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Relationship between β-cell mass and diabetes onset

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Abstract

Regulation of blood glucose concentrations requires an adequate number of β-cells that respond appropriately to blood glucose levels. β-Cell mass cannot yet be measured in humans *in vivo*, necessitating autopsy studies, although both pre- and postmorbid changes may confound this approach. Autopsy studies report deficits in β-cell mass ranging from 0 to 65% in type 2 diabetes (T2DM), and ~70–100% in type 1 diabetes (T1DM), and, when evaluated, increased β-cell apoptosis in both T1DM and T2DM. A deficit of β-cell mass of ~50% in animal studies leads to impaired insulin secretion (when evaluated directly in the portal vein) and induction of insulin resistance. We postulate three phases for diabetes progression. Phase 1: selective β-cell cytotoxicity (autoimmune in T1DM, unknown in T2DM) leading to impaired β-cell function and gradual loss of β-cell mass through apoptosis. Phase 2: decompensation of glucose control when the pattern of portal vein insulin secretion is sufficiently impaired to cause hepatic insulin resistance. Phase 3: adverse consequences of glucose toxicity accelerate β-cell dysfunction and insulin resistance. The relative contribution of β-cell loss versus β-cell dysfunction to diabetes onset remains an area of controversy. However, because cytotoxicity sufficient to induce β-cell apoptosis predictably disturbs β-cell function, it is naïve to attempt to distinguish the relative contributions of these linked processes to diabetes onset.

Keywords

β-cell apoptosis; β-cell mass; pulsatile insulin secretion; type 2 diabetes; type 1 diabetes

Introduction

Diabetes mellitus is defined by hyperglycaemia. In health, blood glucose levels are maintained within a narrow range, primarily by the actions of the hormone insulin. Insulin is released by pancreatic β-cells at an appropriate rate in response to circulating glucose concentrations, the response being modulated by other factors including other circulating nutrients, islet innervation and incretin hormones [1]. Insulin maintains glucose concentrations by constraining the rate of hepatic glucose release to match the rate of glucose clearance [2].

Therefore, regulation of blood glucose concentrations requires an adequate number of pancreatic β-cells that respond appropriately to blood glucose concentrations. The collective β-cell numbers are often referred to as the β-cell mass, and the appropriate release of insulin

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by pancreatic β-cells to circulating glucose as β-cell function, the terms that will be used hereafter in this review.

β-Cell Mass by Autopsy

Because there is as yet no sensitive or specific measure of β-cell mass *in vivo*, there are limited data available on β-cell mass in humans. The data that are available have been derived primarily from autopsy studies [3,4–15]. Autopsy studies to quantify β-cell mass have major limitations, which are listed below. The pancreas is one of the first organs to undergo autolysis [16]. There may be changes in β-cell mass as a consequence of the final illness leading to death, particularly if this is prolonged [17,18]. The clinical information available in relation to autopsies is often limited and unreliable. As many as 40% of patients in hospital with type 2 diabetes (T2DM) are undiagnosed [19]. The extent of the pancreatic dissection at autopsy is usually limited to the pancreatic tail, so that whole pancreas is often not available. When pancreas is available, the reliability of measured pancreatic weight is questionable given the variable amount of interlobular pancreatic fat [20]. There is no means to retrospectively measure insulin sensitivity or insulin secretion to relate to the measured b-cell mass in different individuals. There is no realistic means to obtain pancreas at autopsy from individuals during the presymptomatic phase of declining β-cell function in either type 1 diabetes (T1DM) or T2DM. These limitations not-withstanding, the available data on β-cell mass in diabetes by autopsy are reasonably consistent [3–5,9–13,15,21]

β-Cell Mass in Non-Diabetic Humans

Measured β-cell mass in non-diabetic humans via autopsy studies shows a wide range between individuals, with a mean of approximately 0.8 g [22]. β-Cell mass grows rapidly in childhood, primarily through the mechanism of β-cell replication so that the adult β-cell mass is almost accomplished by 5 years of age [22]. Perhaps surprisingly there is not an obvious secondary phase of growth of β-cell mass in humans during the rapid period of somatic growth in adolescence, perhaps providing an explanation for the peak incidence of both T1DM and T2DM in this age range [23,24]. The wide range in β-cell mass in adults becomes apparent after the childhood growth phase, implying that the rate of growth of β-cell mass during this period has a major impact on the ultimate β-cell mass in adults. In mice, β-cell mass is in part determined by the number of embryonic progenitor cells [25].

It is plausible that the wide range of β-cell mass in adult humans depends in part on the islet progenitor cell pool and the status of the embryo during the period of rapid expansion of differentiated endocrine cells during fetal development. Also, because a number of genes known to regulate pancreatic β-cell cycle have been linked to T2DM in genome-wide association scans [26], it is plausible that part of the variance in β-cell mass in adult humans may be genetically determined.

β-Cell Mass in T1DM

T1DM is believed to be caused by an autoimmune mediated decline in β-cell function and mass, leading eventually to insulin deficiency [27]. Prospective studies of high-risk individuals have shown a progressive decline in β-cell function over many years preceding the onset of hyperglycaemia [28]. At present there is no way of determining to what extent this loss of β-cell function is due to loss of β-cell mass and/or is exclusively due to loss of β-cell function. Indeed, given the fact that cytotoxicity sufficient to induce β-cell apoptosis will predictably impair cell function, it is naïve to attempt to separate these two highly dependent processes. Transient independence from a need for insulin therapy (the ‘honeymoon period’) in many patients shortly after induction of insulin therapy implies a major component of impaired β-cell function superimposed on β-cell loss [29].

Likewise studies of insulin secretion in adults with recent-onset T1DM have revealed residual insulin secretion that was estimated to be approximately 40% of normal [30]. Autopsy studies of β-cell mass in people with recent-onset T1DM have reported a β-cell mass of approximately 10% of normal [9–13,15] (table 1). These studies have usually been carried out in patients who died of diabetic ketoacidosis, and so have a potential systematic bias in favour of cases with a lower β-cell mass at diabetes onset.

The rate of decline in β-cell function (and probably mass) is greater in children with T1DM than adults [31,32], and eventually in both groups there remains minimal insulin secretion or β-cell mass (approximately 1% or less of normal) [3 6,8,33,34]. The decline in both β-cell mass and β-cell function in T1DM (presumably in consequence of cytotoxic T cells) serves to emphasize the interrelated nature of β-cell dysfunction and loss.

β-Cell Mass in T2DM

The onset of T2DM is poorly defined. It has been estimated that most patients with T2DM are not diagnosed until ~10 or more years after disease onset [35]. As in T1DM, prospective studies of T2DM indicate a progressive decline in β-cell function preceding relatively abrupt diabetes onset (figure 1) [36–38]. However there is no means to establish to what extent, if at all, this decline in β-cell function is due to impaired β-cell mass or simply due to declining function.

Autopsy studies of patients with T2DM have revealed a β-cell mass of ~0–65% compared to body mass index-matched controls (figure 2, table 2) [3–5,7,21]. There is also increased β-cell apoptosis compared to controls [4,39], implying that the loss of β-cell mass is likely progressive unless there is concurrently increased β-cell formation. Given the wide range of β-cell mass in non-diabetic humans, the possibility exists that vulnerability to T2DM is based in part upon the β-cell mass accomplished as an adult. In the face of insulin resistance, those individuals with the lowest β-cell mass would have the highest requirement per β-cell for proinsulin and proislet amyloid polypeptide synthesis and processing.

Because β-cell apoptosis in T2DM is characterized by endoplasmic reticulum stress [40,41], a high demand state per β-cell is a plausible precipitating factor in subjects prone to developing T2DM. Moreover, in the face of the unfolded protein response proinsulin synthesis would be constrained [42], possibly contributing to impaired insulin secretion. Additionally, once diabetes ensues, hyperglycaemia per se also likely contributes to both loss of β-cell mass and function [43]. Factors that have been implicated as mediators of this include oxygen free radical toxicity [44]. It has been postulated that excess availability of glucose to the cell leads to increased mitochondrial reactive oxygen species formation which is associated with decreased insulin and PDX-1 mRNA expression, impaired glucose-stimulated insulin secretion and presumably β-cell apoptosis, as recently reviewed in detail [45].

Although there is no way to measure β-cell mass in individuals prior to developing diabetes, obese individuals with impaired fasting glucose (IFG) had an ~50% deficit in β-cell fractional area compared to obese non-diabetics (figure 2) [4]. One explanation for this is that these individuals had IFG because of a low β-cell mass. Alternatively they may have been developing T2DM with a 50% deficit in β-cell mass reflecting a point of inflection between sufficient and insufficient β-cell mass in the face of obesity [46]. It is of interest that people who had a 50% pancreatectomy when acting as living hemi-pancreas donors had a relatively high risk of subsequently developing diabetes by the current blood glucose classification of diabetes [47–49]. On the other hand, most surgical studies on post-partial pancreatectomy suggest that a much higher resection percentage is required to cause diabetes, although follow-up in these studies appears to be short-term for the most part [50].

Animal Studies

Until it is possible to quantify β-cell mass *in vivo*, establishing its role at the onset of T2DM is not possible. For now, it is necessary to seek some guidance from animal studies. However, caution is required when extrapolating findings in animal studies to humans.

Most animal studies in relation to diabetes have been carried out in mice and rats, usually less than one year of age [51–54]. However, in contrast to humans, rodents have a high capacity for pancreas regeneration after partial pancreatectomy and a higher β-cell turnover as adults than in humans or large animals [55–57]. Other studies have been carried out in non-human primates [58], dogs [59–62] and pigs [63, 64]. Given the very high capacity for β-cell formation in young animals (and humans) any intervention seeking to decrease β-cells to find 'the threshold' for diabetes onset should ideally performed after the growth phase for β-cell mass is completed.

A number of studies meet this criteria [59–63,65] (table 3). With an approximately 50% pancreatectomy in dogs, in the short-term, animals show IFG and glucose intolerance and then develop diabetes during the subsequent year (figure 3) [61,62]. In the short-term they had impaired glucose-mediated insulin secretion (by meal or infusion) [59–62]. Because most insulin is secreted in discrete secretory bursts at four-minute intervals, not surprisingly these were also decreased in the fasting state and in particular after glucose stimulation [62]. However because first pass hepatic insulin extraction is directly proportional to the amplitude of portal vein insulin pulses [62,66,67], systemic insulin concentrations did not reflect this marked secretory defect, cautioning that reliance on systemic insulin concentrations to evaluate insulin secretion likely underestimates early defects. Unexpectedly partial pancreas resection in dogs led to insulin resistance [62]. A comparable decrease in β-cell mass (50%) in rats transgenic for human islet amyloid polypeptide (HIP rats) also leads to hepatic insulin resistance and IFG [68].

One possible explanation for this finding is that the impaired pulsatile delivery of insulin to the liver leads to hepatic insulin resistance. Preliminary studies (Matveyenko and Butler, unpublished) support this hypothesis. Prior studies delivering pulsatile insulin into the systemic circulation suggested that insulin pulses are more efficacious than non-pulsatile insulin, but these pulses were too small to realistically recapitulate portal insulin delivery [69–72]. If the postulate that abnormal pulsatile insulin delivery to the liver leads to hepatic insulin resistance is correct, once a threshold-low β-cell mass is reached, attenuation of insulin secretory bursts delivered to the liver would further exacerbate insulin deficiency and the resulting positive cycle between increasing insulin demand and declining β-cell function would be expected to lead to a relatively rapid loss of glycaemic control (figure 1). This is consistent with long-term prospective studies of people at risk of T2DM, which illustrate that blood glucose values do decompensate relatively rapidly (figure 1) [37,38].

Summary

Maintenance of blood glucose concentrations within a narrow range despite wide fluctuations in the rate of glucose entry (for example meals) and clearance (for example exercise) requires a complex system of regulation. Primacy in this regard falls to regulated insulin release in response to glucose levels, which in turn constrains hepatic glucose release and enhances glucose clearance [2].

By definition in diabetes this regulation fails. In both T1DM and T2DM there is a deficit in β-cell mass [3–6,9–13,15,21], impaired glucose-mediated insulin secretion [30,36], and insulin resistance [73]. The relative contribution and order that these changes develop are a matter of controversy. In view of the heterogeneous nature of both T1DM and T2DM, it is

likely that their relative contributions and timing differ widely between individuals. Until a sensitive and specific method is developed to quantify β-cell mass *in vivo*, it is not possible to know the loss of β-cell mass at disease onset. Because loss of mass through cellular attrition surely involves damaged and therefore dysfunctional cells, from a pragmatic point of view it is reasonable to predict that loss of β-cell function precedes loss of mass.

Finally, we predict here that the point of inflection of blood glucose levels is in part due to hepatic insulin resistance developing as a consequence of the abnormal delivery pattern of insulin (attenuated insulin pulses) to the hepatic sinusoid. Further studies are required to test this hypothesis.

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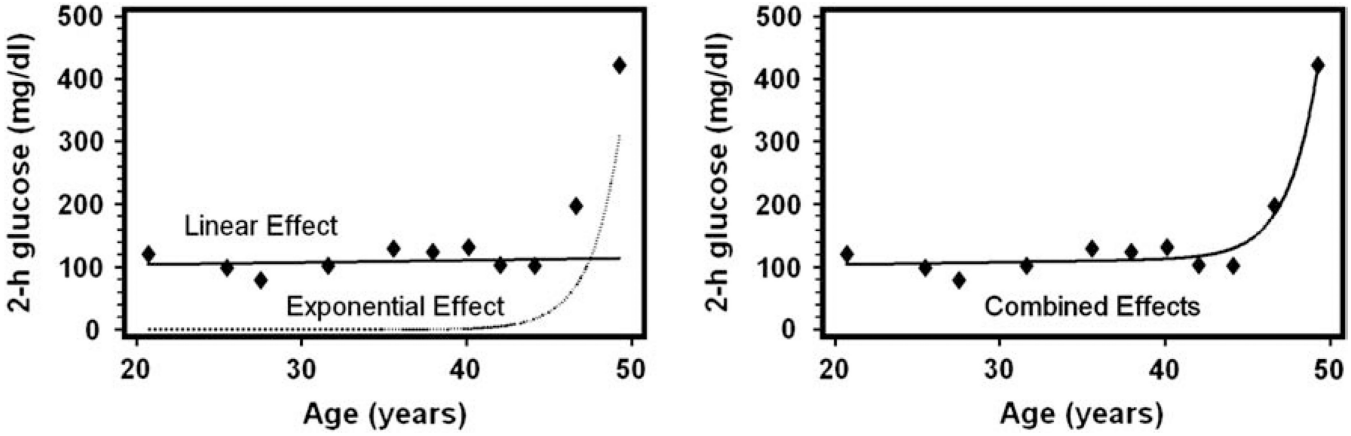

Fig. 1.

Blood glucose values over the years prior to diabetes onset in prospective study. Glucose effects model. Copyright ©2007 American Diabetes Association. From Ref. [37]. Reprinted with permission from The American Diabetes Association.

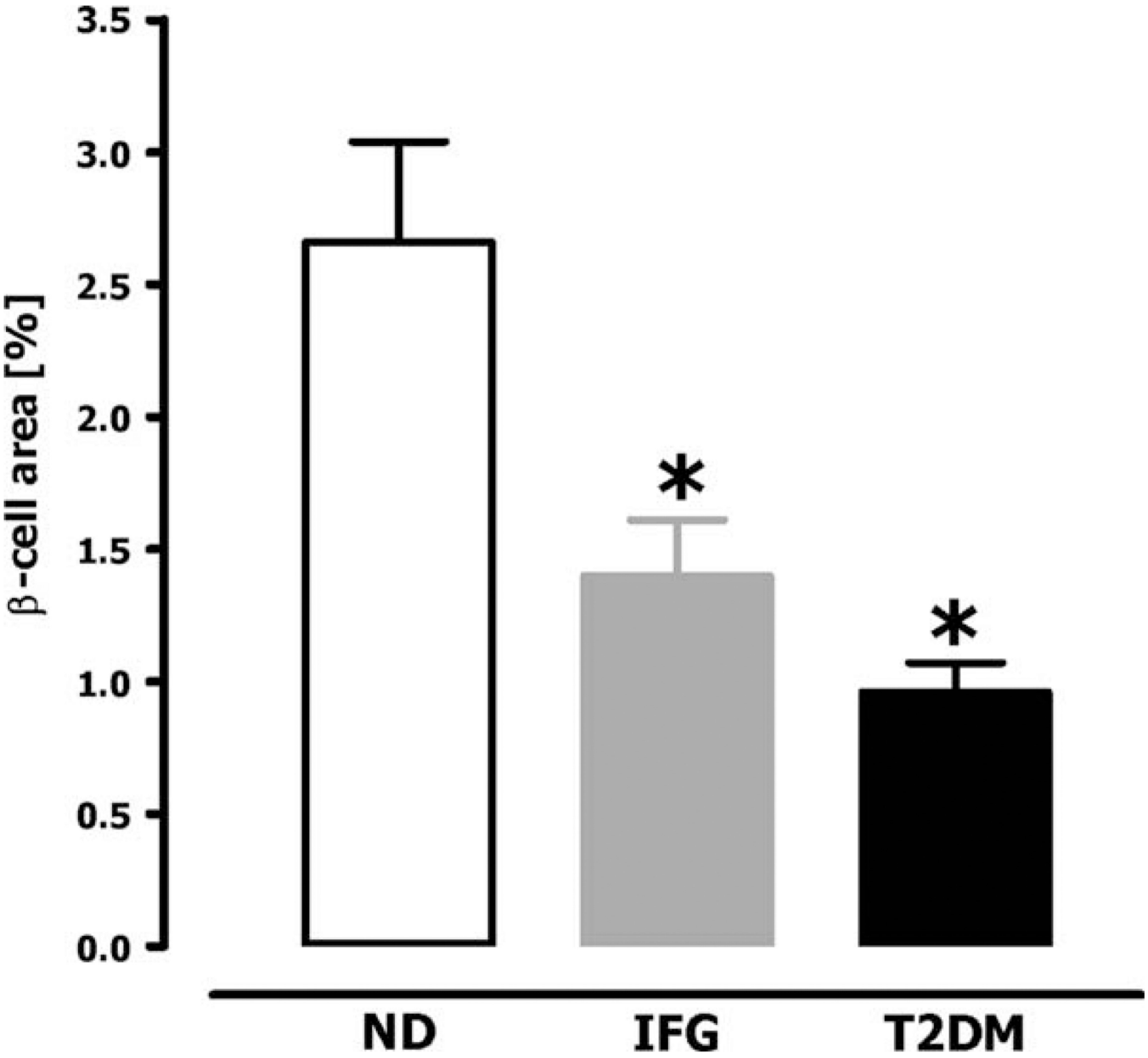

Fig. 2.
Fractional β-cell volume in obese humans [non-diabetic (ND), impaired fasting glucose (IFG) and type 2 diabetes (T2DM)]. Copyright © 2003 American Diabetes Association. From Ref. [4]. Reprinted with permission from American Diabetes Association.

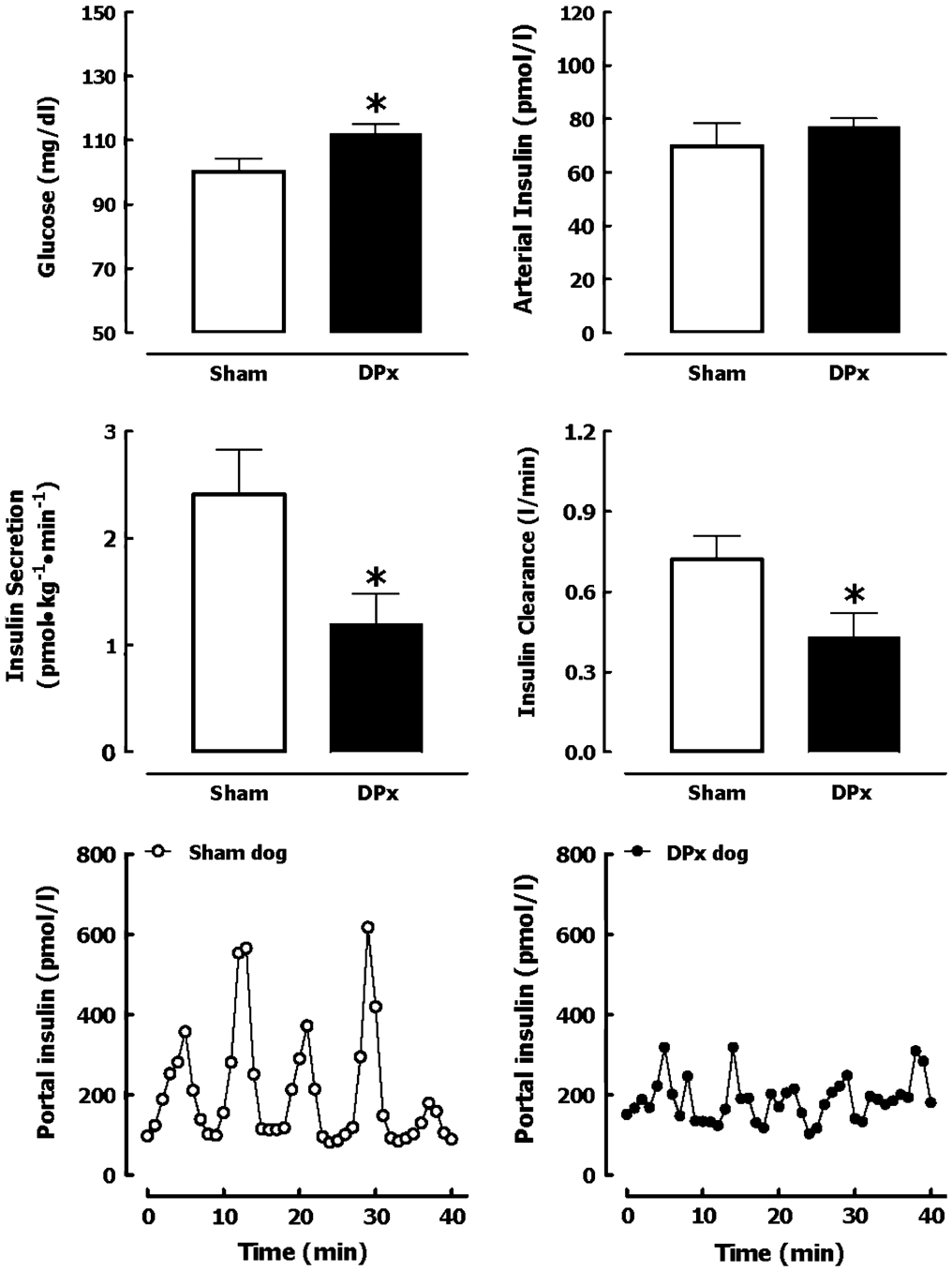

Fig. 3.

Fasting glucose and arterial insulin concentrations in sham-operated dogs and in dogs that underwent 50% pancreatectomy (DPx) (top panels). Corresponding deconvolved insulin secretion rate and insulin clearance rate (middle panels), Nand corresponding representative profiles of portal vein insulin concentrations (lower panels) in sham and 50% pancreatectomized dogs (DPx). Copyright © 2003 American Diabetes Association. From Ref. [62]. Reprinted with permission from The American Diabetes Association.

Table 1

Summary of autopsy studies that examined β-cell mass in patients with recent-onset T1DM

References	N (M/F)	Duration of diabetes	Reported decrease in β-cell mass in recent-onset T1DM
Gepts 1965 [12]	12/10 T1DM, 26 ND	3–180 days	~90–100% decrease in β-cell numbers per section area vs. ND controls
Gepts and De Mey 1978 [13]	7/9 T1DM	3–90 days	~90–100% decrease in β-cell numbers per section area vs. ND control
Kloppel et al. 1984 [9]	1 T1DM, 4 ND	~7 days	~80% decrease in β-cell volume vs. ND controls
Lernmark et al. 1995 [10]	1/1 T1DM, 9 ND	0–4 weeks	~80% decrease in β-cell islet volume density vs. ND controls
Butler et al. 2007 [15]	2/5 T1DM, 6/3 ND	0–3 years	~90% decrease in β-cell area vs. ND controls

Abbreviations: T1DM, type 1 diabetes; ND, non-diabetic.

Table 2

Summary of autopsy studies comparing β-cell mass in patients with T2DM vs. BMI-matched controls

References	N (M/F)	BMI	Reported decrease in β-cell mass in T2DM
Rahier et al. 1983 [7]	4/4 lean T2DM ; 3/5 lean ND	Unknown	No significant difference between T2DM vs. ND
Kloppel et al. 1985 [3]	1/5 obese T2DM; 3/1 obese ND; 7/1 lean T2DM; 4/3 lean ND	29 ± 2 (obese T2DM); 30 ± 1 (obese ND); 21 ± 1 (lean T2DM); 20 ± 2 (lean ND)	~50% decrease in β-cell volume in obese T2DM vs. obese ND~60% decrease in β-cell volume in lean T2DM vs. lean ND
Sakuraba et al. 2002 [21]	10/4 lean T2DM; 10/5 lean ND	21 ± 3 (lean T2DM); 21 ± 3 (lean ND)	~30% decrease in β-cell mass vs. ND controls
Yoon et al. 2003 [5]	15/10 lean T2DM; 10/9 lean ND	22 ± 4 (lean T2DM); 23 ± 3 (lean ND)	~50% decrease in β-cell volume in patients with BMI < 25
Butler et al. 2003 [4]	17/21 obese T2DM; 9/10 obese IFG; 15/16 obese ND; 7/9 lean T2DM; 7/10 lean ND	38 ± 1 (obese T2DM); 37 ± 2 (obese IFG); 36 ± 1 (obese ND); 22 ± 1 (lean T2DM); 23 ± 1 (lean ND)	~50% decrease in β-cell volume in obese IFG vs. obese ND; ~65% decrease in β-cell volume in obese T2DM vs. obese ND; ~40% decrease in β-cell volume in lean T2DM vs. lean ND

Abbreviations: IFG, impaired fasting glucose; T2DM, type 2 diabetes; ND, non-diabetic; BMI, body mass index.

Table 3

Summary of large animal models of reduced β-cell mass and their corresponding metabolic phenotype

Reference	Animal (age)	Extent of β-cell mass decrease	Metabolic phenotype
Matveyenko et al. 2006 [62]	Dog (1–3 years old)	~50% (pancreatectomy)	**i.** IFG and IGT **ii.** ~50–80% decrease in insulin pulse mass **iii.** 40% decrease in hepatic insulin clearance **iv.** 40% decrease in insulin sensitivity
Larsen *et al.* 2003 [64]	Gottengen pig (~1 year old)	~66% (NIA + STZ)	**i.** IFG and IGT **ii.** ~30–40% decrease in insulin pulse mass
Kjems *et al.* 2001 [63]	Gottengen pig (1–3 years old)	~60% (Aloxan)	**i.** IFG, Diabetes and IGT **ii.** ~50–90% decrease in insulin pulse mass **iii.** 40% decrease in hepatic insulin clearance
Stagner *et al.* 1991 [61]	Dog (1 year old)	~50% ventral lobe (pancreatectomy)	**i.** IFG, Diabetes and IGT 3–12 months after pancreatectomy **ii.** 50–90% decrease in fasting and IVGTT insulin levels **iii.** 60% decrease in glucose tolerance after IVGTT
Gotoh *et al.* 1989 [59]	Dog (adult >1 year old)	~35–65% (pancreatectomy)	**i.** 25–50% decrease in glucose tolerance during IVGTT **ii.** 25–50% decrease in insulin secretion during IVGTT
Marincola *et al.* 1984 [60]	Dog (adult >1 year old)	~80% (pancreatectomy)	**i.** IGT **ii.** 50% decrease in fasting portal vein insulin levels **iii.** 50–90% decrease in insulin secretion after IVGTT

Abbreviations: IFG, impaired fasting glucose; IGT, impaired glucose tolerance; IVGTT, intravenous glucose tolerance test; NIA, nicotinamide; STZ, streptozotocin.