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Inadequate β-cell mass is essential for the pathogenesis of type 2 diabetes

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Abstract

For patients with type 1 diabetes, it is accepted among the scientific community that there is a marked reduction in β-cell mass; however, with type 2 diabetes, there is disagreement as to whether this reduction in mass occurs in every case. Some have argued that β-cell mass in some patients with type 2 diabetes is normal and that the cause of the hyperglycaemia in these patients is a functional abnormality of insulin secretion. In this Personal View, we argue that a deficient β-cell mass is essential for the development of type 2 diabetes. The main point is that there are enormous (≥10 fold) variations in insulin sensitivity and insulin secretion in the general population, with a very close correlation between these two factors for any individual. Although β-cell mass cannot be accurately measured in living patients, it is highly likely that it too is highly correlated with insulin sensitivity and secretion. Thus, our argument is that a person with type 2 diabetes can have a β-cell mass that is the same as a person without type 2 diabetes, but because they are insulin resistant, the mass is inadequate and responsible for their diabetes. Because the abnormal insulin secretion of diabetes is caused by dysglycaemia and can be largely reversed with glycaemic control, it is a less serious problem than the reduction in β-cell mass, which is far more difficult to restore.

The relationship between β-cell mass and function is important for understanding the normal metabolic state and pathogenesis of diabetes. Clearly the hyperglycemia of both type 1 and 2 diabetes (T1D and T2D) results from the failure of β cells to provide enough insulin. With T1D β cells are depleted by autoimmune killing and with T2D there is a combination of insufficient β-cell mass and function to meet the demands of insulin resistance. While some have downplayed the importance of loss of β-cell mass [1–3], we think it is of critical importance. A fundamental point is that β-cell mass of an individual with T2D may be in the "normal" range but still be insufficient, which results in climbing blood glucose levels that have adverse effects on β cells, this process being called glucotoxicity [4–8]. Fortunately, the effects of glucotoxicity can be largely reversed by normalization of glucose levels with treatment. However, the only way in which β-cell mass can currently be restored in either

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Author contributions

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Declaration of interests

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T1D or T2D is by pancreas or islet transplantation. The goal of this perspective is to explore the relationships between β-cell mass and function and to explain why deficiency of mass is so important to the pathogenesis of diabetes.

The trap of thinking that β-cell mass is normal in T2D

β-cell mass in human pancreas can be measured by volumetric morphometry and roughly consists of 250 thousand to one million pancreatic islets or around 250 million to one billion β cells [9,10]. In a study of 52 non-diabetic adult humans β-cell mass varied considerably ranging from 0.25 to 1.5 gm [11]. When measured in in either obese of non-obese T2D, there is also great variation and considerable overlap with the non-diabetic controls, but β-cell mass as a group in T2D is clearly lower [11–13]. Because of the overlap of the groups, some conclude that many people with T2D have a normal β-cell mass. However, we argue that this conclusion is incorrect, in that a given β-cell mass in T2D may be within the range of non-diabetic subjects, but it is not normal for that individual. A way to understand this is to appreciate the huge variability of insulin sensitivity and insulin secretion in a normal population. The insulin sensitivity index (S_i; x 10^{-5} min^{-1}/pM) can vary between 2 and 20 (Figure 1) [14]. Likewise, fasting plasma insulin levels in the same population can vary between 20 and 200 pM. In spite of this remarkable variation, fasting plasma glucose levels are normally maintained within a very narrow range of about 70–90 mg/dl, this being largely driven by the β-cell set-point for secretion. Although we cannot yet measure β-cell mass in living subjects, one can predict that insulin sensitivity, secretion and β-cell mass are well correlated in a normal non-diabetic population.

Let us consider several examples. An individual who is insulin sensitive with a low β-cell mass can produce enough insulin to avoid diabetes, and someone with insulin resistance from any of a variety of causes can avoid diabetes because they have a high enough β-cell mass to produce sufficient insulin. What then accounts for the large differences in β-cell mass? There is good reason to think that insulin resistance is the cause of the increased mass, which probably takes place earlier in life when there is more growth potential [15]. Thus, we can guess that a child with insulin resistance will have a better capacity for increasing β-cell mass than an individual who may have been thin and active early in life, but then became sedentary and obese later in life. Diabetes then develops when β-cell mass is inadequate for whatever degree of insulin sensitivity is present. This inadequate β-cell mass could result from insufficient expansion of β-cell mass or increased rate of β-cell death. There must be some people who have reduced capacity for β cell expansion early in life due to genetic and other factors such as intrauterine growth retardation and childhood illness. Others are likely to have an increased rate of β cell death relative to birth that is caused by a great variety of possibilities including ER stress, IAPP toxic oligomers, inflammation, oxidative stress, glucotoxicity, “overwork”, etc. The importance of lipotoxicity has recently be called into question [16]. Questions have also been raised about whether transdifferentiation of α cells to β cells significantly influences β-cell mass [17–20], but these need further study. Taking all of this together, many with T2D will indeed have a β-cell mass that overlaps with the normal range, but for each of those individuals with hyperglycemia the mass is insufficient.

Arguments are also made that individuals with T2D with reduced β-cell mass at autopsy do not really have a reduced number of β cells as some β cells are not identified because they are dedifferentiated and depleted of insulin content [1,2]. Thus, they are not identified with immunostaining for insulin and are therefore considered to be "empty" β cells. However, the weight of evidence indicates that such islet cells that do not contain insulin or other hormones are few in number, being in the range of 1–3%, thus not having a significant effect on measured β-cell volume [21,22]. Another weakness of the empty β-cell argument is that islets are reduced in size in T2D [23], which is what would be expected with preferential loss of β cells, but not if β cells had simply lost their insulin content.

Another issue is whether there is enough reduction in insulin content of β cells to be rate-limiting for secretion. This has been studied with the conclusion that the insulin content per gram of human pancreas in T2D is reduced by only about 30% [11,24], which should have little if any impact on secretion.

Then taking the argument further that people with T2D have a problem with β-cell function but not with mass begs the question of how do the β cells become dysfunctional and dedifferentiated? Abundant data indicates that inadequate mass comes first, which allows glucose levels to rise, thereby subjecting β cells to the abnormal glucose environment that causes glucotoxicity with its accompanying phenotypic changes and impaired insulin secretion [4,6]. We are not aware of any alternative mechanism that would cause the impaired function. Increased demand caused by worsening insulin resistance does not provide a good explanation because as long as glucose levels are controlled β cells continue to have very good secretory function [25,26]. Questions are raised about intrinsic β-cell defects that might exist independently of hyperglycemia. Many of the GWAS genes linked to T2D are related to β-cell function [27], but with the exception of a few types of MODY [28] we are not aware of these being associated with markedly disrupted GSIS as long as glucose values remain in the truly normal range. Thus, the β-cell functional changes of both types 1 and 2 diabetes appear to be largely driven by glucotoxicity rather than by genetics.

Variability of β-cell function as it relates to mass

For any individual with a given β-cell mass, we know that the chronic output of insulin can vary greatly. Just increasing carbohydrate intake for three days will increase insulin secretion [29] and creating insulin resistance by giving nicotinic acid for two weeks will do the same [30], yet in neither situation would there be a meaningful increase in β-cell mass. With the insulin resistance of obesity, a given β-cell mass chronically secretes more insulin. β-cell mass as determined from study of cadaver pancreases is increased in obese subjects, but only modestly, with estimates being only about 20–50% more than that of normal weight individuals [11,12,31]. Yet, the rate of insulin secretion over a 24-hour period is 100% more than normal [25,26].

Glucotoxicity is another example of how insulin secretion from a given mass of β cells can vary enormously. We know that even very modest elevations in glucose are associated with and probably cause obliteration of first-phase glucose-stimulated insulin secretion and with further increases in glucose there is a marked loss of insulin secretion in response to not only

glucose alone but also to glucose potentiation of insulin secretion by other secretagogues such as arginine or isoproterenol [4,32–36]. Fortunately, the effects of glucotoxicity are largely reversible. We know that insulin secretion can be rapidly and dramatically improved after gastric bypass [37] as well as by aggressive insulin treatment of T2D [38]. We also know that insulin secretion is greatly improved when individuals with new-onset T1D enter a partial remission or "honeymoon" phase [39].

To understand variability of secretion, β-cell heterogeneity must also be considered. This heterogeneity has been studied for many years [40,41], but is now much better understood [42–47]. We can now appreciate that at any chronological age of a person or animal, there are β cells that are young, old, senescent or dying and that the proportions of these change over time. Not only do β cells differ, but islets do as well. Thus, in human islets the overall ratio of β cells to α cells has been reported to be 2.4/1 but there can be great variability between islets, with some islets consisting mostly of α cells or, vice versa, mostly of β cells [48,49]. In addition, there can be great variation of aging markers between islets; for example, in old mice the aging marker insulin-like growth factor receptor 1 (IGFR1) can be present as determined by immunostaining in most of the β-cells in one islet and completely absent in β cells in another islet from the same pancreatic section [42]. It seems likely that secretion from these different kinds of β cells will vary considerably.

The increased secretion driven by insulin resistance could mean that most β cells increase their insulin secretion but in addition, that there is probably a group of less active cells that are recruited. In rats, a population of inactive islets have been identified using markers of hypoxia that might be considered "sleeping islets" [50,51]. When demand for secretion was increased by partial pancreatectomy, some of these islets became better oxygenated and functional, and when demand was reduced, the number of these less active islets increased. For technical reasons it has not been possible to show that this phenomenon is occurring in humans.

Expansion of β-cell mass: Replication and neogenesis

In early life insulin secretion must increase to meet the demands of growing organs that require insulin. While increased insulin secretion from existing cells can contribute to this demand, expansion of β-cell mass is required, and this results from a combination of β-cell neogenesis and self-duplication [6,15,52]. We think the neogenesis comes mainly from the normal growth of the pancreas, such that when new pancreatic lobes form they contain new islets [53]. When there is increased demand from the insulin resistance in rodents, the increase in β-cell mass appears to come mainly from self-replication. This can best be appreciated by studies of db/db mice [54], Zucker Diabetic Fatty (ZDF) rats [55], and from the genetic induction of insulin resistance in mice by such maneuvers as knocking out insulin receptors in the liver [56]. Support for the key contribution of self-replication comes from the impressive increase in islet size due mainly to increased β-cell numbers without similar expansion of other islet cell types such as α cells. The capacity of β cells to replicate has been studied mostly in relatively young rodents, so we must be careful about extrapolations to human. Nonetheless, we know that, as is the case for rodents [57,58], the potential for replication in humans falls with age [15]. Yet it has become clear that a low level of replication continues

later in life[5960] and the expansion of beta cell growth in adult humans is supported by increased relative volume of beta cells and increased islet size in in non-diabetic subjects with insulin resistance [61].

One can ask if glucose-driven β-cell hyperplasia can be found in humans during the progression to T1D but very few pancreases end up being available for the possibility to be properly studied. However, there was a very provocative report in 1907 of a 10-year old boy who died of diabetes [62]. At autopsy while there was an overall decrease in beta cell volume per field, a population of islets was found that had a volume about double that measured in islets of 5 control subjects. We know that the destructive process of islet inflammation is very patchy in that the β-cells of some islets are completely destroyed while β cells in many other islets look perfectly normal [63]. Thus it seems plausible that as overall β-cell volume fell the rising glucose levels could push "healthy" islets of a child to develop this β-cell hyperplasia. This concept is further supported by the study of pancreases from deceased subjects with T1D by Gepts in 1965 [64]. For subjects between the ages of 8–20 those with recent onset T1D ("acute juvenile diabetes") had higher median islet area than non-diabetic controls, 8·8 ± 0·8 versus 5·5±0·9 $\mu^2 \times 10^3$ (p= 0·013). Similar findings were observed by Maclean and Ogilvie [65] and Cecil [66].

In spite of earlier doubts by some, we now know that substantial postnatal islet neogenesis takes place [6,67]. Pancreas growth in early life occurs partly through the formation of new lobes containing new islets. Neogenesis also occurs during pancreas regeneration as has been well documented with partial pancreatectomy studies in rodents [68], and It appears that many if not most of these new islets developed as new pancreatic lobes were forming [53]. There are various other conditions in which neogenesis appears to be stimulated. In obese subjects there are increased numbers of insulin stained cells in the ducts and some can be found to have coalesced with a budding-like appearance [12]. In addition, subjects with well-documented insulin resistance have increased numbers of cells in ducts with double-immunostaining for insulin and duct marker cytokeratin 19 (CK19) [61]. Moreover, a study of pancreases from subjects with impaired glucose tolerance and newly diagnosed T2D reported both increased numbers of insulin positive cells in pancreatic ducts and of single or small clusters of cells double positive for insulin and glucagon or somatostatin [69]. Pregnancy is associated with increased β-cell mass and there is evidence for a contribution from neogenesis [70,71]. There is good reason to think that the increase in β-cell self-replication in response to insulin resistance is driven by glucose metabolism. It has been shown with *in vitro* experiments that glucose can stimulate replication [72] and a reduction in replication is found in high fat fed mice with heterozygous knockouts of glucokinase [73,74]. However, the mechanisms responsible for enhanced neogenesis are poorly understood.

There is enormous interest in finding ways to regenerate β-cells either by stimulating replication or neogenesis. However, while there is exciting progress elucidating the mechanisms of β-cell replication [75] and the complexities of neogenesis [76], finding a path to the clinic remains challenging.

Correlation of β-cell mass with tests of insulin secretion and the concept of secretory reserve

Knowing that β cells have excess capacity for secretion fits with the concept of secretory reserve, this being secretion that can be employed when needed. This can be appreciated by employing the acute insulin response to arginine when glucose levels are acutely elevated (AIRmax), which in some but not all circumstances can be correlated with β-cell mass [77,78]. In particular, AIRmax has been shown to correlate well with the number of islets required for successful islet auto transplants. However, it may be that the AIRmax only measures insulin release from an available secretory component. To develop the argument about secretory reserve, let us assume that a normal individual with 100% β-cell mass secretes insulin at 50% capacity and therefore has 50% in reserve, the response to AIRmax would come from this readily available 50% compartment. This situation may be very different for an individual with an auto-islet transplant, whose transplanted islets might have little or no reserve capacity because the number of islets available for autotransplants is usually marginal. This could mean their secretory reserve component is depleted. It also seems likely that as T1D progresses the increased pressure for insulin secretion from a declining β-cell mass would deplete this reserve (Figure 2).

There are many situations in which the insulin secretory reserve compartment might be depleted. To meet the demands of insulin resistance insulin secretion is increased from a given mass of β cells through a combination of getting more secretion from less active cells and boosting secretion from already active cells. There must then be a point when recruitment is no longer possible, i.e., the secretory reserve is used up. Thus, in T2D insulin secretion is likely reduced by a combination of lost reserve and glucose toxicity from hyperglycemia. We know that glucose toxicity is largely reversible [38,79], perhaps best demonstrated in subjects with T2D who undergo gastric bypass surgery[37], and we expect that β-cell reserve could be restored meaning that major benefits could be obtained by lowering blood glucose levels as can be achieved with the many treatment options now available.

Evidence that the tipping point for β-cell mass is about 50%: Lessons from T2D and partial pancreatectomies

We know from multiple autopsy studies that of both lean and obese subjects with T2D have a reduction of β-cell mass in the range of 40–60% [11–13]. These data fit very well with what we have learned from partial pancreatectomies in humans and animals. There is no precise magic number for how much β-cell mass must be lost to develop diabetes, but if β-cell mass is 75% of normal, normoglycemia is maintained but when mass is 25% of normal, hyperglycemia can be expected. We have found that removing 90% of a pancreas of a young rat is a borderline situation in that at 14 weeks after the surgery, some of the rats are clearly diabetic while others have glucose values only slightly higher than normal, representing a rat equivalent of impaired glucose tolerance [80]. We have found that there is substantial β-cell regeneration in these rats such that β-cell mass 10–12 weeks after the surgery is about 40% of normal [68]. In dogs, surgical removal of 50% of the pancreas also resulted in glucose

intolerance [81], which fits with 50% loss of β-cell mass being an approximate tipping point. In a baboon study with varying degrees of diabetes induced by streptozocin, in vivo measures of β-cell function were markedly impaired when 40–50% of the β-cell mass was still present [33]. There have been a number of hemi-pancreas transplants done in humans such that individual donate about 50% of their pancreas to a recipient with T1D, but it has become clear that the donors have increased risk of developing diabetes. A follow-up study published in 2008 evaluated 15 donors who had hemi-pancreatectomies at the University of Minnesota between 1997 and 2003, with the finding that 43% had either glucose intolerance or diabetes [82]. Another study followed 37 patients after removal of about 50% of their pancreases for either benign or malignant neoplasms and found similar results [83].

There is great interest in whether regeneration of the endocrine pancreas occurs after partial pancreatectomy in humans. We know that beta cell regeneration occurs in young rats after partial pancreatectomy, but this capacity might be lost with age. This question was studied in individuals who had follow-up surgery after partial pancreatectomies for neoplasms; there was no evidence that β-cell regeneration had taken place [84].

Another issue is whether removal of the head versus the tail makes a difference because of differing distributions of β-cells. The conclusion that the tail of the pancreas has more islets than the head in part stems from the fact that uncinate lobe, which originates from the embryonic ventral anlage, has pancreatic polypeptide (PP) rich islets with fewer β cells. However, the uncinate lobe accounts for only about 10% of the pancreas [85]. The other 90% originates from the dorsal anlage, which includes that body and the tail. Studies of human pancreas indicate that the tail contains modestly more insulin per gram and a higher β-cell volume than the head [11,86].

What is the relationship between β-cell mass and function in the state of impaired glucose tolerance (IGT)?

The finding that obese individuals with impaired fasting glucose levels have a 40% reduction in β-cell mass [12] raises important questions about how this happens. A simple interpretation is that the increased demand caused by insulin resistance over many years has led to an unfavorable balance between rates of β-cell birth and death. We know that the stress of insulin resistance as elicited in mice by the insulin receptor antagonist S961 or a high fat diet leads to the appearance of markers of aging and senescence in β cells [42,43], although the association with cell death in this model has not yet been established. It will be difficult to use AIRmax or other tests of insulin secretion to obtain meaningful information about β-cell mass in IGT because there would be some glucotoxicity in play, even with very minor elevations in plasma glucose levels [32]. It seems likely that the reserve component of secretion is at least partially depleted.

Understanding changes in β-cell mass and function during the progression to T1D

For a typical case of T1D anti-insulin antibodies might appear at about age 2 followed by intensification of the autoimmune process such that at age 13 during puberty frank hyperglycemia occurs. There are reasons to think that β-cell mass could be in the range of 50% of normal at that time point because some of these individuals enter a “honeymoon” period with very good glucose control that can last for a few months. Interestingly, insulin responses to AIRmax prior to decompensation and probably afterwards during the honeymoon appear to be not very different than normal [39,87]. One way to explain this is that as β-cell mass gradually fell due to autoimmune destruction, there was increased pressure on the remaining β cells to secrete more insulin, which would come from both the hypothetical available component and the reserve component, although with time this reserve could be depleted. Thus, a subject on the cusp of developing hyperglycemia, but still normoglycemic, could have lost 50% of their β-cell mass but what is left would have no inactive reserve compartment. The residual cells would be fully active resulting in secretory responses similar to a non-diabetic subject.

How much β-cell mass is required for β-cell replacement therapy?

We now have considerable clinical experience with islets transplanted into the liver via the portal vein, yet only limited understanding of how much surviving β-cell mass is required to normalize glucose levels. Although techniques have improved enough so that insulin independence can more often be obtained with islets obtained from a single cadaver donor [88], there still is a major early loss of whatever number of β-cells are transplanted. Most of this loss is probably from hypoxic cell death which occurs within the first few days [89], and there is likely an additional significant contribution from the immediate blood-mediated immune response (IBMIR) [90]. These successful single donor transplants are usually achieved when recipients are small and insulin sensitive. Over the past 15 years people achieving insulin-independence typically had glucose values that were in the IGT range [91], which was in marked contrast to subjects receiving whole pancreas transplants, who typically have full correction of their glycemic control. Therefore, for most people who are insulin-independent with islet transplants, we can say that their functional β-cell mass is borderline, yet we can only speculate about their volumetric β-cell mass. Insulin secretion from transplant recipients with insulin-independence at the University of Pennsylvania was evaluated with AIRmax with the finding that responses were still only about 50% that of controls [92].

While we know that transplanted islets can function well in various locations, with the best studied being liver, kidney and muscle, work is still underway to understand how their function differs from islets at home in their native pancreas. However, based on a large experience with human and animal transplants, we can assume that islets in a transplant site function only modestly less well than those in the pancreas. We can also expect that what we have learned about reserve capacity for islets in the pancreas will be more-or-less the same for islets in a transplant site. Therefore, whether transplanting cadaveric islets or islet cells

derived from stem cells, the best results should be obtained if the volume of β cells in a transplant site is large enough to have reserve capacity. It seems unrealistic to expect any meaningful capacity for β-cell expansion, but having insulin secretory reserve should extend the longevity of graft function.

Conclusion

After decades of study of the relationship between β-cell function and mass in humans and animals as they relate to diabetes we can conclude that β-cell dysfunction is important but largely reversible. However, insufficient β-cell mass continues to be a more daunting problem.

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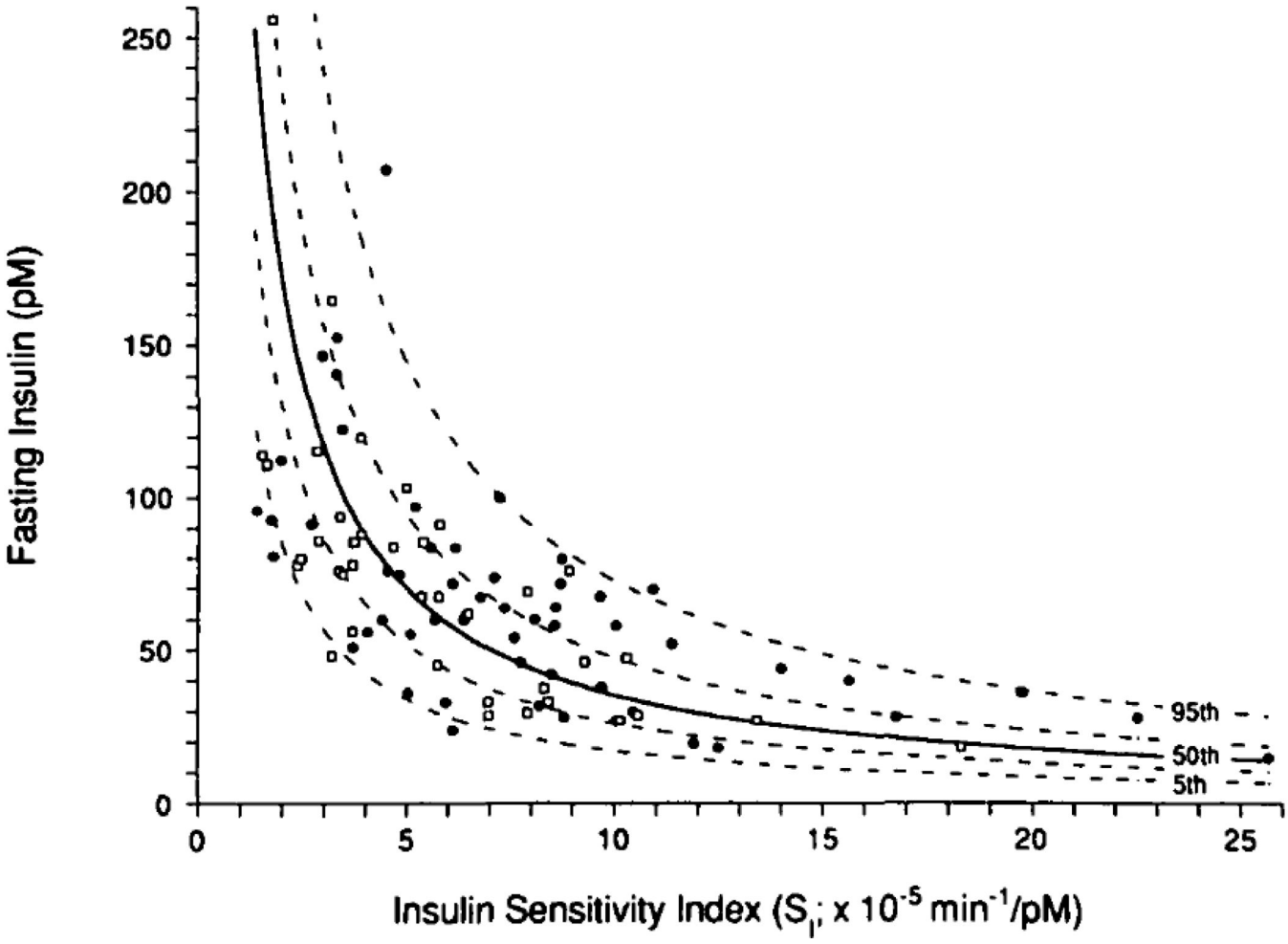

Figure 1. The relationship between S_1 and fasting insulin.

Study of 55 males and 38 females, shown by best fit relationship for the 5th, 25th, 75th and 95th percentiles. This demonstrates the marked variations in insulin sensitivity and fasting insulin levels in a non-diabetic population. Yet, there is an obvious correlation with insulin levels rising as insulin sensitivity decreases. Reproduced from Kahn et al. [14] with permission from the American Diabetes Association.

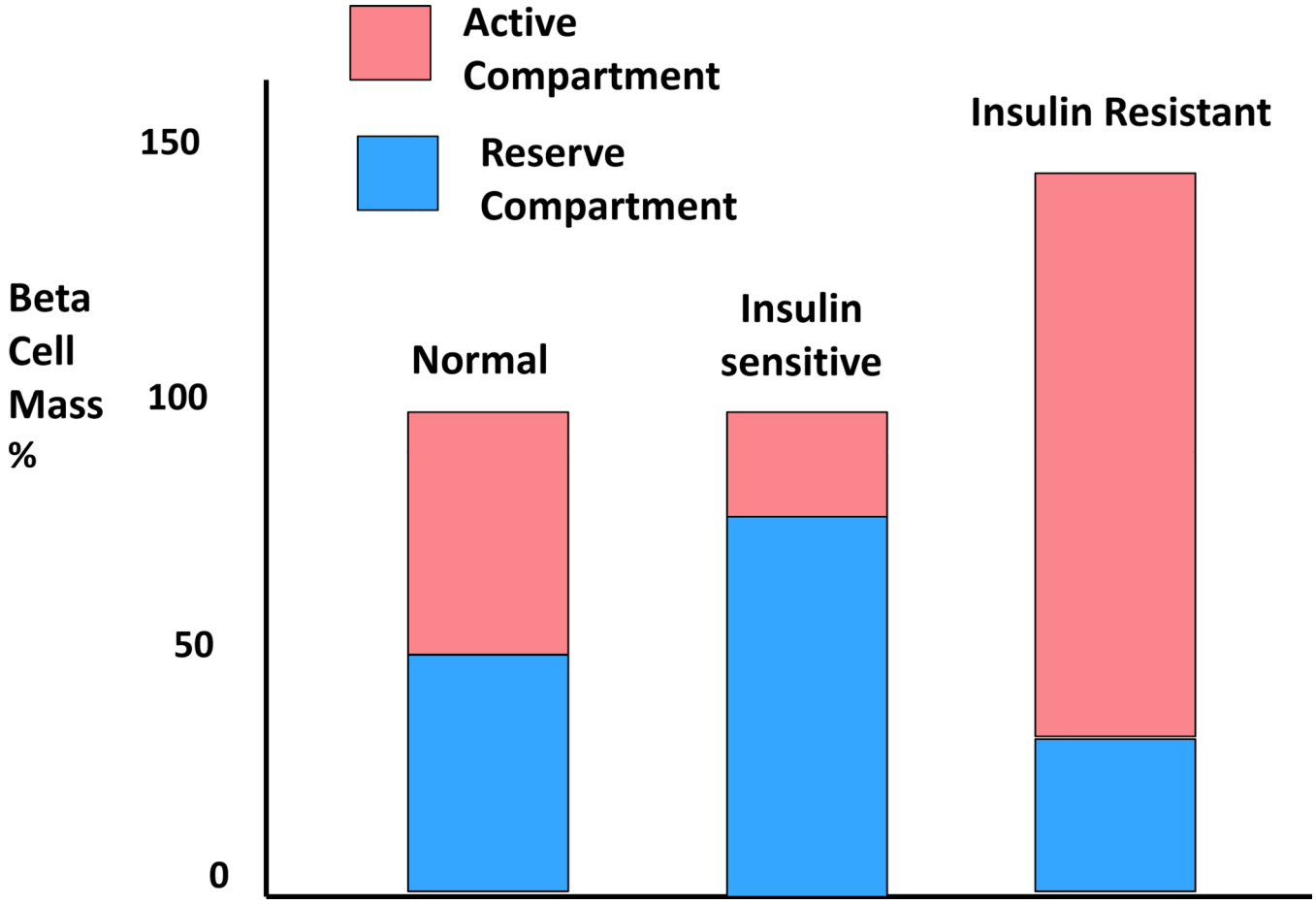

Figure 2. Hypothetical secretory reserve concept.

This figure depicts the activity of a hypothetical insulin secretory reserve compartment with changes that may occur with differences in insulin sensitivity or with a fall in β-cell mass with T1D. The β-cell mass of the Y-axis could represent either actual mass or effective mass, or a mixture thereof.