ABSTRACT

Objective: To elucidate why diabetes is so difficult to treat despite the present tools and pharmacologic armamentarium and to provide insights into emerging therapies by describing human and rodent data that demonstrates the ability to transform progenitor cells within the adult pancreas into new islets.

Methods: A literature review focused on the distinctions between human and rodent islets.

Results: We are beginning to elucidate important differences between the architecture and composition of the islets of Langerhans in humans and rodents. In contrast to rodent islets, human islets are more heterogeneous in cellular composition and have more prominent intra-islet vascularity, with smooth muscle-containing blood vessels that are not present in rodent islets. Some studies report that more than 70% of human beta cells have direct physical contact with other cell types, whereas others describe that smaller human islets possess features more typical of rodents, while larger islets exhibit greater vascularity and a cellular distribution distinct from centrally clustered beta cells surrounded by a mantle of alpha and delta cells found in rodents.

Conclusions: The differences between the islets of mice and men may influence why treatments hailed as reversing diabetes among rodents have not been successfully translated into humans. Increased understanding of the complexities within the human islet may yield unique insights into reversing diabetes in humans. (Endoc Pract. 2013;19:301-312)

Abbreviations: DCCT = Diabetes Control and Complications; GAD = glutamic acid decarboxylase; GLP-1 = glucagon-like peptide-1; Reg = regenerative

INTRODUCTION

Differences Between Human and Rodent Islets

In recent years, human islet structure and cellular organization have been more carefully scrutinized, leading to new questions and controversies regarding the differences between islets in man and mouse. Although there is consensus on the cell types seen within human and rodent islets, a lower proportion of beta cells are found in humans compared with rodents. There is also ongoing debate on topographic endocrine cell arrangement within human islets.

While there are also many similarities, the composition, architecture, innervation, and function of human islets are quite different than those seen in mice (1-4). Human beta cells often are not the only cell clustered in the center of an islet as they are in rodents. In contrast to mice, some studies have demonstrated that more than 70% of human beta cells have direct physical associations with other endocrine cells (e.g., alpha, delta, and gamma/pancreatic polypeptide cells), suggesting that unique paracrine interactions may occur between beta cells and their immediate neighbors (1). Other studies have reported heterogeneity among human islets, including different architecture within islets depending on their size. For example, some small human islets have been found to have similar architecture to rodent islets (5-8).
Orci and Unger (6) have shown human islets with alpha and delta cells located in the mantle and grouped against capillary walls within the core of beta cells. Others have proposed that human islets are subdivided into lobules or subunits comprised of clusters of beta cells surrounded by alpha cells (7-9), and these lobules are separated by vascularized connective tissue and nonbeta cells (9). Conversely, Grube and colleagues (8) proposed a human islet in which endocrine cells were organized in a ribbon-like manner rather than as separated subunits. Bonner-Weir and O’Brien (10) point out the relative certainty of most mammalian species having a nonrandom pattern with a core of beta cells surrounded by a discontinuous mantle of nonbeta cells; however, there is clearly a more complex arrangement with many different islet profiles in humans and other primates.

Controversy over the differences and similarities between the islets of mice and men continues with new compositional analyses. The research teams led by Cabrerra, Brissova, and others have shown that human islets are a heterogeneous mix of cell types without classic central beta cells surrounded by alpha cells that contain significant intra-islet vasculature (Fig. 1) (1-4). Bosco and colleagues have found that different sized human islets have different compositions, with smaller islets having more centrally positioned beta cells with surrounding alpha cells and peripheral blood vessels, while bigger islets have larger percentages of alpha cells within the central portion of the islet with greater numbers of vasculature cells penetrating islets with increasing size (5).

Although there appears to be heterogeneity among human islets, studies have shown that compared to rodent islets, those in human and nonhuman primates have increased proportions of alpha and delta cells (which are more dispersed throughout the islet) and a lower proportion of beta cells (1-3). Furthermore, rodent islets have fewer alpha and delta cells relative to beta cells, and these are primarily found in the islet periphery (2).

Human and nonhuman primate islets have better developed and more prominent internal vasculature than rodents (1-4). The blood vessels within the human islet contain a larger proportion of smooth muscle cells, which has implications for sympathetic nervous system innervation. Conversely, rodent islet vasculature consists mainly of endothelial tubes devoid of smooth muscle cells that occupy a smaller physical space within the islets (4). Thus, sympathetic nerves may regulate the secretion of several hormones within human islets via the regulation of local blood flow and play a greater role in human islet function, compared to rodents.

Parasympathetic nervous system innervation patterns also vary between humans and mice. Human islets differ in their cholinergic neuronal innervation, with additional evidence suggesting that humans may be more dependent on glucagon regulation than mice. These findings are underscored in the 2012 review by Unger and Cherrington describing that the juxtaposition of functioning beta cells is critical for glucagon regulation from alpha cells (11). Without appropriate intra-islet insulin and amylin secretion from beta cells, there is aberrant feedback to alpha cells, resulting in unregulated glucagon hypersecretion, which may directly lead to diabetic symptoms (11).

The capacity of the autonomic nervous system to regulate blood glucose levels through islet innervation suggests that the human islet may have a uniquely different reaction to emotional stress. The prominent differences in islet

Fig. 1. Architecture of mouse and human islets. The above images demonstrate differences between islets in men and mice. Insulin staining is in red, glucagon in green, and somatostatin in blue. The black areas distinctly seen within the human islet are occupied by blood vessels. Reprinted with permission, Copyright 2006, Proceedings of the National Academy of Sciences of the United States of America. 2006; 103(7): 2334-2339.
complexity also suggest the importance of paracrine communication within the islet. Also striking are the presence of complex endocrine networks and neuronal feedback mechanisms between islets, peripheral vasculature, and the central nervous system that are necessary to maintain a narrow range of glycemic control.

**Glucose Homeostasis in Man**

The unique vasculature and innervation of human islets suggests that they respond differently to emotional and environmental cues compared to rodents. The mouse lifespan is just 12 to 18 months, compared to 7 decades in man, and their islets are structured accordingly. Unlike humans, rodents eat relatively constantly, and data reflects that rodents may not be as dependent on alpha cell regulation. Published data collected after the 44-day fast of performance artist David Blaine demonstrated that Blaine’s glucose levels were in the normal range, at 5.2 mmol/L (93.7 mg/dL), with an insulin level of 3.6 mU/L, which was below the range of control subjects (4.0 to 20 mU/L). Furthermore, his insulin-like growth factor 1 (IGF-1) level was 65.00 µg/L, which was well below the mean IGF-1 of controls (210.88 µg/L) (12). Prior to eating and after the 44-day fast, his cortisol was higher than the control range (770 nmol/L vs. 200 to 600 nmol/L, respectively), which implies that in addition to glucagon and other islet hormones, cortisol may play an important role in metabolism maintenance under fasting conditions (12).

Thus, humans possess exquisitely evolved islets that maintain great plasticity to maintain euglycemia, even in times of prolonged fasting. Consistent with these findings is the ability of beta and delta cell mass to increase in obese individuals. Older literature on glucose tolerance testing demonstrates that beta cells do not respond as robustly when there is carbohydrate deprivation prior to a glucose load. Furthermore, false positive findings have been described when patients have not adequately carbohydrate loaded, due to beta cell downregulation during periods of low carbohydrate intake or fasting.

**Maintaining Normoglycemia in Mice and Men**

As we look for innovative treatments to restore beta cell function, it is important to understand how normally functioning islets work. Clearly, beta cell loss is the sine qua non for both type 1 and 2 diabetes, and this loss also imbalances other pancreatic hormones. For example, studies have consistently shown that both in type 1 and 2 diabetes, there is compensatory alpha expansion as the number of beta cells decreases (13,14). As alpha mass expands without inhibitory feedback, excessive glucagon further dysregulates glucose metabolism.

Glucose levels are slightly lower in humans than in rodents. Despite this difference, homeostasis is maintained within a very narrow range in both species due to exquisite intercommunication within islet complexes (1-4). Sensor data from nondiabetic humans demonstrate that 80% of all measured glucose levels range from 60 to 100 mg/dL, with mean postprandial peak glucose levels <120 mg/dL (15). Linear regression curves from the Diabetes Control and Complications Trial (DCCT) and the United Kingdom Prospective Diabetes Study (UKPDS) showed that A1C levels above 5.5% are associated with more complications (16,17). This data is supported by A1C levels from the European Prospective Investigation into Cancer (EPIC)-Norfolk trial among nondiabetic individuals, which found that A1C levels above 5.5% are associated with significantly increased risk for vascular-related morbidity and mortality (18).

Glucose homeostasis requires an adequate number of completely functional islets, as illustrated by the inability to restore normoglycemia among diabetic patients despite intensive insulin regimens. The DCCT investigators set, as a major treatment outcome goal, a mean A1C over the trial period of ≤6.05% without an increased risk for hypoglycemia (16). This goal was not achieved with insulin replacement (i.e., one of the multiple hormones missing in diabetes). The relationship between distinct cell types within the islet and abnormalities that result from beta cell loss, including amylin, glucagon, somatostatin, pancreatic polypeptide, and islet ghrelin dysfunctions, remains to be elucidated.

Sensor-augmented pumps were recently shown to decrease A1C levels from 8.3% to 7.5% over 12 months, with further reduction to 7.4% after an additional 6 months of treatment. These achievements were made without associated weight gain or hypoglycemia observed in the DCCT cohort. Despite technologic advances in sensors and pumps, sensor-augmented pump therapy did not improve A1C levels as much as in the DCCT decades ago (19,20). This underscores the importance of restoring beta function and communication within the islet complex.

**Islet Development in Mice and Men**

The highly organized structure of the islet is already in place by the 10th week of human fetal pancreas development. By this stage, islets stain for insulin, glucagon, somatostatin, pancreatic polypeptides, and islet ghrelin within beta, alpha, delta, gamma, and epsilon cells, respectively (21-24). The process of new islet formation occurs almost exclusively during fetal development when the pancreas is being populated with islets for the first time (23,24). New islets in adult humans are formed almost exclusively following acute pancreatic injury, pancreatic stones, partial pancreatectomy, and perhaps during pregnancy (25-30). Bonner-Weir, Carlotti, Stewart, Meier, and others have demonstrated clear distinctions in the replication capacity between the beta cells of rodents and humans (31-34). Beta cell regeneration from pre-existing beta cells is the major form of glucose regulation in healthy adults and rodents, but there is greater responsiveness to beta regeneration in
rodents, possibly due to their continuous eating patterns. For example, in response to obesity, there is as much as a fivefold greater increase of rodent beta cells compared to humans. Similarly, rodents exhibit up to a fourfold increased ability over that of humans to expand the beta cell population during pregnancy (35,36).

In humans, Meier and colleagues investigated beta cell mass from infancy to adulthood on pancreata obtained at autopsy from 46 donors (from 2 weeks to 21 years of age) and compared the findings to those from 135 similarly aged individuals (33). In contrast to rodents, beta cell expansion occurs in early childhood without a secondary beta cell growth phase during adolescence. This study also found that there was no increase in islet number over time. Kassem and colleagues reported that human beta cell replication progressively decreased from 3.2% at 17-32 weeks of gestation to 1.1% perinatally (34). After birth, beta cell replication drops further, to reach less than 0.1% in young adults (34). These data are consistent with findings that human beta cell mass is established in the first two or three decades of life. A study of human pancreatic tissue collected from 13 patients who underwent partial pancreatectomy demonstrated that, unlike rodents, a 50% pancreatectomy does not trigger any significant beta cell regeneration in adult humans (37).

In both rodents and humans, diabetes results from aberrant beta cell function and diminished insulin secretion. Loss of functioning beta cells leads to complex dysfunction within the islet. Recently, ghrelin-producing epsilon cells have been identified within developing and adult islets (38). This discovery is consistent with findings of abnormal ghrelin secretion among children with new-onset type 1 diabetes and with the hypothesis that ghrelin plays a protective role in type 2 diabetes (39,40). Similar to ghrelin, impaired pancreatic polypeptide secretion from gamma cells has been reported in humans with both type 1 and 2 diabetes (41,42). Pancreatic polypeptide administration has been shown to improve abnormal glucose metabolism in type 2 diabetes, to improve insulin sensitivity, and to reduce the insulin requirement of type 1 patients on insulin pump therapy (41,42).

Transient elevation in glucose not only results in coincident secretory pulses of insulin and amylin from beta cells, but also in pulses of somatostatin from delta cells (43). Somatostatin fulfills multiple paracrine regulatory roles in the islet, including a tonic inhibitory influence on insulin and glucagon secretion (44). Somatostatin is also implicated in the nutrient-induced suppression of glucagon secretion (44). Furthermore, in a number of trials among type 1 patients, somatostatin treatment has been associated with improvements in glucose metabolism (44-47). Amylin is cosecreted with insulin from beta cells. The amylin analog, pramlintide, has been shown to reduce A1C levels, diminish preprandial insulin requirements, blunt high and low glycemic excursions, and suppress postprandial glucagon levels (48).

Dr. Elliott Joslin knew that insulin was a diabetes treatment rather than a cure (49). A functional beta cell population is necessary to maintain islet homeostasis. The loss of beta cells leading to dysfunction in other islet cell types is consistent with autopsy studies of type 1 and 2 diabetes patients, which demonstrated reductions in both beta cell number and mass and total islet number and mass in humans with diabetes (50,51). The individual contributions of each of the islet hormones are still emerging, as is the importance of their intricate crosstalk. Restoration of beta cells within islets is critical for glucose homeostasis.

**Future Therapies**

As we search for new diabetes therapies that may address the underlying disease mechanisms, the question becomes how to restore beta cell mass and numbers within a functioning islet. The generation of beta cells and islets from both umbilical stem cells and mesenchymal stem cells for subsequent transplantation is being utilized both in vitro and in human trials via intravenous delivery of mesenchymal stem cells to type 1 diabetics (52-54). Recently, studies using the glucagon-like peptide-1 (GLP-1) receptor agonist liraglutide to treat type 1 patients demonstrated improved glycemic control and weight loss, and 2 patients with baseline stimulated C-peptide levels of 0.6 and 0.8 nmol/L were able to discontinue insulin without loss of glycemic control (55). GLP-1 receptor agonists may prove to play a useful role in both type 1 and 2 diabetes control, and recent results demonstrate the importance of glucagon suppression among patients with diabetes.

Some teams have questioned the presence of pancreatic progenitor cells and whether new islets can be formed from nonendocrine pancreatic tissue, and find only a limited ability of the ductal epithelium to differentiate into islets, even in regenerative settings (56-58). Others have developed methods for the ex vivo expansion of human pancreatic nonendocrine and progenitor cells into islets (53,54). There is further debate on whether islet progenitors constitute a separate population of cells or are a specialized ductal cell. Pioneering work by Bonner-Weir and others provides compelling data that the ductal epithelium houses progenitor cells that can be transformed into new islets (59).

D’Allesandro and colleagues developed methods for enriching culture medium to facilitate in vitro transformation of human nonendocrine tissue and found that more than half of human nonendocrine cells were capable of transforming into islets (60). Similarly, Parenteau et al expanded human pancreatic progenitor cells in vitro (61). King and colleagues successfully transplanted rat beta cells without other cell types and normalized glucose homeostasis in rats (62). The lack of donor pools of human islets
and beta cells has limited such studies in humans; however, another possibility is to deliver ex vivo-generated beta cells and islets to patients. The umbilical vein is used for injecting donor islets, which function in the liver rather than the pancreas.

Several groups have demonstrated the ability to reprogram rodent alpha cells into beta cells, which may or may not be feasible in humans (63,64). Soos, Hawley, and others have developed monoclonal antibodies to the insulin receptor, which will provide a unique therapeutic approach (65,66).

Islet Agonists

Islet agonists are a relatively new interest and are now in human clinical trials. The aim of islet agonist therapy is to transform one’s own ductal progenitors into islets. Currently, two human trials are underway that are based on older ductal ligation studies demonstrating new islet formation. While there remains debate whether there is beta cell expansion after ductal ligation in rodent models, many teams have consistently found that ductal ligation leads to new islet formation.

The concept that ductal ligation might induce new pancreatic islet formation was first proposed by Frederick Banting. Three decades prior to Banting’s work, the French histologist Édouard Laguesse reported that the islet population was primarily formed during embryogenesis (67). However, Laguesse also described the ability of the islet to grow postnatally through a process of metamorphosis from cells within and surrounding ductal tissue. The idea that ductal progenitor cells can be transformed into new islets remains a leading hypothesis of how new islets form in adulthood.

The regenerative powers of the pancreas were conceptualized more than a century ago. According to Moses Barron, “Attempts at regeneration of injured pancreatic tissue manifest themselves in definite hyperplasia of the ducts” (68). Barron’s observation led Banting to ligate pancreatic ducts in dogs and collect the remaining pancreatic secretions, which led to the discovery of insulin (69). Prior to the widespread availability of insulin, surgeons performed partial pancreatectomies on diabetic children in the hopes of stimulating islet regeneration (70). Although benefits from these novel procedures were described, they were short-lived, perhaps because of ongoing autoimmune destruction.

The ability to generate fully functional human and rodent pancreatic islets through the differentiation of nonendocrine progenitor cells has been shown by Vinik, Gershengorn, Bonner-Weir, Levine, and others (59,71-74). These findings are consistent with Laguesse’s early observation that ductal cells are the niduses for new budding islets.

Progenitor cells, too, have the ability to proliferate and expand in response to signaling cues from surrounding injured pancreatic tissue (75-77). The transformation of pancreatic progenitor cells into fully functional islets is one of the greatest opportunities for therapies that truly address the underlying etiology of diabetes.

The terms “islet neogenesis” and “beta cell regeneration” are often used synonymously, but the two processes are very different. New islet agonist therapies specifically refer to treatments that generate beta cells within the context of new islet formation. With the elucidation of the human genome, Levetan, Zenilman, Perfetti, and others identified the expression of a specific regenerative (Reg) gene encoding a protein product that is associated with new islet formation from ductal progenitors (78-80). Bioactive regions of this protein have demonstrated the abilities to restore normoglycemia via islet neogenesis from extra-islet pancreatic tissue in animal models and to generate new islets in humans (81-88).

There is typically no Reg expression after fetal development. Vinik, Rosenberg, Kapur, Watanabe, Zenilman, and others have provided evidence that Reg plays a direct role in stimulating islet neogenesis formation from nonendocrine pancreatic tissue (78,84-86). Two recent studies were conducted in rodents using BrdU labeling of the beta cell lineage, which distinguishes whether new beta cells are being derived from replicating beta cells or nonendocrine tissue. The Section of Islet Cell and Regenerative Biology at Joslin Diabetes Center found that Reg peptide was present in the newest islets formed from branching proliferating ducts (87). The Departments of Beta Cell Regeneration at the Hagedorn Research Institute and Peptide and Protein Chemistry at Novo Nordisk reported a twofold increase in the volume of new small islets developing from nonendocrine tissue using two different Reg peptides (88). Five days after treatment with the Reg peptides, there were increased levels of new islet markers necessary for islet formation, including NGN3, NKX6.1, SOX9, and INS, indicating that Reg is a catalyst for islet neogenesis (88). When Reg was inhibited with a blocking antibody in an animal model of pancreatic injury, there was attenuated recovery, suggesting that Reg may have both protective and regenerative roles following acute pancreatic injury (89).

Figure 2 depicts the transformation of a progenitor cell within the pancreatic ductal population into a new islet. The single, larger black cell on the left represents the presence of Reg, and the pink cell represents a progenitor cell within the ductal population. The presence of Reg is noted throughout the formation of the earlier, smaller islet formed from the progenitor. Blue, red, and green indicate beta, alpha, and delta cells, respectively. Reg is present in the early small islets that have just budded off from the exocrine populations but is not present in the larger more mature islets (87).

The micrographs in Figure 3 demonstrate the in vitro ability to separate pancreatic progenitor cells from ductal cell populations and expand that pool of pancreatic
progenitor cells. The panel on the right demonstrates the budding of newly formed islets from progenitor cells, which are circled. A human Reg receptor has been identified within human pancreatic ductal cell populations and has been shown to promote downstream cellular activation that leads to new islet formation. When Reg interacts with its receptor, it is hypothesized to activate many transcription factors that promote new islet production (49,90). The organ specificity for Reg was illustrated when a tagged Reg protein (labeled with fluorescein isothiocyanate) was administered to rodents. Interestingly, only the pancreatic ducts exhibited fluorescence (91).

Human Trials with Islet Agonists
To date, several teams have demonstrated the ability of Reg peptides to reverse diabetes and induce normoglycemia in rodent models (48,81-83). Utilizing human ductal cells isolated from islets following cadaveric pancreas removal, Li et al demonstrated that a Reg peptide augments and enhances the in vitro differentiation of nonendocrine cells into islet-like clusters (82).

Human trials with a Reg peptide elicited a 27% rise in stimulated C-peptide by day 56 among type 1 patients ($P = .0058$), and type 2 patients had twice the reduction in A1C ($P = .009$) at days 90 and 120, with nearly a threefold reduction in A1C evident 30 days after washout ($P = .0013$) (83). All type 1 patients had baseline C-peptide levels ≤0.3 ng/mL; however, they were not treated with any immune tolerance agents to protect new islet formation from subsequent immune attack (83). It is important to note that 22% of patients in one of the active treatment arms had >50% increase in the 65-kd form of glutamic acid decarboxylase (GAD65) antibody titer, while no change was noted in the placebo group (83).

Cytokine-induced beta cell death preferentially affects newly forming beta cells in type 1 diabetes (92). Increased GAD65 antibody titer may be a marker of the formation of new islets (that contain new beta cells), and autoimmunity to newly formed beta cells may have negatively impacted study outcomes in terms of A1C and stimulated C-peptide. We hypothesize that there could have been a more significant rise in stimulated C-peptide if patients had
be entirely successful as a primary study endpoint, there are evidently long-term immune benefits from some of the immune tolerance agents tested in clinical trials among patients with new-onset type 1 diabetes. For example, cyclosporine was administered to 40 new-onset type 1 patients between the ages of 7 and 15 years, and 67.5% of them were able to cease insulin treatment, with half remaining insulin-free at 1 year. Treated patients also had significantly lower levels of islet cell antibodies compared to controls, with no secondary side effects, but all patients required insulin after 6 years (93,94). Another study reported persistent improvement in memory T and B cell responses 4 years after GAD vaccine administration (95). Similarly, two anti-CD3 antibodies have been shown to preserve remaining endogenous insulin as long as 5 years after a single course of therapy (96,97). Recently, Faustman and colleagues completed a small study of the Bacillus-Calmette-Guerin (BCG) vaccine in humans with chronic type 1 diabetes and found that each of the BCG-treated subjects had more than 50% of their C-peptide values above the 95th percentile of reference subjects (98). Despite these successes, none of these agents have allowed patients to become insulin-free; the role of these agents is to prevent autoimmune attacks on remaining functioning beta cells rather than generate new islets. Two studies using type 1 nonobese diabetic (NOD) mouse models showed that in late-stage diabetes and among mice with marked elevations in glucose (350 to 400 mg/dL), diabetes was only reversed with (I) a combination of an immune tolerance agent and a Reg peptide or (2) an immune tolerance agent plus a combination of the extra-pancreatic growth factors gastrin and epidermal growth factor (99,100). Among type 2 patients, lifestyle modifications and/or medications are recommended to prevent death of beta cell populations contained within newly formed islets.

An optimal glucose milieu is required for new islet growth, and there are many protective feedback loops to avoid hypoglycemia. Consequently, islet formation occurs within a narrow window of mild hyperglycemia during embryonic pancreatic endocrine cell differentiation (101,102). We hypothesize that a two-step process will be necessary to reverse type 1 diabetes: an immune tolerance agent followed by an islet agonist. In type 1 diabetes, delivery of the immune tolerance agent prior to the islet agonist will theoretically preserve newly formed islets. Hypothetically, the optimal initiation of islet agonist treatment in patients with both new-onset and existing type 1 diabetes is at the time of the immune nadir after therapy with an immune tolerance agent. Exogenous insulin must be reduced because glucose is critical to islet neogenesis, and new islet formation will not occur in conditions of hypoglycemia. Formation would also not optimally occur under extreme hyperglycemia (103).

It is important to consider that much controversy remains regarding the use of rodent models to study diabetes. Despite successes that have led to many extraordinary antidiabetic therapies, unpredicted outcomes have occurred in humans that were not seen in preclinical rodent trials. Conversely, a lack of success in rodents may not necessarily predict the outcomes in humans, especially when studying human peptides in rodent models. Roep and Atkinson stated that “on a number of counts, we would argue that animal models have limited value when it comes to teaching us about Type 1 diabetes in humans” (104).

An immune tolerance agent will not be necessary to reverse type 2 diabetes, but the maintenance of new islets will require risk factor modifications that impact beta cell apoptosis. The current hypotheses of the origin of type 2 diabetes involve many factors, including genetics, inflammation, free fatty acids, and others, many of which can be environmentally modified. New islets will only be maintained by addressing disease origins. We hypothesize that glucagon-modulating agents such as dipeptidyl peptidase-4 (DPP-4) inhibitors and GLP-1 receptor agonists may have a synergistic effect with islet agonists.

Figures 4 and 5 show theoretical models for reversing type 1 and 2 diabetes, respectively.

**CONCLUSION**

The islets of humans are more complex than their rodent counterparts and likely reflect the evolution of human islets to maintain glucose homeostasis through both short and long periods of fasting and to adapt quickly to environmental and emotional stressors. Increasing beta cells within islets is critical to restoring glucose homeostasis in diabetic patients.

Many studies are currently ongoing, including intravenous delivery of mesenchymal stem cells to type 1 patients. Preclinical studies in rodents have demonstrated the potential ability to convert alpha cells into beta cells. The ability to stimulate the insulin receptor with a monoclonal
Fig. 4. Theoretical model for reversal of type 1 diabetes. This figure presents a model for reversing type 1 diabetes based upon the delivery of an immune tolerance agent prior to administration of an islet agonist agent. Based on a rise of 27% ($P = .0057$) in stimulating C-peptide among pre-existing type 1 patients by day 56 of treatment with an Islet Agonist (57), the potential exists to further improve endogenous insulin production if an immune tolerance agent is utilized prior to the administration of an Islet Agonist. After significant islet population is restored, it may be possible to maintain patients without exogenous insulin by using Islet Agonist and immune tolerance agent boosters.

Fig. 5. Theoretical model for reversal of type 2 diabetes. This figure represents a schematic for the potential reversal of type 2 diabetes utilizing an islet agonist with the ability to restore euglycemia if lifestyle and/or type 2 diabetes agents are utilized.
islets may also improve the use of exogenous insulin in the future. There are two Reg peptide therapies currently in clinical trials, based on the hypothesis that Reg is a key initiating factor for islet neogenesis.

Future therapies focusing on the generation of islets from adult progenitor cells within the human adult pancreas may hold the key to reversing diabetes, with the caveat that patients with type 1 diabetes will likely require treatment with an immune tolerance agent to protect new islets, and type 2 patients will require lifestyle modifications and/or medication to protect newly formed islets.

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DISCLOSURE

Dr. Claresa Levetan is a shareholder in CureDM Holdings LLC, and is a founder of Perle Bioscience, but is not a shareholder. Ms. Pierce has no multiplicity of interest to disclose.

REFERENCES


15. Christiansen JS. What is normal glucose? – Continuous glucose monitoring data from healthy subjects. Presented at: 42nd Annual Meeting of the European Association for the Study of Diabetes; September 14-17, 2006; Copenhagen, Denmark.


104. Roep BO, Atkinson M. Animal models have little to teach us about Type 1 diabetes: 1. In support of this proposal. *Diabetologia*. 2004;47:1650-1656.