined nature of studies that could be included.

A search was performed in PubMed, Medline and Embase up to September 7, 2016; see Supplementary Table S1[1] for the complete search strategy. Studies were eligible if they examined the effect of a single bout of exercise or regular exercise training following any type of ITx procedure. No study was excluded due to type of participant (e.g., animal or human), study design (e.g., randomized, controlled trials or pre-post design). Studies were excluded if they did not report on glucose, insulin, or counterregulatory hormones such as glucagon, epinephrine, norepinephrine, growth hormone, or cortisol.

Studies were assessed for eligibility by two reviewers (DF, JY) and data was extracted to characterise the exercise intervention (i.e., frequency, intensity, type, and time), the participant characteristics (i.e., species, age, sex, and body mass index), type and timing of ITx procedure, and the changes in the outcome variables of interest.

Due to the anticipated heterogeneity in population, ITx procedure, and study design, meta-analyses were not anticipated or conducted.

RESULTS AND DISCUSSION

Of the 277 studies identified, only five pertained to exercise in animals having undergone islet transplantation. There were no identified studies of human islet transplant recipients performing physical activity. The remainder of this review will assess these studies once they have been placed in context.

[1] Detailed search strategy information can be found in Supplementary Table S1.

ISLET TRANSPLANT PROCEDURES

Human islets used for transplantation are isolated from healthy cadaveric organ donors, which generally have been deemed unsuitable for whole pancreas transplant. It is important that the cold ischemic time for the pancreas is short since long durations decrease islet yield and function (McCall and Shapiro 2014). The islets from the donor cadaver are separated from the pancreatic exocrine tissue that surrounds them through islet isolation using collagenase (Bruni et al. 2014). Following a brief period of culture, to allow for recovery from damage that may result from the isolation process (Bruni et al. 2014), the islets are transplanted into the recipient's liver via the hepatic portal vein under local anesthesia. Recipients must take lifelong immunosuppressant drugs (Shapiro 2012) to prevent the rejection of these foreign cells.

The indications and contraindications for ITx have been described previously (Senior et al. 2012), but primarily people with frequent severe hypoglycemia episodes (requiring assistance from third parties), severe glycemic lability (unpredictable swings from hypo- to hyperglycemia), or severely impaired awareness of hypoglycemia are included. Prognostically, ITx can achieve long-term insulin independence as shown by Shapiro et al. (2000) and Ryan et al. (2002). Even in the absence of insulin independence, most patients maintain endogenous insulin secretion which is associated with improved blood glucose control (as measured by glycated hemoglobin (HbA_{1c})), fewer hypoglycemic episodes, and a decreased reliance on exogenous insulin (Barton et al. 2012). Paty et al. (2006), using continuous glucose monitoring, also showed that in the absence of insulin independence, the presence of C-peptide (which islets co-secrete with insulin (Silverthorn et al. 2013) was associated with fewer hypoglycemic events and more stable blood glucose (Paty et al. 2006).

One factor that is involved in the effectiveness of ITx is the site at which islets are transplanted. A study of humans by Kendall et al. (1997) suggested that islets transplanted into intrahepatic sites lacked proper glucagon secretion during hypoglycemia while those infused into intraperitoneal sites did not. In addition, patients with islet cells transplanted into the liver did not attain normal hypoglycemic

counterregulation or improved symptom recognition during a hypoglycemic clamp (Paty et al. 2002). However, Kemp et al. (1973) concluded that the liver provided the most promising results in comparison to the subcutaneous space and peritoneal cavity in diabetic rats, with the subcutaneous space being the least effective site.

RECENT INITIATIVES

Efforts to improve ITx have involved testing the efficiency of new engraftment sites which may reduce procedural risks, provide immunologic protection, or permit easier monitoring of transplanted islets. The liver has historically been the primary transplant location (Agarwal and Brayman 2012) with alternate sites including the subcutaneous space, kidney, spleen, pancreas, omentum, gastrointestinal wall, peritoneal cavity, and immune privilege sites (Bruni et al. 2014) (ex. brain (Niederkorn 2006)). Other locations under investigation include within bone marrow and muscles (Vantyghem et al. 2014).

The subcutaneous space holds potential due to its accessibility but may not be ideal because of low blood supply to the area (Bruni et al. 2014). Recently, Pepper et al. (2015) determined a way to initiate blood vessel growth by temporarily placing a catheter under the skin before ITx. This procedure may attenuate the negative characteristics of engraftment at this location. Currently, this has only been evaluated in rats but plans are in place to test this method in humans (Pepper et al. 2015).

The need for lifelong immunosuppression is a major barrier preventing the widespread use of ITx. The major risks and side effects of current immunosuppression include gastrointestinal-, neuro-, and nephrotoxicity, and an increased risk of infection and cancer (Ryan et al. 2004). To decrease the need for immunosuppression, encapsulated islets are being explored to avoid antigen recognition and islet destruction by the immune system (Fiorina et al. 2008; Krishnan et al. 2014). A study of mice by King et al. (2003) found that while non-encapsulated islets resulted in better glucose tolerance and blood glucose control, encapsulation provided the cells with protection against immune destruction and lowered blood glucose concentrations. The wide variety of immunological options are discussed in more detail in a recent review on the subject (Fiorina et al. 2008) .

The limited supply of pancreas organ donors is the most prominent limitation to increasing accessibility to ITx (Shapiro 2012). Generally more than one donor is required for one T1D individual to achieve insulin independence, so much effort has been focused on increasing the success of single-donor transplants by optimizing the number of functional islets isolated from each pancreas. Future endeavors may include improving isolation techniques and identifying the donor requirements that result in the best possible yield (Shapiro 2012). Human stem cells, an alternate source of islets which is being explored, have the potential to provide an unlimited supply of insulin-producing beta cells (Shapiro 2012; Bruni et al. 2014). Pig islets may also be compatible in the human body to offset the insulin deficit faced by people with T1D (Shapiro 2012).

GLUCOREGULATION AND HYPOGLYCEMIA IN ITx PATIENTS

Recent studies have examined transplanted islet function under conditions of insulin-induced hypoglycemia (Kendall et al. 1997; Rickels et al. 2005) but very few have examined islet function or glucose regulation during exercise, with none to date in humans. Since exercise has profound effects on glucose regulation, carries risks for hypoglycemia in T1D, and is a key component to both physical and mental health, it is important to understand its acute effects in ITx recipients.

While ITx provides clear benefits in terms of glucose regulation, some studies have noted its limitations in humans. For example, Paty et al. (2002) observed normal insulin suppression but impaired glucagon and epinephrine release during a three-hour stepped hypoglycemic clamp (Paty et al. 2002). The authors concluded that the counterregulatory response to hypoglycemia and symptom awareness were not restored in comparison to non-T1D controls even though the patients were independent of exogenous insulin and had a mean (±SEM) HbA_{1c} of 5.8±0.1% (Paty et al. 2002). Similarly, another study using a stepped hyperinsulinemic-hypoglycemic clamp with intrahepatic ITx patients found appropriate insulin suppression, but an irregular glucagon response: glucagon concentrations returned to baseline shortly after hyperinsulinemia was induced in the ITx group, where a significant increase over baseline was seen in the control group. In spite of this, final glucagon concentrations were not significantly different

between the groups (Rickels et al. 2005). However, the blood glucose threshold required for a counterregulatory response and symptom presentation in intrahepatic ITx patients has been assessed to be normal when compared to non-T1D controls (Rickels et al. 2007). In addition, a recent study by Rickels et al. (2015) monitored the response of intrahepatic ITx patients to insulin-induced hypoglycemia and found that C-peptide (and therefore insulin secretion) was suppressed, glucagon secretion was restored (increased during hypoglycemia rather than suppressed as in T1D patients (Katsura et al. 1993)), and epinephrine release was improved. These developments allowed the patients to avoid hypoglycemia by stimulating endogenous glucose production (Rickels et al. 2015).

The improved outcomes seen in the more recent study (Rickels et al. 2015) may be due to advances in the ITx procedure itself or perhaps more precise and reliable testing methods that have been developed over the years. All of the published studies to date have been relatively small ($n \leq 12$ per study). They do, however, suggest that ITx may not completely replicate normal physiology to provide perfect physiological glycemic control. This may be of particular importance in situations where larger stresses, such as physical activity, are placed on the regulatory mechanisms.

EXERCISE AND ITx

Exercise and Blood Glucose Control in T1D

In T1D, regular exercise has been shown to be associated with greater longevity (Moy et al. 1993), improved cardiovascular function (Diabetes…1990), and a lower risk of diabetes-related complications such as neuropathy (Kriska et al. 1991; Balducci et al. 2006), retinopathy (Waden et al. 2008), and cardiovascular disease (Waden et al. 2008). In an individual without T1D, the onset of moderate aerobic exercise causes a slight decrease in blood glucose that triggers the release of glucagon and the suppression of insulin (Ruderman et al. 2002). The plasma half-life of endogenous insulin is four to six minutes (Duckworth et al. 1998) resulting in lower levels of circulating insulin during exercise. This ensures that sufficient blood glucose is available to compensate for the increased glucose disposal due to muscle contraction.

In individuals with T1D, the required changes in insulin during aerobic exercise cannot occur, as the half-life of insulin injected or infused subcutaneously can be several hours resulting in relative hyperinsulinemia as a common occurrence during exercise. In addition to exogenous insulin not decreasing at exercise onset (Camacho et al. 2005), subcutaneous insulin may be absorbed more rapidly because of changes in blood flow during exercise (Holt et al. 2010). These factors, along with the increase in non-insulin mediated transport of glucose into cells during aerobic exercise (Thorell et al. 1999) increases the risk of hypoglycemia.

Exercise as a Beta-Cell Preserving/Enhancing Agent

Exercise may also have additional benefits after T1D individuals have undergone ITx. It has the potential to preserve beta cells, enhance their function, increase their growth or decrease their death (Coskun et al. 2004; Choi et al. 2006; Park et al. 2007; Kiraly et al. 2008; Laker et al. 2011). Studies in rats have found that exercise is beneficial to beta cells by improving function (maintenance of appropriate insulin to glucose ratio and insulin secretion capacity)(Choi et al. 2006; Kiraly et al. 2008; Delghingaro-Augusto et al. 2012), preventing destruction (via apoptosis or oxidative stress)(Coskun et al. 2004; Choi et al. 2006; Kiraly et al. 2008), reversing damage (Choi et al. 2006; Laker et al. 2011), and increasing mass (via increased number and size of beta cells)(Choi et al. 2006; Park et al. 2007; Kiraly et al. 2008; Laker et al. 2011). Human studies, although limited, show that exercise can improve the function of beta cells in people with type 2 diabetes (Bloem and Chang 2008; Slentz et al. 2009; Malin et al. 2013). For these reasons, exercise may assist in maintaining the integrity of implanted islets and decrease physiological stress to improve glucoregulation in ITx patients.

A study by Choi et al. (2006) showed that the progression of diabetes was delayed and beta cell mass was increased when 90% pancreatectomized rats performed treadmill running for 30 minutes four times a week. In the same study (Choi et al. 2006), exercise also reversed the detrimental effects of dexamethasone, a corticosteroid that increases insulin resistance. Coskun et al. (2004) found that implementing a daily swimming regime for 12 weeks, four of which occurred before introduction of streptozotocin (STZ), prevented the destruction of beta cells and decreased oxidative stress in STZ-

induced diabetic rats. Moderate exercise training (10 min./day) was the most beneficial in comparison to light (5 min./day) and heavy (15 min./day) (Coskun et al. 2004). Another study of diabetic rats concluded that voluntary running leads to improved beta cell function, preserved islet insulin stores, and conservation of glucose-induced insulin hypersecretion (Delghingaro-Augusto et al. 2012). Furthermore, beta cell maintenance and the prevention of oxidative stress were benefits of exercise demonstrated by Kiraly et al. (2008) in rats that swam for one hour per day, five days a week for 13 weeks. Also, beta cell mass restoration, the prevention of mass loss, and increased insulin secretion resulted from 20-60 minutes of treadmill running five days a week for four weeks in a study conducted by Laker et al. (2011). The rats in this study underwent fetal growth restriction which is associated with reduced beta cell mass (Laker et al. 2011). As the above studies demonstrate, exercise has beneficial effects on beta cells and may be an important aspect of T1D treatment. As exercise may play a beneficial role in graft survival, it is important to determine whether there remains a risk of hypoglycemia associated with exercise in ITx patients.

Exercise in ITx

Whether or not exercise is still associated with a risk of hypoglycemia after ITx in humans is currently unknown. Our systematic literature search identified five studies examining the effects of exercise after ITx in animal models. No human studies examining glycemic control in ITx patients in response to exercise were identified. Pre-clinical studies conducted in rats and dogs (Portis et al. 1990; Houwing et al. 1995a; Houwing et al. 1995b; Omer et al. 2004) may however provide valuable information on the topic. A summary of existing studies can be found in Table 1.

A study involving 12 male and female adult mixed-breed dogs (six non-T1D controls and six with auto-islet transplants [i.e. pancreatectomized dogs had their own islets transplanted into their spleen, therefore α cells were also ectopic]) measured glycemic responses to 60 minutes of moderate-intensity (~60% maximum heart rate) treadmill exercise in the fasting state (Portis et al. 1990). There were no significant differences in plasma glucose between groups at baseline or during exercise (Portis et al. 1990). Plasma glucose concentration decreased with exercise in both groups but took longer to return to baseline in the ITx dogs than the control group, with the change from baseline being significant ($p<0.05$)

between groups at 30 minutes post-exercise (Portis et al. 1990). None of the animals became hypoglycemic during the study (Portis et al. 1990). The autografted dogs also displayed reduced insulin suppression with the intergroup difference being significant at 45 minutes into exercise (Portis et al. 1990). Additionally, the authors noted that epinephrine and glucagon responses were highly variable among autografted dogs in comparison to control dogs and that they were significantly correlated in transplant dogs but not in controls (Portis et al. 1990). The groups displayed similar norepinephrine responses. Amidst these metabolic differences, all of the dogs maintained euglycemia which suggests that the various mechanisms responsible for glucose control during exercise differed in relative importance between the ITx and control animals (Portis et al. 1990).

Houwing et al. (1995b) carried out a study on male rats (weighing 270-380g) with STZ-induced diabetes (eight intraportal isotranplant recipients and eight non-T1D controls) and found the increase in non-esterified fatty acid (NEFA) to be more pronounced ($p<0.05$) in ITx animals than controls during 15 minutes of strenuous swimming. They also observed that insulin levels decreased similarly between transplanted and control rats during exercise (Houwing et al. 1995b). However, a slower ($p<0.05$) return to baseline insulin levels was observed in the ITx rats after exercise compared to controls (Houwing et al. 1995b). Insulin suppression during exercise was present in both groups unlike the study by Portis et al. (1990). This discrepancy may be due to transplantation site since the dogs received islets in the spleen while the liver was used in the rats. The researchers suggested that the mechanism responsible for the euglycemia that the rats maintained was the sympathetic activity stimulated by exercise (Houwing et al. 1995b). However, evidence suggests that parasympathetic innervation (Rodriguez-Diaz et al. 2012) plays an important role in beta-cell function and that the site of transplantation (Korsgren et al. 1993) affects the reinnervation of islets. Additionally, the ectopic alpha cells in the pancreatectomized dogs may have altered their counterregulatory response as discussed below.

A different study of swimming exercise using the same rat model (weight between 300-380 g, STZ-induced diabetes, isotransplanted islets) found that plasma insulin and glucose levels before, during, and after exercise were comparable between portal vein ITx (transplantation of 50% of normal pancreatic

endocrine volume) and non-T1D control groups (Houwing et al. 1995a). Immediately after exercise onset, ITx rats displayed a slower increase in NEFA than controls (Houwing et al. 1995a). However, the researchers concluded that ITx had normalized energy metabolism during the 20-minute exercise period (Houwing et al. 1995a). This study provides evidence for the usefulness of ITx treatment since it was able to withstand the physiological stresses of exercise while maintaining normal glucose concentrations.

Houwing et al. (1997) performed further research on swimming male (weighing ~330g), STZ rats after islet isotranplantation and concluded that euglycemia was maintained during 15 minutes of exercise when islets were transplanted into the spleen and beneath the kidney capsule. Blood glucose, plasma insulin, and plasma epinephrine levels in intrasplenic and kidney subcapsular ITx rats were similar to controls (Houwing et al. 1997). However, plasma norepinephrine was lower than controls in both transplant groups but similar between the two transplantation sites (Houwing et al. 1997). The normoglycemia that the rats maintained was likely due to the reinnervation of noradrenergic nerve fibers in the transplanted islets (Houwing et al. 1997).

A more recent study found that allotransplantation of islets did not attenuate the drop in blood glucose resulting from moderate-intensity treadmill exercise (30 minutes at 24 m/min up a 5% grade) in male, STZ-induced T1D rats weighing between 200 and 240g (Omer et al. 2004). This was explained by blunted insulin suppression and an inappropriate glucagon response observed in all of the rats that were studied regardless of whether the islet cells were placed in the liver, kidney, or peritoneal cavity (Omer et al. 2004). This occurrence of hypoglycemia disagrees with the aforementioned findings of near-normal blood glucose control during exercise in animal studies. This result is highly relevant to clinical ITx which is performed in patients at increased risk for hypoglycemia and accords with anecdotal reports of hypoglycemia induced by exercise in ITx patients (P.A. Senior, personal communication, 2016).

The above contradiction may be explained by the duration of exercise performed. Most of the studies (Houwing et al. 1995a; Houwing et al. 1995b; Houwing et al. 1997) that observed good glycemic control chose a duration of exercise that was approximately half of that used in the study (Omer et al. 2004) that identified hypoglycemia. The one study that observed normal glucoregulation amid a longer

exercise duration was the one conducted by Portis et al. (1990) in which the dogs were pancreatectomized and therefore had alpha cells in the spleen. This differs from the rat studies since alpha cells maintain their integrity in the presence of STZ (Li et al. 2000) and would therefore still be present in the pancreas. Portis et al. (1990) noted a strongly significant correlation between glucagon and epinephrine ($r=0.81$, $p<0.001$) in the transplant dogs while no such relationship was measured in the rat studies that observed euglycemia (Houwing et al. 1995a; Houwing et al. 1995b; Houwing et al. 1997). Perhaps, the link that was established between glucagon released from the transplanted alpha cells and endogenous epinephrine allowed the dogs to display proper glucagon secretion, although variable, in the absence of appropriate insulin suppression.

In addition, most studies that applied exercise eight or more weeks after transplantation (Portis et al. 1990; Houwing et al. 1995a; Houwing et al. 1995b) found that euglycemia was maintained while Omer et al. (Omer et al. 2004) observed hypoglycemia between four and six weeks after ITx. The shorter post-transplant time may not have been sufficient for islet reinnervation (Houwing et al. 1995b). While the site of implantation likely plays a role in the quality of glycemic control, the above studies do not point to a clear conclusion with the first four studies (Portis et al. 1990; Houwing et al. 1995a; Houwing et al. 1995b; Houwing et al. 1997) finding promising results in the spleen, liver, and kidney while the last study (Omer et al. 2004) reported poor results in the liver, kidney, and peritoneal cavity. All of these factors require further investigation to accurately assess if ITx animals are at an increased risk of hypoglycemia when compared to controls.

FUTURE DIRECTIONS

To the best of our knowledge, there are currently no published studies on the acute effects of exercise on blood glucose levels in humans following ITx. Clinical trials that test the effects of different types and durations of exercise are needed in order to learn what prescriptions are in the best interest of ITx patients. To this end, the first step is determining the risk of hypoglycemia during physical activity in this population. Furthermore, if this risk still exists in ITx patients, it is important to understand the

mechanisms involved to gain insight into how to best manage it. Finally, whether or not these mechanisms change as time since transplant increases should also be explored.

CONCLUSIONS

Glucose regulation during exercise is complex and even more so in people with T1D where hypoglycemia is a major risk of, and barrier to, exercise. Animal studies suggest that physiological glucose regulation may not be completely restored by ITx and that there may be a risk of hypoglycemia that varies with transplantation site as well as the duration of exercise. There are currently insufficient data to ascertain the role that time since transplantation plays in the precision of glucose regulation during exercise. Exercise may have important benefits in ITx recipients but greater understanding of the potential risks of hypoglycemia during or after exercise in this high risk population is required.

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STUDY	DESIGN							CHANGE DURING EXERCISE (POST-EXERCISE)				
	Animal Model	**Controls**	**Exercise Type**	**Duration**	**Intensity**	**Site of ITx**	**Time Post-Transplant**	**Insulin** (C-peptide for Omer (2004))	**Glucagon**	**Epinephrine**	**NE**	**Conclusion**
Portis (1990)	Male and female pancreatecto-mized and autografted dogs	Non-T1D	Treadmill	60 min.	Moderate (60% max HR, 100 m/min, 12% grade)	Spleen	12-19 months	Initial decrease followed by increase at 15 min. Δ insulin different from controls at 45 min ($p<0.05$).	Increased ($p<0.05$ vs. pre) High intragroup variability	Increased ($p<0.05$ vs. pre) High intragroup variability	Increased ($p<0.05$ vs. pre)	Euglycemia
						Control		Decreased	Increased ($p<0.05$ vs. pre)	Increased ($p<0.05$ vs. pre)	Increased ($p<0.05$ vs. pre)	
Houwing (1995a)	Male inbred albino Oxford rats (300-380g); STZ-induced diabetes; isotransplanta-tion	Non-T1D	Swimming	20 min.	Moderate (0.22 m/s)	Liver	8-12 weeks	Increased at onset but then decreased until exercise cessation	-	-	-	Euglycemia
						Control		Increased at onset but then decreased until exercise cessation	-	-	-	
Houwing (1995b)	Male inbred albino Oxford rats (270-380g); STZ-induced diabetes; isotransplanta-tion	Non-T1D	Swimming	15 min.	Moderate (0.22 m/s)	Liver	≥8 weeks	Decreased	-	Increased with platform lowering into water. Decreased throughout exercise, remaining above baseline.	Increase	Euglycemia
						Control		Decreased during exercise, and returned to baseline faster than ITx ($p<0.05$)	-	Same as above.	Increase	

Houwing (1997)	Male inbred albino Oxford rats (330g); STZ-induced diabetes; isotransplanta-tion	Non-T1D	Swimming	15 min.	Moderate (0.22 m/s)	Spleen	3 weeks	Decreased	-	Increased with platform lowering into water. Decreased during exercise, remaining above baseline.	Increased (p<0.05 vs. pre) but lower than controls (p<0.05)	Euglycemia
									-			
						Kidney		Decreased		Same as above.	Increased but lower than controls (p<0.05)	
									-			
						Control		Decreased		Same as above	Increased	
Omer (2004)	Male Lewis rats (200-240g); STZ-induced diabetes; allotransplan-tation	Non-T1D	Treadmill	30 min.	Moderate (24 m/min, 5% grade)	Liver (non-encap)	4-6 weeks	Increased (p<0.01 vs. controls and pre)	Increased (p<0.05 vs. pre)	-	-	Hypoglycemia
						Kidney (non-encap)		Decreased (ns)	Increased (ns)	-	-	
						Peritoneal (encap)		Increased (p<0.01 vs. controls and pre)	Increased (p<0.05 vs. pre)	-	-	
						Peritoneal (non-encap)		Decreased (ns)	Increased (p<0.05 vs. pre)	-	-	
						Control		Decreased	Decreased	-	-	

Table 1. Study design and changes in hormone concentration observed in studies involving exercise in animal ITx models.
Note: T1D= type 1 diabetes; ITx =islet cell transplantation; encap =encapsulated islets; NE= norepinephrine