

PATHOPHYSIOLOGY OF INSULIN SECRETION

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Summary

Defects in pancreatic islet B-cell function play a major role in the development of diabetes mellitus. Type 1 diabetes is caused by a more or less rapid destruction of pancreatic B cells, and the autoimmune process begins years before the B-cell destruction becomes complete, thereby providing a window of opportunity for intervention. During the preclinical period and early after diagnosis, much of the insulin deficiency may be the result of functional inhibition of insulin secretion that may be at least partially and transiently reversible. Type 2 diabetes is characterized by a progressive loss of B-cell function throughout the course of the disease. The pattern of loss is an initial (probably of genetic origin) defect in acute or first-phase insulin secretion, followed by a decreasing maximal capacity of insulin secretion. Last, a defective steady-state and basal insulin secretion develops, leading to almost complete B-cell failure requiring insulin treatment. Because of the reciprocal relation between insulin secretion and insulin sensitivity, valid representation of B-cell function requires interpretation of insulin responses in the context of the prevailing degree of insulin sensitivity. This appropriate approach highlights defects in insulin secretion at the various stages of the natural history of type 2 diabetes and already present in individuals at risk to develop the disease. To date none of the available therapies can stop the progressive B-cell defect and the progression of the metabolic disorder. The better understanding of the pathophysiology of the disease

should lead to the development of new strategies to preserve B-cell function in both type 1 and type 2 diabetes mellitus.

Résumé

Le déficit de la fonction de la cellule B des îlots de Langerhans du pancréas joue un rôle essentiel dans le développement du diabète sucré. Le diabète de type 1 résulte d'une destruction plus ou moins rapide des cellules B et ce processus d'origine auto-immune débute bien des années avant que la destruction des cellules B ne soit complète, ce qui offre l'opportunité d'une fenêtre pour une intervention thérapeutique. Durant la période pré-clinique et dans les suites du diagnostic, une part non négligeable de la déficience insulinaire peut résulter d'une inhibition fonctionnelle de la sécrétion d'insuline, anomalie réversible au moins de façon partielle et transitoire. Le diabète de type 2 est caractérisé par une perte progressive de la fonction de la cellule B dans le décours de la maladie. Cette anomalie comporte d'abord une perte précoce (probablement d'origine génétique) de la sécrétion aiguë (phase précoce) d'insuline, suivie par une diminution de la capacité maximale insulinosécrétoire. Enfin apparaît un déficit de la sécrétion d'insuline basale, traduisant un épuisement presque total de la cellule B qui conduit à l'insulinoréistance. En raison de la relation hyperbolique entre l'insulinosécrétion et la sensibilité à l'insuline, une appréciation correcte de la fonction de la cellule B nécessite l'interprétation de la réponse insulinaire en fonction de la sensibilité à l'insuline concomitante du sujet. Cette approche a clairement mis en exergue un déficit de la sécrétion insulinaire aux différents stades de l'histoire naturelle du diabète de type 2, déficit déjà présent chez les sujets à risque de développer la maladie. Aucun des traitements disponibles actuellement ne peut enrayer la perte, apparemment inéluctable, de la fonction de la cellule B et la détérioration métabolique qui s'en suit. La meilleure connaissance de la physiopathologie de la maladie devrait amener au développement de nouvelles stratégies visant à préserver la fonction de la cellule B, que ce soit dans le diabète de type 1 ou de type 2.

Key-words : B-cell - Diabetes mellitus – Insulin resistance - Insulin secretion – Pathophysiology

Defective function of the pancreatic B cells is now accepted to be a hallmark of type 1 and type 2 diabetes mellitus. The importance of the specific B-cell destruction in type 1 diabetes has long been accepted leading to an absolute insulin deficiency (1). On the contrary, the necessity of a pancreatic defect in type 2 diabetes has been disputed for many years (7) and has only recently been widely appreciated (11).

The aim of the present concise review is to briefly describe the physiology of insulin secretion in normal man and to highlight the main abnormalities of insulin secretion capacity and dynamics in both type 1 and type 2 diabetes, two entities in which, for various reasons, the B-cell function is profoundly affected at the different stages of the natural history of the disease.

Physiology of insulin secretion

The B cell of the pancreas secretes equimolar amounts of C-peptide and insulin (22). In the normally functioning B cell, the vast majority (> 95 %) of proinsulin is converted to insulin and C-peptide before release and the proinsulin to insulin ratio is less than 5 %. Approximately, 50 to 60 % of the insulin secreted by the pancreas into the portal system is removed during its initial passage through the liver (first pass effect) that leads to a 2-3 times

greater concentration of insulin in the portal vein compared with a peripheral vein. Basal insulin secretion is critical to the maintenance of basal euglycaemia. Quantitatively, pancreatic insulin secretion in the basal state varies from 0.25 to 1.5 U/h in normal subjects and accounts for 50 % or more of the 24-hour integrated insulin secretion. Evidence exists for rapid oscillations in the basal insulin levels with periods of 9 to 14 minutes (24). Several studies have convincingly shown that equal amounts of insulin presented to target organs have improved action when delivered in a pulsatile manner (16).

Both basal insulin secretion and meal-related insulin secretion are regulated by glucose, although other nutrients (amino acids, fat-derived products), hormones (glucagon, gastric inhibitory polypeptide, glucagon-like peptide-1 or GLP-1) and neural factors affect insulin release. The intravenous glucose tolerance test (IVGTT) is classically used for evaluating glucose-regulated insulin secretion and B-cell function. In response to intravenous glucose, insulin is released in a biphasic pattern (9,38). The first phase (acute) insulin response to glucose (AIR_{glucose}) begins within 1 minute after an IV glucose bolus, peaks between 3 and 5 minutes, and lasts up to 10 minutes. The insulin released from the pancreas during this first phase has already been synthesized and stored in the secretory granules of the B cell. The second phase insulin response to glucose begins just after the glucose bolus (but is not evident until 10 minutes later) and lasts as long as the hyperglycaemia persists (so it is much more sustained during an hyperglycaemic clamp than after an IVGTT). This second phase insulin response depends primarily on insulin stores, but is also regulated by new protein synthesis within the B cell. Unlike the first phase, the second phase insulin release is directly proportionate to the steady state glucose concentration immediately preceding the glucose bolus. Thus, when evaluating second phase insulin responses it is critical to achieve comparable steady glucose concentrations as best obtained during a hyperglycaemic glucose clamp. While the oral glucose tolerance test (OGTT) is a good measure of overall glucose tolerance, it is less accurate to evaluate insulin secretion and B-cell function. Nevertheless, the so-called insulinogenic index ($\Delta \text{insulin}_{0-30 \text{ min}} / \Delta \text{glucose}_{0-30 \text{ min}}$) has been proposed to evaluate early insulin response and has been shown to be highly related to the AIR_{glucose} during an IVGTT (28).

A strong negative relationship has been demonstrated between cephalic insulin release and initial glucose increment after a glucose load, suggesting that an early surge of insulin secretion could exert a restraining effect on rising blood glucose (10). Furthermore, an inverse correlation was reported between plasma insulin levels 30 min after an oral glucose load and the plasma glucose concentration attained in the second hour, suggesting that the effects of an acute (first-phase) insulin secretion significantly impact subsequent glucose tolerance (11). The amount of insulin released during first-phase secretion suggests a more likely effect on the liver (inhibition of glucose hepatic output) than on peripheral tissues (stimulation of muscular glucose uptake) (10).

The large insulin response to meal intake, in spite of the moderate increase in circulating glucose levels, is due to the so-called incretin action. This effect is due to gut hormones ("incretins") that are released into the circulation following meal ingestion and stimulate insulin secretion post-prandially. One of the most important incretins is GLP-1 (12). Interestingly, several animal studies demonstrated that GLP-1 may increase insulin secretion not only by promoting B-cell function through a direct insulinotropic action, but also through stimulation of B-cell mass by augmenting B-cell proliferation and inhibiting B-cell apoptosis. This might be important for the concept of treating type 2 diabetes (12).

It has been demonstrated that the magnitude of AIR to nonglucose stimuli (such as arginine, glucagon or epinephrine) is dependent of the prestimulus glucose level (6,25). The slope of the straight line relating the magnitude of AIR to the ambient plasma glucose level at which it was measured is defined as the slope of glycaemic potentiation. Although the slope

of potentiation can be a useful measure of B-cell function, it is a combined measure that is influenced both by changes in insulin secretory capacity and changes in sensitivity of the B cell to the potentiating effects of glucose. To determine which of these two factors is responsible for the changes in slope, one must complete the dose-response curve and from it calculate two parameters : AIRmax or maximal acute insulin response is a measure of the insulin secretory capacity of the pancreas whereas PG-50, defined as the ambient glucose level at which the half-maximal AIR response occurs, is an index of the sensitivity of the B cells to the potentiating effects of glucose (PG-50 and glucose sensitivity are inversely related) (9,38).

It is noteworthy that islet B-cell function is regulated by tissue insulin sensitivity. Evaluation of the relationship of islet function to insulin sensitivity suggests that in glucose-tolerant subjects a reciprocal relationship exists in which insulin secretory capacity and glucose potentiation of insulin secretion increase to compensate for decreasing sensitivity of the peripheral tissues to insulin (Figure 1). This ability to adapt may explain why states of insulin resistance such as obesity are characterized by hyperinsulinaemia with little hyperglycaemia (32). This finding suggests that insulin resistance is a regulator of insulin secretion and that a component of this regulatory mechanism involves enhanced B-cell responsiveness to glucose. Intact cross-talk between insulin secretion and insulin action persists after post-gastroplasty recovery of ideal body weight in severely obese patients (17). Interestingly, in contrast to the findings in obesity, the B cell does not appear to adapt to the insulin resistance of aging (8). The frequency of glucose intolerance in older individuals may therefore be determined in part by this relative impairment of islet function.

The hyperbolic relationship between insulin sensitivity and insulin responses has important implications for estimating the adequacy of a B-cell response in humans. As differences in insulin sensitivity must be balanced by reciprocal changes in insulin release in order to maintain glucose tolerance, it is apparent that although insulin responses may be identical in groups of subjects, if insulin sensitivity is not the same, B-cell function is different. Thus, it is essential to consider insulin sensitivity and insulin responses together when evaluating B-cell function and when assessing the importance of B-cell function to glucose tolerance after both intravenous and oral stimulation (2,11,14).

Pathophysiology of insulin secretion in type 1 diabetes

The majority of patients who have had type 1 diabetes for more than 3 years have essentially no endogenous insulin secretion either in the basal state or in response to meals. While the clinical onset of type 1 diabetes is usually abrupt and dramatic, it is now known that the underlying autoimmune destructive process may take place over months or years before the overt clinical presentation (1). During this time the individuals are asymptomatic and have first normal glucose tolerance that progressively deteriorates to impaired glucose tolerance. The earliest marker of impaired B-cell function in type 1 diabetes appears to be a loss of the ability of glucose to potentiate non-glucose secretagogues (38). The next detectable abnormality is loss of the acute (or first phase) insulin response to intravenous glucose (37). By the time that clinical type 1 diabetes is present, the usual pattern of B-cell function is for individuals to have no potentiation slope, lack of first and second phase insulin response to glucose, low to normal fasting insulin level, and a reduced but still detectable insulin response to intravenous glucagon or arginine (37,38). Several studies confirm that although some endogenous insulin secretion is usually present at the onset of clinical diabetes (positive C-peptide), its subsequent rate of decline may vary considerably. The rate of decline is classically much faster in children and adolescents than it is in adults.

In general, stimulated C-peptide is about 20 % of normal at the onset of clinical type 1 diabetes, in agreement with animal studies suggesting that over 80 % of the functioning B cells need to be destroyed before overt diabetes will develop (1). Whether B-cell death in type 1 diabetes is due to apoptosis or necrosis or a combination of both has not been clarified (18). The almost inevitable subsequent loss of B cells may be slowed to some extent by attention to strict metabolic control. Following initiation of insulin therapy, numerous patients undergo a partial remission, during which insulin doses may be markedly reduced or even insulin therapy can be withdrawn completely. This so called “honeymoon period” occurs largely because of a transient improvement in B-cell function, along with an improvement in insulin sensitivity. The mechanism responsible for this improvement in insulin secretion is unknown. One theory is that chronic severe hyperglycaemia overdrives the residual B cells and desensitises or exhausts them. Then, treatment with exogenous insulin lowers the plasma glucose level, reducing the drive and allowing the residual B cells to recover and to regain partial function. Unfortunately the honeymoon period is usually transient (this phase rarely lasts more than a few months), perhaps because of continuing autoimmune damage of the residual B-cell population (1). Even after treatment with exogenous insulin is once again instituted, the presence of some endogenous insulin secretion has been shown to reduce glycemic swings and improve the overall metabolic control. Recent data from the Diabetes Control and Complications Trial (DCCT) demonstrated that even modest levels of B-cell activity at entry in the study were associated with reduced incidences of retinopathy and nephropathy, while continuing C-peptide (insulin) secretion is also important in avoiding severe hypoglycaemia, the major complication of intensive insulin therapy (34). Attempts have therefore been made to preserve endogenous insulin secretion in newly diagnosed type 1 diabetic patients using various immunosuppressive or other techniques, but so far success has been limited. If apoptosis is the main common mode by which B cells die in response to immune attack by cytokines and/or T-cells in type 1 diabetes, it may be possible to develop novel strategies to prevent this mode of B-cell death, thereby preventing or delaying the onset of the disease (18).

New therapeutic strategies can restore B-cell function in type 1 diabetic patients and those patients can be free from insulin therapy (27). B-cell replacement therapy could be by whole-pancreas transplants, islet transplants, implants of insulin-producing cells, or induction of ectopic expression of insulin (4). Whereas the first is a reality and the second has had recent promising success, the other strategies are being explored in experimental animals. However, it appears that insulin secretion capacity may progressively decrease with time, whatever the method used for B-cell replacement. Therefore, further efforts should be made to better know the pathophysiology of these new sources of insulin release in order to preserve insulin secretion and protect against metabolic deterioration in such individuals (4).

Pathophysiology of insulin secretion in type 2 diabetes

Type 2 diabetes accounts for 80-90 % of all diabetes in most countries. However, diabetes is a far more heterogeneous disease than the current classification into type 1 diabetes and type 2 diabetes implies (30). About 10 % of Caucasian patients with presumably type 2 diabetes have glutamate acid decarboxylase (GAD) antibodies or so-called latent autoimmune diabetes in adults (LADA). In addition, among patients with early onset of familial diabetes younger than 40 years, about 15 % carry mutations in MODY (Maturity Onset Diabetes of the Youth) or mitochondrial genes (36). It has been demonstrated that carriers of MODY mutations (even glucose-tolerant individuals) are characterized by a severe impairment of insulin secretion (20,36). In patients with newly diagnosed type 2 diabetes in

the UKPDS, autoantibody detection (identifying patients with LADA) has been shown more powerful to predict subsequent insulin dependency than other classical predictive factors using stepwise logistic regression analysis, and this observation has been confirmed in other Scandinavian studies (3). These data clearly emphasize the heterogeneous nature of “type 2” diabetes and stress the importance of defining the underlying subtypes when studying the pathogenesis of the disease, and especially the respective contributions of defects in insulin secretion and insulin sensitivity (20,36).

Controversy exists regarding the primacy of the contribution of defects in insulin sensitivity *versus* insulin secretion to the development of type 2 diabetes (31). Basal insulin concentrations in patients with type 2 diabetes have been reported as either elevated, reduced or normal. In addition, cross-sectional studies examining plasma insulin responses during OGTTs have found an inverted U relationship between the 2-h plasma glucose level (a generally recognized index of glucose tolerance) and the 2-h plasma insulin level. This pattern has been interpreted to indicate that early on, as glucose tolerance decreases, there is increased insulin secretion and, therefore, that insulin resistance, rather than insulin deficiency, is responsible for the development of impaired glucose tolerance. However, it is difficult to compare fasting insulin levels of different individuals unless they are matched for both the steady state glucose concentration and body adiposity (as a marker of insulin resistance) (32). When such matching is performed, it is evident that there is a marked insulin secretory defect in all patients with type 2 diabetes (Figure 2). Thus, hyperinsulinaemia, even if appropriate for the prevailing hyperglycaemia, does not necessarily indicate normal B-cell function. In addition, the interpretation of OGTT data may be questioned as it does not take into consideration the importance of the kinetics of insulin release and the dependence of insulin secretion upon the prevailing plasma glucose concentrations. Clearly there is a progressive decrease in the early (30 min) plasma insulin response as glucose tolerance deteriorates. These and other observations provide evidence that there is impaired pancreatic B-cell function before the onset of impaired glucose tolerance (IGT) and that late hyperinsulinaemia may actually be the result of an inadequate B-cell response to the hyperglycaemia due to impaired early insulin release and may not necessarily indicate the presence of insulin resistance. Thus, the misleading dichotomy established between insulin deficiency (*versus* impaired insulin release) and insulin resistance has led to a general underemphasis of the issue of the appropriateness of B-cell function (11). It has become clear that B-cell function should be interpreted in the context of the degree of insulin sensitivity. Failure to take into account the hyperbolic relationship between B-cell function and insulin sensitivity has been misleading. By accounting for this interaction, it has been clearly demonstrated that subjects at high risk for developing type 2 diabetes (older individuals, women with a history of gestational diabetes or polycystic ovary syndrome, subjects with impaired glucose tolerance) have impaired B-cell function. Despite the fact that it has long been the prevalent view that insulin resistance is the main genetic factor predisposing to development of type 2 diabetes, the recent literature better supports the case of impaired insulin secretion being the initial and main genetic factor predisposing to type 2 diabetes (11). Evidence to support this view can be found especially in studies in people at high risk to subsequently develop type 2 diabetes as discordant monozygotic twins or first-degree relatives of patients with type 2 diabetes (11).

In patients with IGT or in the early stages of type 2 diabetes, first-phase insulin release is almost invariably lost. This defect results in an impaired inhibition of endogenous (liver) glucose production and plays a pathogenic role in postmeal hyperglycaemia. Therefore, the restoration of the dynamics of insulin secretion following a meal should be seen as a rational therapeutic approach in the treatment of type 2 diabetes because it induces an overall improvement in glucose tolerance with the advantage of possibly lowering chronic

hyperinsulinaemia (10). Whereas type 2 diabetes is characterized by an absent first phase insulin release to intravenous glucose, second phase insulin release is still sensitive to glucose and therefore partially maintained in patients with compensated diabetes. These responses are maintained by hyperglycaemia until plasma glucose can no longer rise sufficiently to compensate for impaired insulin secretion. Generally decompensation occurs in patients with fasting plasma glucose levels greater than 200-250 mg/dl (15). The United Kingdom Prospective Diabetes Study (UKPDS) clearly showed that type 2 diabetes is a progressive disorder, and that the relentless decline in glycaemic control over years is undoubtedly related to a decrease in B-cell function (35). We previously reported that insulin secretion decompensation (as assessed during an intravenous glucagon test) in face of insulin resistance (as assessed during a euglycaemic hyperinsulinaemic clamp) and further progressive failure explain much of the natural history of type 2 diabetes and the progression towards insulin requirement (29,31) (Figure 3).

Indices of B-cell function that are independent of plasma glucose level or that account for the effect of hyperglycaemia reveal a marked impairment of insulin secretion early in type 2 diabetes. Alterations in pulsatile insulin release and ultradian oscillatory insulin secretion can be observed (24,33). The B cell is also unable to oscillate in concert with the fluctuations in plasma glucose induced by an oscillating glucose infusion. Inefficient proinsulin processing to insulin leads to increased proinsulin to insulin ratio. This abnormality does not appear to be secondary to the increased secretory demand but rather reflects a yet-undefined abnormality of B-cell function in the insulin secretory process. A reduction in the release of islet amyloid polypeptide (IAPP-, known also as amylin) has been observed in established type 2 diabetes. Finally, the slope of glycaemic potentiation and AIR_{max} are both markedly reduced whereas PG-50 is normal. Thus, there is a major reduction in the capacity of type 2 diabetic patients to secrete insulin despite normal sensitivity of the B cells to the potentiating effects of glucose (14,25).

The mechanism for the defect in glucose regulation of insulin secretion in subjects with type 2 diabetes is largely unknown (26). Some data suggest that the islet mass is reduced and therefore the capacity of the pancreas to secrete insulin is diminished in type 2 diabetes. Recent observations showed that the major defect leading to a decrease in B-cell mass in type 2 diabetes is increased apoptosis (5). However, the reduction is not sufficient to explain the marked defect in insulin secretion. The functional B-cell loss exceeds the expected impact of a 20-50 % loss of B cells reported at autopsy. This loss may be explained by the simultaneous deposition of amyloid, a product of human IAPP normally produced in the B cell and secreted along with insulin (26). It has been hypothesized that the process of amyloid fibril formation impairs function early (as evidenced by disproportionate hyperproinsulinaemia) and leads to late B-cell failure and eventual death (14, 26). Studies to impair such fibril formation offer the possibility of developing preventive means for the relentless downhill course of the disease, which is one of the most important current clinical problems in type 2 diabetes management. Recent animal findings with B-cell-specific disruption of the insulin receptor suggest that impaired insulin secretion might be a result of insulin resistance in the B cells themselves (13). The loss of first-phase insulin secretion after glucose challenge seen in these BIRKO (Beta cell Insulin Receptor Knock Out) mice resembles what is seen in human type 2 diabetes. These data suggest that signals mediated by the insulin receptor are essential for the release of insulin secretory vesicles. Finally, once diabetes is established, chronic hyperglycaemia and hyperlipidaemia can exert deleterious effects on B-cell function, respectively referred to as glucotoxicity and lipotoxicity (21). It is conceivable that glucotoxicity and lipotoxicity interdependently converge toward the generation of damaging effectors on B-cell function.

Conclusions

In vivo pancreatic B cells adjust their output of insulin to compensate for changes in the sensitivity of tissues to the hormone or for changes in B-cell number or function. It seems likely that indices of insulin secretion, which either take into account the ambient glucose level or are independent of it, could detect B-cell dysfunction in individuals before it is severe enough to result in the fasting hyperglycaemia characteristic of diabetes. Strictly speaking, absolute insulin deficiency rarely occurs except in patients with type 1 diabetes of several years duration. Relating measures of insulin secretion to the degree of insulin resistance should allow the identification of individuals with more subtle B-cell defects. Realizing that insulin sensitivity is a major determinant of the degree of B-cell function and that interpretation of B-cell function must be performed in the light of the prevailing degree of insulin sensitivity, it is clear that defects in islet B-cell function are absolutely critical to the development of type 2 diabetes. Using this approach, it has been demonstrated that defects in B-cell function are present long before the diagnostic criteria for diabetes have been met and that such relative insulin secretion defect may be used to detect individuals at risk to develop type 2 diabetes. The physiological consequences of the insulin secretion defect are many. Without the acute burst of early-phase insulin release, the normal processing of proinsulin to insulin and the physiological pulsatility of insulin secretion, dysregulation of the glucose metabolism occurs in the liver and the peripheral tissues. The loss of the early surge of insulin release plays a crucial role in postmeal hyperglycaemia and may require specific therapeutic intervention. This becomes even more apparent if the role of postmeal hyperglycaemic state in determining overall metabolic control and cardiovascular risk profile is taken into consideration. A sufficient and appropriate treatment that stops the progressing failure of the B cells based on an understanding of the pathophysiology is still not available. Currently, major effort is being expended to identify individuals at high risk for development of both type 1 and type 2 diabetes, because they are candidates for the therapeutic trials that might delay or prevent the onset and progression of clinical diabetes, especially by preserving B-cell mass and/or function.

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Figure 1 : Hyperbolic relationship between acute insulin response to glucose ($AIR_{G\ 0-10\ min}$) and insulin sensitivity (S_I) measured during a frequently-sampled intravenous glucose tolerance test. The curve was derived from the results obtained in a personal series of 89 subjects with variable body mass indices and normal glucose tolerance. Results of obese subjects with impaired glucose tolerance (IGT) are below the curve, evidencing a defect of insulin secretion in face of insulin sensitivity, as compared to matched obese subjects with normal glucose tolerance (NGT) or lean controls (unpublished results).

Figure 2 : Relationship between the insulin response evaluated during an oral glucose tolerance test and fasting blood glucose levels. Insulin response is evaluated by

the absolute $AUC_{0-180 \text{ min}}$ of plasma insulin levels (left panel) or by the $AUC_{0-180 \text{ min}}$ of plasma insulin levels divided by corresponding blood glucose concentrations (right panel) in lean controls (1), obese subjects with normal (2) or impaired (3) glucose tolerance, and in obese subjects with type 2 diabetes of progressively increased severity (from 4 to 8) (mean \pm SEM of 12 to 30 subjects). When insulin response is evaluated according to ambient plasma glucose levels and body weight, insulin secretory defect appears as early as impaired glucose tolerance develops (adapted from references 30-32).

Figure 3 : Hypothetical scheme of the natural history of type 2 diabetes mellitus : changes in insulin secretion and insulin sensitivity in six groups of subjects, three without obesity ("lean") and three with obesity ("obese"). The upper broken line separates non-diabetic subjects (with normal glucose tolerance) and non-insulin-requiring diabetic patients while the lower broken line separates non-insulin-requiring and insulin-requiring diabetic patients. Results are expressed as mean \pm SEM (adapted from reference 31).