

The effects of declining β -cell mass in the development of diabetes

BY QINGHUA WANG M.D., PH.D.

Over 2 million Canadians have diabetes and numerous epidemiologic studies indicate that the prevalence of prediabetic and diabetic populations will continue to increase both in Canada and worldwide.¹ This is partially because the prevalence of diabetes increases with older age and, as the general population continues to age, the number of people with diabetes will rise substantially. According to the World Health Organization (WHO), the number of people with diabetes worldwide is estimated to rise from 140 million at present to 300 million by the year 2025.^{1,2} The majority of people with diabetes (over 90%-95%) have type 2 diabetes, which occurs when the pancreas does not produce enough insulin and/or the body cannot effectively use the insulin that is produced. The landmark United Kingdom Prospective Diabetes Study (UKPDS) demonstrated that type 2 diabetes is a progressive disease and this progression results primarily from the declining function of pancreatic β -cells.^{3,4}

Glucose homeostasis

Under normal conditions, blood glucose levels are maintained within a narrow physiological range. This maintenance involves the endocrine pancreas, liver, peripheral insulin responsive tissues, muscle and fat (Figure 1). Insulin (produced by the pancreatic β -cells) and glucagon (secreted from the pancreatic alpha cells) are the major hormones that regulate blood glucose levels. When blood glucose levels rise (eg, after ingesting a meal), insulin secretion increases and acts on the liver to suppress glucose production. Furthermore, insulin stimulates glucose uptake by peripheral muscle and fat, thereby lowering blood glucose. Glucagon secretion is suppressed in response to increased blood glucose and, as a result, hepatic glucose production is reduced.

Insulin resistance

Insulin resistance is defined as the reduced response to insulin by peripheral tissues (ie, muscle and fat) that, in turn, impairs glucose transport into these tissues. This process is important, particularly in controlling glucose concentration after food ingestion.^{5,6} When insulin binds to its receptor at the cell surface, a pathway consisting of a number of important signaling molecules (including PI 3-K and Akt) is activated. As a result, the glucose transporter, GLUT4, translocates to the cell surface from an intracellular compartment in order to facilitate glucose uptake.^{5,7} Defects in glucose transport pathways may result in insulin resistance, leading to hyperglycemia and concomitant hyperinsulinemia. Hyperinsulinemia is generally a consequence of pancreatic β -cells producing more insulin in an attempt to combat the hyperglycemia that results from insulin resistance.^{8,9} In addition, insulin resistance can also occur in the liver where a normal concentration of insulin is not able to suppress hepatic glucose production.^{10,11}

As a consequence of insulin resistance, the body's requirement for insulin is typically increased. In the early stage of insulin resistance, blood glucose levels can generally be main-



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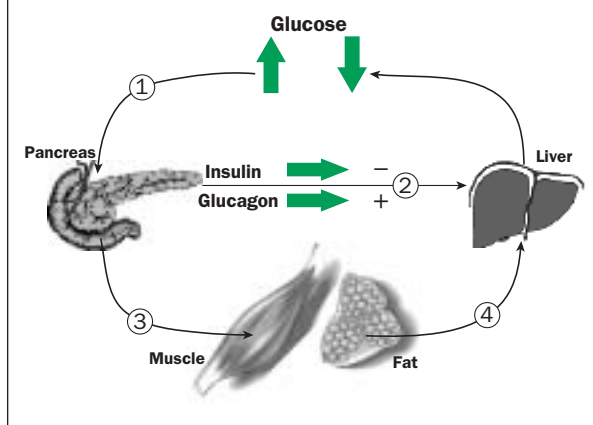
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Figure 1: Glucose homeostasis is controlled mainly by insulin and glucagon, involving 3 major organs: the pancreas, the liver and muscle/fat

- 1) Glucose increases insulin secretion and decreases glucagon release from pancreatic β -cells and α -cells, respectively.
- 2) Insulin suppresses, while glucagon stimulates, hepatic glucose production in the liver
- 3) Insulin promotes glucose uptake in muscle and fat cells
- 4) Free fatty acid (FFA) produced by the fat cells can be supplied to the liver for glucose production.



tained within the normal physiological range as a result of increased insulin output from islet β -cells. In type 2 diabetes, however, hyperglycemia occurs despite hyperinsulinemia, the latter being an unsuccessful compensatory response of the islet β -cells. At this stage, the β -cells may be functioning at maximum capacity and, as the peripheral insulin resistance progresses, the pancreas may lose its capacity to produce enough insulin to meet body needs, resulting in diabetes.^{11,12}

β -cell mass and β -cell dysfunction

A functional β -cell mass is an important factor in regulating glucose homeostasis. Maintenance of the β -cell mass is a dynamic process, undergoing both increases and decreases to maintain glucose levels within a narrow physiological range.^{1,3-6} Long-term adaptation of pancreatic islets to increased demands for insulin has been achieved mainly by increasing β -cell mass.^{13,14} This compensatory mechanism ensures maintenance of euglycemia in healthy individuals. The β -cell mass is controlled mainly by a balance between β -cell survival and β -cell death,¹⁵ according to the following equation:¹⁶

$$d(\beta\text{-cell mass})/dt = \beta\text{-cell survival} - \beta\text{-cell death}$$

with β -cell survival = neogenesis + proliferation, and β -cell death = necrosis + apoptosis.

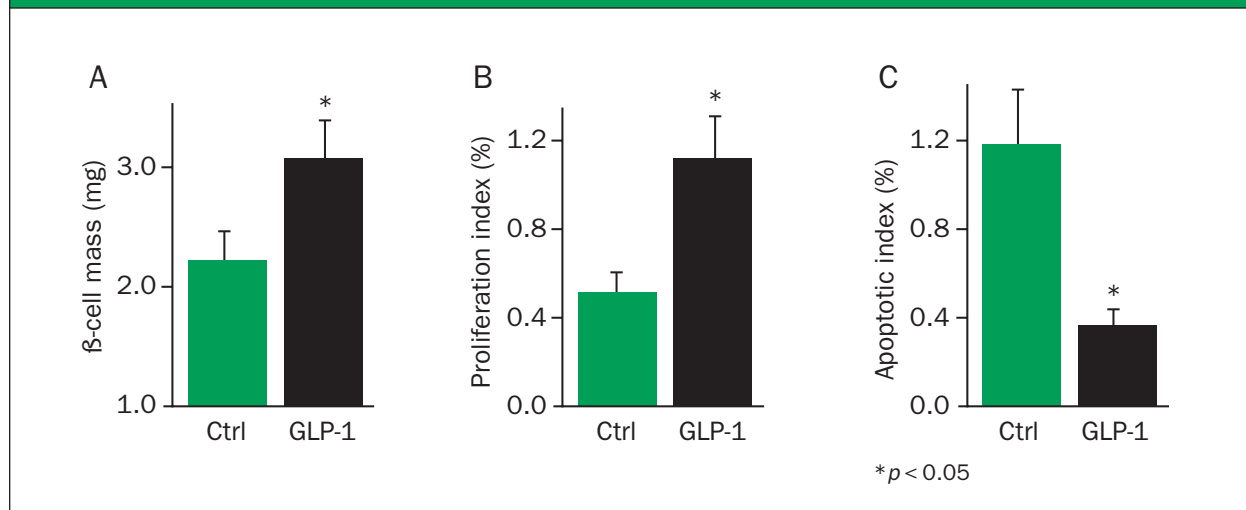
Well-differentiated islet β -cells undergo mitosis at a constant rate.¹⁷ β -cell proliferation can be stimulated by nutrients such as glucose and amino acids^{17,18} and growth factors such as growth hormone, the insulin-like growth factors, and the intestinal hormone, glucagon-like peptide-1 (GLP-1).^{19,20} It is believed that the β -cell mass is regulated in a glucose-dependent manner. Studies using human islets have demonstrated that β -cell proliferation increases during the first 24 hours of incubation of islets containing high glucose concentrations (33.3 mM), whereas a longer incubation time with the same glucose concentrations decreases the rate of β -cell proliferation.²¹ However, the increased rate of the β -cell apoptosis caused by high glucose concentrations was found to change minimally after 24 to 48 hours.²¹ It is conceivable, therefore, that long-term exposure of islets to high concentrations of glucose leads to a loss of β -cell mass due to both increased β -cell death and decreased β -cell proliferation.^{22,23} The observation of “glucotoxicity” may reflect glucose-induced loss of β -cells.²⁴ In fact, it has been demonstrated that in patients with long-standing type 2 diabetes, β -cell mass is reduced by 20%–40%.²⁵

Apoptosis is the main cause of pancreatic β -cell death, not only in type 1, but also in type 2 diabetes. During the development of type 2 diabetes, defects in insulin action in the periphery usually precede the development of glucose intolerance as the pancreas attempts to compensate for insulin resistance by increasing insulin production and secretion either by enhancing cellular secretory capacity or increasing cell mass.^{11,26} When the β -cell loses its compensatory capacity and insulin secretion is unable to keep pace with underlying insulin resistance, glucose intolerance and eventually, overt hyperglycemia occur.²⁷ Hyperglycemia can, in turn, exacerbate defects in pancreatic cell function causing apoptosis of cells.^{22,23} In addition to the glucotoxicity that is commonly seen in type 2 diabetes patients, elevated plasma free-fatty acid (FFA) concentrations may increase β -cell apoptosis. Studies using Zucker Diabetic Fatty (ZDF) rats, a model of type 2 diabetes, suggest that increased circulating FFA and islet lipid accumulation suppress insulin secretion due to lipotoxicity that also leads to β -cell apoptosis.^{28,29}

β -cell mass versus insulin resistance

Early in the development of insulin resistance, insulin released by the β -cells increases as a result of an enlarged β -cell mass that is compensating for the reduction in insulin sensitivity.^{30,31} Enhancing insulin secretion can

Figure 2: After 14 days of GLP-1/Ex4 treatment in prediabetic db/db mice, there was: A. Enhancement of β -cell mass; B. Increased β -cell proliferation; and C. Decreased apoptosis³³



compensate for insulin resistance, further reinforcing the concept that diabetes results only when there is an inadequate functional β -cell mass. Numerous studies support the notion that if β -cell compensatory capacity is maintained, insulin resistance on its own is not sufficient to trigger the onset of diabetes.^{27,32} For example, the majority of patients with insulin resistance as a result of obesity do not develop diabetes because their capacity for β -cell compensation is maintained and only 15%-20% of these individuals become diabetic.^{5,31} Furthermore, studies of the Pima Indians of Arizona demonstrate normal glucose tolerance despite insulin resistance and obesity.²⁷ Maintaining euglycemia requires constantly increasing amounts of insulin over time. As long as the cells can keep pace with demand, diabetes can be avoided. However, the inability of the β -cells to compensate for increased insulin requirements occurs early in disease development.

β -cell mass and the onset of diabetes

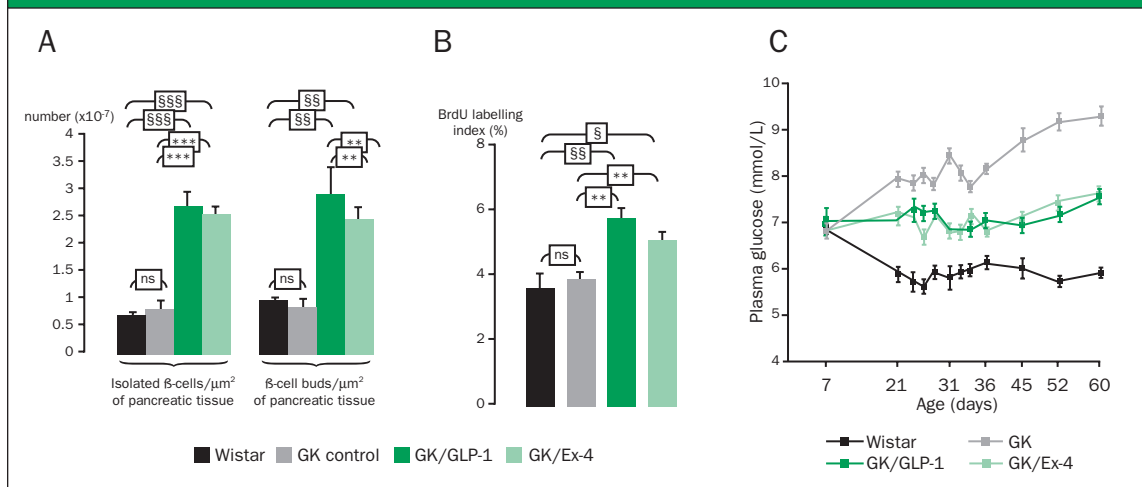
Our hypothesis is that restoring insulin to adequate levels by enhancing functional β -cell mass at an early stage improves glucose tolerance and prevents or delays the onset of diabetes.^{12,27} This hypothesis was recently verified in prediabetic db/db mice.³³ Because of a lack of a functional leptin receptor, db/db mice spontaneously develop obesity, insulin resistance, and glucose intolerance at 4 to 6 weeks of age that progresses to frank diabetes by 8 weeks of age. To study whether an increased functional β -cell mass prevents or delays the development of diabetes in these prediabetic obese mice, daily injections of exendin-4 (Ex4), a long-acting analog of

GLP-1, were given to 6-week-old mice for a period of 2 weeks. GLP-1 is an insulinotropic hormone secreted from cells in the gastrointestinal tract in response to the ingestion of nutrients¹⁹ and is known to increase β -cell mass.³⁴⁻³⁹ A variety of biological functions of GLP-1 have been identified, including stimulation of glucose-dependent insulin secretion and suppression of glucagon release.²⁰ Because of its attractive biological properties, it has been proposed that GLP-1 be used as a therapeutic agent for the treatment of hyperglycemia in patients with Type 2 diabetes.²⁰

After 14 days of treatment with GLP-1/Ex4, the β -cell mass significantly increased as a result of enhanced β -cell neogenesis and proliferation, as well as decreased β -cell apoptosis, in the treated db/db mice compared with their untreated mates (Figure 2). The enhancement of the β -cell mass in these obese mice was coupled with increased islet insulin storage and enhanced insulin secretion as evaluated by both *in vitro* and *in vivo* insulin secretion assays.³³ Although insulin resistance remained, glucose tolerance significantly improved in the GLP-1/Ex4-treated mice. Most important, at 8 weeks of age, fasting blood glucose levels were in the normal range (<7 mM) in GLP-1/Ex4 treated mice. Their untreated mates developed frank diabetes, suggesting that enhancement of β -cell mass by GLP-1 prevents, or at least delays, the onset of diabetes in obese insulin-resistant individuals.³³

These findings are further supported by a recent study in prediabetic Goto-Kakizaki (GK) rats.³⁴ The GK rat is a well-characterized type 2 diabetic lean rat model. Both *in vivo* and *in vitro* studies have demonstrated that glucose-induced insulin secretion is

Figure 3: Enhancing β -cell mass by GLP-1/Ex4 (A,B) improves fasting glucose tolerance (C) in prediabetic GK rats³⁴



§§§ $p < 0.001$ §§ $p < 0.01$ § $p < 0.05$ vs Wistar rats; *** $p < 0.001$ ** $p < 0.01$ * $p < 0.05$ vs untreated GK rats

markedly reduced in the adult GK rat due to decreased total β -cell mass (up to 50%) and depleted pancreatic insulin stores (up to 60%).⁴⁰ Diabetes spontaneously develops in these rats after 3-4 weeks of age.^{40,41} In the study, prediabetic GK rats received a daily injection of GLP-1 or Ex4 for 5 days after birth (from days 2 to 6) and the rats were examined for 2 months. A significant enhancement of the total β -cell mass was found in the GLP-1/Ex4-treated GK groups relative to untreated controls (Figure 3). This was attributed to an increase in β -cell proliferation and neogenesis.³⁴ Consistent with the findings in the db/db mice, GLP-1 or Ex4-treated GK rats had increased pancreatic insulin content and improved insulin secretion in response to glucose challenge.³⁴ Treatment with GLP-1 and Ex4 clearly delayed the onset of basal hyperglycemia in the adult GK rats (Figure 3).³⁴

Given that diabetes increases with age, studies using old Wistar rats, a rodent model of glucose intolerance in aging,⁴² demonstrated that enhancement of β -cell mass by GLP-1 was associated with normalization of the insulin response to glucose challenge,^{35,42} further illustrating the importance of a functional β -cell mass in maintaining normal glycemia.

In humans, assessing cell mass is much more difficult since it can only be directly measured in a cadaver pancreas. As well, measurement of circulating plasma insulin is not a direct measure of

insulin secretion because approximately 50% of secreted insulin is cleared by first pass in the liver.⁴³ Thus, various indices are employed as substitute markers of cell function *in vivo*. The physiologically-based homeostasis model assessment (HOMA) index of β -cell function is often used for evaluating β -cell function in human studies.^{44,45} Consistent with data from animal studies, recent studies from Lugari et al⁴⁶ using the HOMA score to estimate β -cell function, suggest that the β -cell deterioration due to failure of the GLP-1 peptide might contribute to development of overt type 2 diabetes. The notion that insulin resistance does not lead to type 2 diabetes in the absence of cell dysfunction is also supported by the evidence that in maturity-onset diabetes of the young (MODY), individuals can develop diabetes in the absence of insulin resistance,³⁰ further highlighting the relative importance of β -cell defects in the pathogenesis of the disease.

Conclusion

Functional β -cell mass is important in regulating glucose homeostasis and a decline in β -cell mass is a hallmark of type 2 diabetes. Insulin resistance does not lead to type 2 diabetes in the absence of cell dysfunction. Evidence that the enhancement of β -cell mass prevents or delays the onset of diabetes in insulin-resistant individuals suggests that enhancing functional β -cell mass will be useful in preventing and treating human type 2 diabetes.

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Abstract of interest

Glucagon-like peptide-1 treatment delays the onset of diabetes in 8 week-old db/db mice.

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AIMS/HYPOTHESIS: Glucagon-like peptide-1 ameliorates the symptoms of diabetes through stimulation of insulin secretion and enhancement of beta-cell mass. We have therefore investigated the effects of glucagon-like peptide-1 on the development of diabetes, using db/db mice as a model of Type II diabetes.

METHODS: The potent glucagon-like peptide-1 analogue Exendin-4 or vehicle (control) was administered (i.p.; 1 nmol/kg) to obese 6-week old db/db mice daily for 14 days (n=10).

RESULTS: By 8 weeks of age, control db/db mice developed hyperglycaemia (fasting: 10.4±0.5 mmol/l), hyperinsulinaemia and impaired glucose tolerance. However, Exendin-4 treatment prevented hyperglycaemia (fasting: 6.1±1.0 mmol/l, p<0.01), with reduced plasma insulin concentrations (p<0.001) and improved glucose tolerance (p<0.05). Peripheral insulin sensitivity was not affected. However, insulin release in vivo and in vitro from the perfused pancreas was improved by Exendin-4, as were pancreatic insulin concentrations (0.54±0.02 vs 0.32±0.01 micro g/mg protein, p<0.05). These changes occurred in conjunction with increased beta-cell mass (3.01±0.31 vs 2.22±0.22 mg, p<0.05) and proliferation (BrdU(+) beta-cells: 1.08±0.20 vs 0.47±0.11%, p<0.05), as well as decreased apoptosis (Tunel (+) beta-cells: 0.37±0.06 vs 1.20±0.21%). Western blot demonstrated increased expression of Akt1 (by fivefold, p<0.01) and p44 MAP kinase (by sixfold, p<0.01), and decreased activation of caspase-3 (by 30%, p<0.05).

CONCLUSION/INTERPRETATION: Our results suggest that Ex4 treatment delays the onset of diabetes in 6-8 week old db/db mice, through a mechanism involving Akt1 and expansion of the functional beta-cell mass.

Diabetologia 2002;45(9):1263-73

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This publication is made possible by an educational grant from

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