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Defining and characterising the progression of type 2 diabetes

VIVIAN A FONSECA

Abstract

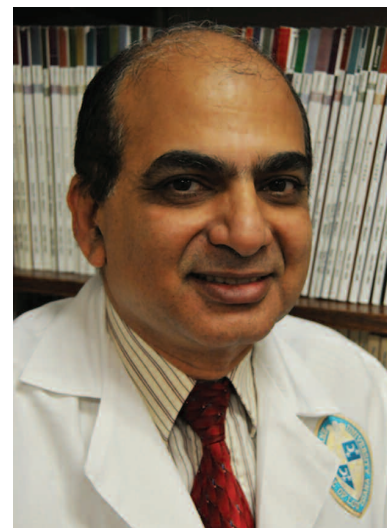
Type 2 diabetes is a progressive disease characterised by worsening of multiple abnormalities and loss of glycaemic control over time. An increasing need for glucose-lowering treatments is emphasised by the almost inevitable failure of monotherapy and occurrence of weight gain. Longer survival times and development of type 2 diabetes at a younger age also increase the risk of developing microvascular and macrovascular complications. A hallmark of type 2 diabetes mellitus is declining pancreatic β -cell function, which begins years before diagnosis and continues throughout the disease process. This deterioration continues despite initiation of numerous therapies, as these interventions lower glucose but do not directly slow β -cell decline and dysfunction. Defects in α -cell function are also important contributors to disease progression. New therapies that can counter these abnormalities without causing weight gain or hypoglycaemia continue to be assessed.

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Key words: β cell, glycaemic control, impaired glucose tolerance, pathogenesis, type 2 diabetes.

Introduction

Type 2 diabetes mellitus is a progressive disease in which the risks of myocardial infarction, stroke, microvascular events and mortality are all strongly associated with hyperglycaemia.¹ The disease course is primarily characterised by worsening of insulin resistance and a decline in β -cell function. The process is manifested clinically by deteriorations in multiple parameters, including HbA_{1c}, FPG and postprandial glucose levels. Several classes of glucose-lowering agents are available, but their use may be associated with hypoglycaemia and a risk of weight gain, which in some cases may worsen insulin resistance. Moreover, as β -cell function continues to deteriorate, these agents become less effective over time. The following review will synthesise our current understanding of the role played by



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deteriorating β -cell function and many other abnormalities linked with the progression of type 2 diabetes. Then, it will briefly discuss our improved understanding of these abnormalities provided by the scientific groundwork for novel therapies that may help achieve and maintain good glycaemic control.

Characteristics of disease progression

Loss of glycaemic control

Major clinical trials provide ample evidence of the increasing loss of glycaemic control over time in type 2 diabetes. For example, the landmark UKPDS, which involved 3,867 patients with newly diagnosed type 2 diabetes, showed that intensive therapy with a sulphonylurea or with insulin substantially lowered HbA_{1c} and FPG compared with conventional therapy (diet followed by a sulphonylurea). Over a median follow up of 11 years, however, both HbA_{1c} and FPG achieved with these therapies subsequently increased and reached levels similar to those seen with conventional therapy.² Metformin decreased HbA_{1c} and FPG in the first year of treatment among overweight patients, but both variables again subsequently increased.³ A similar pattern was observed more recently in ADOPT, which compared treatment with rosiglitazone, metformin and glyburide in 4,360 obese subjects recently diagnosed with type 2 diabetes followed for a median of 4 years. Initially, both HbA_{1c} and FPG levels decreased with all three agents; by 6 months, however, both variables began to rise in all treatment groups. Glyburide had the greatest

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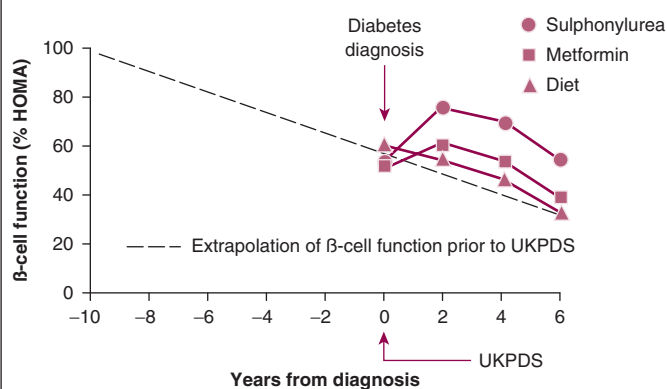
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Abbreviations and acronyms

ADOPT	A Diabetes Outcome Progression Trial
FPG	fasting plasma glucose
GLP-1	glucagon-like peptide 1
HbA _{1c}	glycosylated haemoglobin A _{1c}
IGT	impaired glucose tolerance
NPH	neutral protamine hagedorn
UKPDS	United Kingdom Prospective Diabetes Study

Figure 1. Decline in β -cell function in UKPDS over 6 years in patients with type 2 diabetes remaining on their allocated therapy: diet, sulphonylurea or metformin



Key: HOMA = homeostasis model assessment; UKPDS = United Kingdom Prospective Diabetes Study
Adapted from UK Prospective Diabetes Study Group.⁶ Modified with kind permission from The American Diabetes Association Copyright © 1995.

annual increases in HbA_{1c} and FPG (by 0.24% and 0.3 mmol/L [5.6 mg/dL], respectively), followed by metformin (by 0.14% and 0.1 mmol/L [2.7 mg/dL], respectively) and rosiglitazone (by 0.07% and < 0.1 mmol/L [0.7 mg/dL], respectively).⁴

Beta-cell decline

Another hallmark of type 2 diabetes mellitus is a decline in β -cell function, which begins as early as 12 years before diagnosis and continues throughout the disease process.⁵ Using the homeostasis model assessment to quantify β -cell function, UKPDS 16 demonstrated that, in 4,209 patients with newly diagnosed type 2 diabetes, β -cell function continued to deteriorate in association with progressively increasing hyperglycaemia over 6 years of follow up. Neither sulphonylurea nor metformin treatment significantly halted the decline in β -cell mass and function (figure 1).⁶

As β -cell function continues to decline, monotherapy failure (in ADOPT defined as FPG > 10.0 mmol/L [> 180 mg/dL]) is almost inevitable. In the above-mentioned ADOPT trial, monotherapy with metformin, rosiglitazone and glyburide all failed over time, despite differences in the rates of decline. At 5 years, the cumulative incidence of monotherapy failure was 15% with rosiglitazone, 21% with metformin and 34% with glyburide (figure 2).⁴

Complications

Hypoglycaemia

ADOPT showed a 39% rate of non-serious hypoglycaemia with glyburide monotherapy, whereas rates in rosiglitazone- and metformin-treated patients were 10 and 12%, respectively (no serious hypoglycaemia was reported).⁴ Given that many, if not most, patients with type 2 diabetes will have to advance to insulin therapy while they continue to take oral agents, they are likely to be exposed to an even higher risk of hypoglycaemia. Regardless of the type of insulin used, treating to target goals is associated with a greater likelihood of hypoglycaemia.⁷

In the Treat-to-Target trial, overweight adults with inadequate glycaemic control while taking one or two oral agents received glargine or human NPH insulin at bedtime.⁷ The trial's primary outcome was the percentage of patients reaching HbA_{1c} of 7% or lower without any episode of symptomatic nocturnal hypoglycaemia. Approximately 60% of patients in each treatment group achieved HbA_{1c} of 7% or lower; however, only 33% and 27% of glargine and NPH-treated patients, respectively, were able to achieve that endpoint without experiencing any episode of documented nocturnal hypoglycaemia. Although severe hypoglycaemia was uncommon with either type of insulin, the rate of all symptomatic hypoglycaemic events with glargine and NPH was 13.9 and 17.7 events/patient-year, respectively.⁷

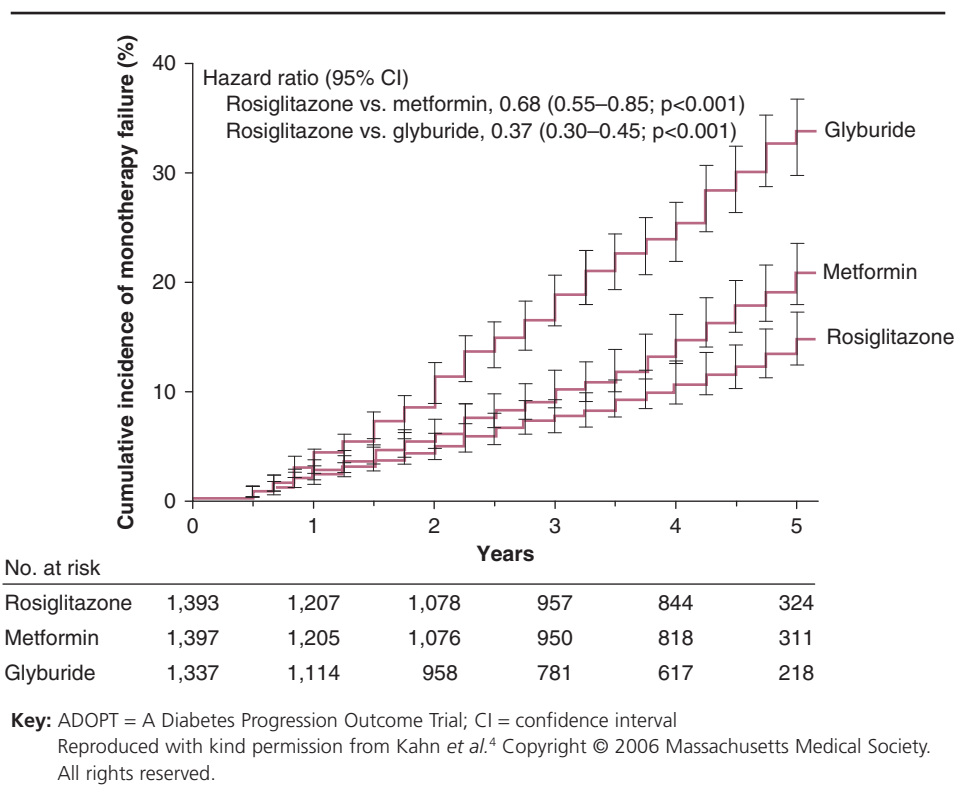
Weight gain

Weight gain is another common concern as type 2 diabetes progresses. In UKPDS 34, patients treated with insulin experienced the greatest weight gain over 10 years. Weight gain was less in those given sulphonylurea treatment; weight gain was lowest and similar in the conventional (diet) and metformin-treatment groups.³ Subsequently, the Treat-to-Target trial found that mean weight gain at the end of 6 months was 3.0 kg and 2.8 kg with bedtime glargine and NPH insulin, respectively.⁷ In ADOPT, mean weight gain among patients taking rosiglitazone was almost 5 kg over 5 years. In contrast, in the glyburide group, mean weight gain of 1.6 kg occurred in the first year, but stabilised thereafter, and weight decreased by approximately 3 kg in the metformin group.⁴ Metformin is the only established treatment that is essentially weight-neutral.

Microvascular and macrovascular complications

Longer survival times and development of type 2 diabetes at younger ages increase the risk of developing duration-dependent complications.⁸ Here again, data from the UKPDS are instructive: in UKPDS 16, 18% of patients, all of whom were presumed to be clinically healthy, had a clinical endpoint within 6 years of diagnosis. Microvascular and macrovascular events occurred in almost 6% and 12% of patients, respectively. Further, within that time frame, 4% of all patients died from a diabetes-related cause.⁶ With 10 years of follow up in UKPDS 33, 21% of intensively treated patients and 38% of conventionally treated patients experienced any diabetes-related endpoint; diabetes-related deaths occurred in 10% and 11% of the intensively and

Figure 2. Kaplan-Meier estimates of the cumulative incidence of monotherapy failure at 5 years in ADOPT. Treatment failure was defined as FPG > 180 mg/dL. Bars indicate 95% CI



conventionally treated groups, respectively, while under 1% and 11% of the respective groups had microvascular events (defined as retinopathy requiring photocoagulation, vitreous haemorrhage and fatal/non-fatal renal failure).² Similar findings were reported in ADOPT; over a median of 4 years of follow up in newly diagnosed type 2 diabetes patients, cardiovascular events (i.e., myocardial infarction, congestive heart failure and stroke) were reported in 4.3%, 4.0% and 2.8% of rosiglitazone, metformin and glyburide-treated patients, respectively.⁴

Complications in diabetes mellitus are influenced by the average level of chronic hyperglycaemia as well as the daily fluctuations. UKPDS 35 showed highly significant associations between development of diabetes complications, including death, across the broad range of exposure to hyperglycaemia, with no evidence of a lower threshold. Each 1% reduction in mean HbA_{1c} was associated with reduction in risk of 21% for any endpoint related to diabetes ($p < 0.0001$).¹

Pathogenesis

Pancreatic β cells normally respond to insulin resistance by increasing their output of insulin to meet the needs of tissues. Development of type 2 diabetes essentially stems from a failure of the β -cell to adequately compensate for insulin resistance. Beta-cell dysfunction progresses over time and is well advanced by the time plasma glucose levels are in the diabetic range.⁹ It also begins well before diabetes is conclusively diagnosed^{5,10} and continues to worsen after diabetes develops.

Two acquired defects have been implicated with regard to impaired glucose secretion: glucotoxicity, whereby β cells become decreasingly sensitised to the presence of glucose; and lipotoxicity, whereby accumulated fatty acids and their metabolic products deleteriously affect β cells. In glucotoxicity, chronic hyperglycaemia can, for example, deplete insulin-secreting granules from β -cells, lessening the amount of insulin available to be released in response to new glucose stimuli. Lowering glucose levels permits regranulation of β cells, and a better acute insulin response follows. In lipotoxicity, prolonged increases in free fatty acid levels adversely affect the conversion of pro-insulin to insulin and eventually affect insulin secretion.^{9,11–14} The mechanisms of glucotoxicity and lipotoxicity remain to be fully elucidated; the exact mechanisms responsible for impaired β -cell function have yet to be conclusively proved.¹⁰

Obesity also plays a role in the complex pathophysiology of type 2 diabetes. Visceral adiposity is an established contributor to insulin resistance.^{15,16} Many obese persons, who have insulin resistance, progress to diabetes. Yet some do not: their β cells continue to function adequately and they are able to maintain glucose homeostasis and compensate for increasing insulin resistance with increasing insulin secretion. This suggests a genetic predisposition to β -cell failure.¹⁷ A genetic subtype of the disease characterised by diagnosis at age under 25 years, β -cell dysfunction, an autosomal dominant mode of inheritance and heterozygous mutations in β -cell transcription factors have

been identified as the most common defects in early-onset type 2 diabetes.¹⁸ To date, five genetic mutations have been identified, and in 80% of affected individuals a genetic cause for their disease is recognised.¹⁹

The acute insulin response

The natural course of β -cell function suggests that the acute insulin response plays a major role in determining glucose tolerance over time. Weyer and colleagues measured parameters of insulin secretory dysfunction and insulin resistance among Pima Indians, who have a high rate of type 2 diabetes.²⁰ Over a mean of 5.1 years, progressors (who transitioned from normal to IGT and then to diabetes) differed significantly from non-progressors (who retained normal glucose tolerance on at least three consecutive evaluations) in their acute insulin response. Specifically, in progressors, acute insulin response decreased by 27% during the transition from normal to IGT and by 51% during the transition from IGT to diabetes. In non-progressors, acute insulin response did not change during the transition from normal to IGT, and actually increased by 30% overall.²¹

More recently, the Insulin Resistance Atherosclerosis Study extended this finding to other ethnic groups. Festa *et al.* assessed longitudinal changes in β -cell function over 5.2 years in African American, Hispanic and non-Hispanic white subjects by measuring the acute insulin response relative to the insulin sensitivity index using frequently sampled intravenous glucose tolerance tests. Again, the main determinant of glucose tolerance status during follow up was the change in acute insulin response. Normal glucose tolerance was maintained by a compensatory increase in insulin secretion, while failure to increase insulin secretion led to IGT, and a decrease in insulin secretion led to overt diabetes.²² The progressive decrease in insulin secretion, particularly the first phase of insulin secretion that occurs acutely after an increase in glycaemia, is likely the most critical β -cell defect in the development of type 2 diabetes.

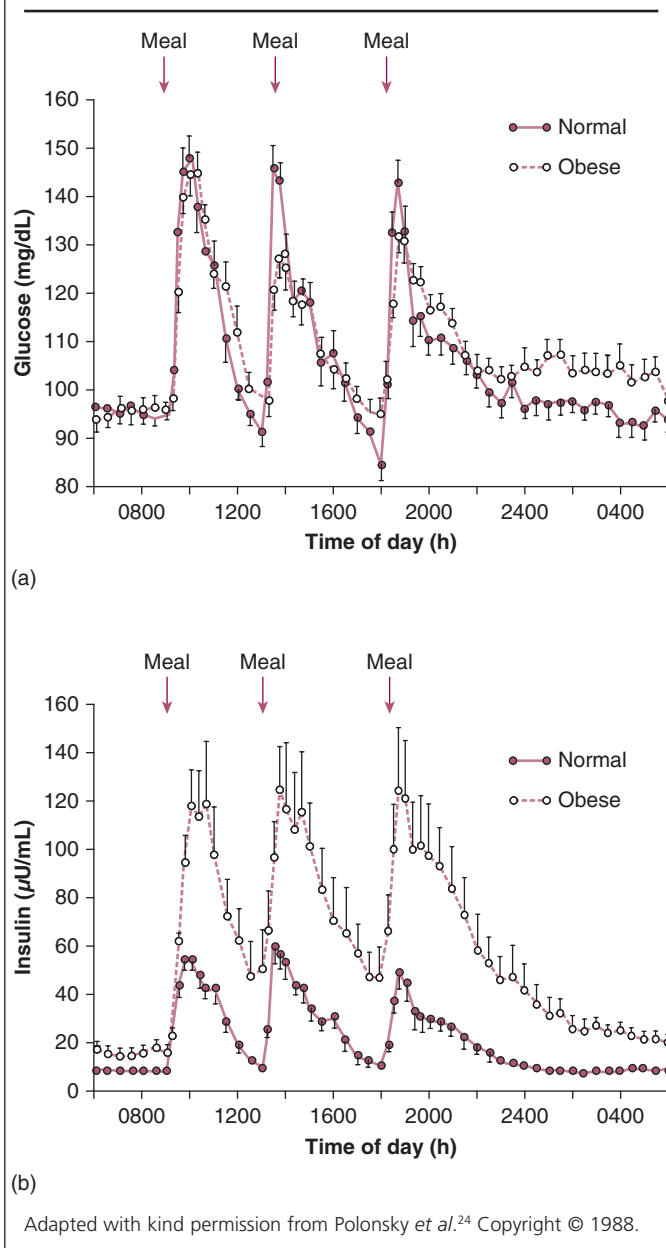
Mechanisms responsible for changes in insulin levels

Normal β -cell adaptation to insulin resistance can occur through increased insulin secretion from each β -cell or an increase in the β -cell mass. Some individuals have a reduced insulin secretion or reduced β -cell mass but normal glucose levels; they have sufficient insulin sensitivity to ensure adequate insulin secretion. In insulin-resistant persons or persons with type 2 diabetes, there is inadequate insulin secretion from each β -cell or an inadequate β -cell mass for the levels of prevailing insulin sensitivity.^{21,23}

When blood glucose is elevated, insulin secretion is stimulated and glucagon secretion is suppressed. The converse occurs when blood glucose is decreased. These actions are critical to maintain normal glycaemia. They also provide the classic response to a meal. Although the failing β -cell loses its ability to respond to glucose, not all responses are diminished. For example, insulin secretion in response to amino acids and stimulation by some hormones such as GLP-1 may be maintained.

Polonsky *et al.* showed that both normal-weight and obese persons maintained a normal and very similar 24-h glucose response to meals. However, the groups differed in their mean insulin secretion, which was significantly higher in obese subjects

Figure 3. Mean 24-h profiles of plasma concentrations of glucose (A) and insulin (B) in normal and obese subjects



than in their normal-weight counterparts (62.9 vs. 24.1 μ U/mL, $p < 0.003$) (figure 3). In addition, these investigators found that insulin secretion in obese subjects failed to return to baseline between meals.²⁴ Loss of normal minute-to-minute pulsatile insulin secretion is believed to be a major contributor to the development of type 2 diabetes. When people are no longer able to produce the insulin needed to maintain normal glycaemia glucose levels rise and they develop diabetes.

Causes of decreasing insulin levels

Beta-cell toxicity results from exposure to high levels of glucose and lipids, particularly free fatty acids that accumulate in the β -cell.

Prentki and colleagues describe a nutritional model of type 2 adipogenic diabetes in which excessive carbohydrate and fat intake causes hyperinsulinaemia in association with increased hepatic lipoprotein secretion, adipose tissue growth and increased free fatty acid levels in genetically susceptible persons. Together with episodes of postprandial hyperglycaemia, elevated free fatty acid levels cause muscle and liver insulin resistance and increase hepatic glucose production. The same stimuli also promote insulin biosynthesis and secretion as well as β -cell growth. In later stages, however, the progressive rise in insulin resistance, combined with alterations in β -cell gene expression and signalling induced by rising levels of free fatty acids, cause β -cell failure. Overt diabetes occurs as a result of this β -cell decompensation, with altered insulin secretion and apoptosis possible contributing factors.²⁵

Attempts to quantify β -cell failure include the work of Wallace and Matthews, who plotted HbA_{1c} against time to derive a coefficient of failure for subjects with diabetes on constant monotherapy. Using longitudinal glycaemia data from the UKPDS, they showed that the mean coefficients of failure with chlorpropamide and glibenclamide were 0.34 $\text{HbA}_{1c}\%$ /year and 0.50 $\text{HbA}_{1c}\%$ /year, respectively.²⁶ The coefficient of failure has several advantages in assessing β -cell failure rates: it uses rates of change, rather than absolute values, in β cells; it can use other measures of glycaemia besides HbA_{1c} and can incorporate new measures of glycaemia as they become available; and it allows comparisons between trials and thus meta-analyses.²⁶

By showing that HbA_{1c} will increase by about 1% every 2 years even with existing therapies, Wallace and Matthews have provided an urgent reminder that patients with diabetes require repeated and vigorous intervention. Failure to implement such interventions, owing to 'clinical inertia' or patient non-compliance, results in worsening glucose control and perpetuates a vicious circle of hyperglycaemia and glucose toxicity in relation to β -cell function and insulin action. Importantly, failure of β -cell function in the later stages of the disease is further compounded by the complications of diabetes and by the likelihood of significant comorbidities in elderly patients.

Beta-cell mass deficits

Although β -cell function is paramount, decreasing β -cell mass is emerging as an important factor in progression of type 2 diabetes. Beta-cell mass is increased by neogenesis and replication. In persons who do not have diabetes, these activities are countered by apoptosis, thereby maintaining a balance in β -cell mass. In persons who are insulin-resistant, the number of islets and β cells, in the presence of increased insulin demand, often increase. Multiple factors, including an increased number of islets and β cells, have been posited as causative.

In animal models of insulin resistance, there is both replication of existing β -cells and neogenesis from ductal precursor cells. In the Zucker diabetic fatty rat model (a model of non-insulin-dependent diabetes mellitus) Pick and co-workers determined β -cell mass and replication rates using immunohistochemistry and morphometry. In non-diabetic but obese rats, the size of the islets increased, regardless of whether they were stained for insulin or glucagon. In

contrast, obese diabetic rats showed slight decreases in the amount of insulin stained, while glucagon was either maintained or increased. The β -cell replication rate was significantly greater in Zucker diabetic fatty rats than in either lean control or obese non-diabetic animals ($p < 0.05$). This is evidence of a time-dependent failure of β -cell mass to increase sufficiently. In addition, this study found that an increased rate of apoptosis, rather than a decreased rate of neogenesis, is likely the major factor responsible for reduction in β -cell mass in this animal model.²⁷

In a human autopsy study, Butler *et al.* examined pancreatic tissue from lean and obese subjects without diabetes, subjects with IFG and subjects with type 2 diabetes. The groups with and without diabetes included both lean and obese individuals. Subjects with IFG and type 2 diabetes had a relatively reduced β -cell mass, whether they were lean or obese. Obese subjects without diabetes had an approximately 50% increase in relative β -cell volume. Obese subjects with IFG or type 2 diabetes had 40% and 63% deficits, respectively, in relative β -cell volume compared with obese subjects without diabetes. These *in vivo* findings suggest that decreased number of β -cells, rather than decreased volume of individual cells, causes a decrease in β -cell mass. Subjects with IFG also had decreased relative β -cell volume, suggesting that this is an early process and mechanistically important in the development of type 2 diabetes.²⁸

In a more recent autopsy series, Ritzel *et al.* investigated the relationship between β -cell mass and blood glucose levels in persons with well-documented blood glucose histories. They plotted individual data points for blood glucose versus relative β -cell volume in cadavers that were obese but not diabetic, obese with IFG and obese with type 2 diabetes. There was a significant, curvilinear relation between β -cell volume and fasting blood glucose level. Beta-cell deficiency beyond 1.1% was associated with a steep increase in blood glucose with each further decrement in β -cell mass.²⁹

Abnormalities in the pancreatic islets may also contribute to deficits in β -cell mass with type 2 diabetes. Deng and colleagues systematically compared pancreatic islets isolated from persons with type 2 diabetes with those from non-diabetic cadaveric organ donors. Subjects with type 2 diabetes had significant decreases in β -cell mass ($p < 0.001$ vs. normal subjects). In addition, induced insulin secretion from islets of donors who had diabetes was significantly less than that of control subjects ($p < 0.05$). In the cohort of persons with diabetes, in which mean disease duration was 4 years, islet yield decreased as disease duration lengthened.³⁰

Imaging studies substantiate that the pancreas declines in size as type 2 diabetes progresses. More than 20 years ago, we used ultrasound to show some decrease in early type 2 disease and a significant decrease in later-stage disease in which patients were insulin dependent and had declining β -cell function and mass.³¹ Using computerised tomography, Goda *et al.* subsequently calculated pancreatic volume and pancreatic volume index in a healthy control group, as well as in type 1 and type 2 diabetes groups. Both parameters were greatest in the healthy group and lowest in the group with type 1 diabetes. Subjects with type 2 diabetes did not differ significantly



Key messages

- Diabetes is a progressive disease
- Over time β -cell function declines, weight increases and development of complications make patient management difficult
- Recent studies have focused on markers of this disease progress that help identify targets for disease modification

compared with control subjects,³² possibly because patients with both early and late-stage disease were included.

Alpha-cell pancreatic function

Although the focus herein has been on β -cell function, some attention must be paid to pancreatic α -cell function and its increasingly recognised role in the pathogenesis of diabetes. As with the pancreatic β cell, α -cell function is complex: in essence, glucose and a variety of hormones and substrates work to regulate glucagon secretion in a coordinated manner. Similar to β -cell dysfunction in type 2 diabetes, abnormalities of α cells reflect impaired glucose sensing. Among the defects in α -cell function in type 2 diabetes are relative glucagon hypersecretion at normal and elevated levels of glucose and an impaired response to hypoglycaemia. The incretin hormone GLP-1, which promotes assimilation of ingested nutrients via a glucose-dependent stimulation of insulin release, apparently improves α -cell glucose sensing. Thus, GLP-1-based therapies have shown efficacy in improving and potentially normalising α -cell function and may also prove to be useful in improving glycaemic control in diabetes.³³

Conclusions

In type 2 diabetes β -cells fail to adapt to the chronic increased demand caused by insulin resistance. This failure appears to be related to a reduction in insulin secretion per islet as well as a reduction in the total number of islets. Progressive loss of β -cell function and, to a lesser extent, reduced β -cell mass lead to worsening glycaemic control. Although they lower glucose, current therapies do not slow this progressive loss of β -cell function and mass, and their use is also associated with hypoglycaemia and weight gain. Thus, the need for additional glucose-lowering therapies that can halt β -cell deterioration without contributing to weight gain continues.

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