REVIEW

Importance of quantifying insulin secretion in relation to insulin sensitivity to accurately assess beta cell function in clinical studies

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Abstract

Insulin sensitivity and insulin secretion are mutually related such that insulin resistance is compensated by increased insulin secretion. A correct judgement of insulin secretion therefore requires validation in relation to the insulin sensitivity in the same subject. Mathematical analyses of the relationship between insulin sensitivity and insulin secretion has revealed a hyperbolic function, such that the product of the two variables is constant. This product is usually called the disposition index. Several techniques may be used for its estimation such as data derived from the frequently sampled i.v. glucose tolerance test, the oral glucose tolerance test or the glucose-dependent arginine stimulation test or the euglycemic hyperinsulinemic clamp technique in combination with a test on insulin secretion. Using these techniques the compensatory increase in beta cell function in insulin resistance has been verified in obesity, in pregnancy and after glucocorticoid administration as has the defective beta cell function as the underlying cause of impaired glucose tolerance and type 2 diabetes. Similarly, combined analysis of insulin sensitivity and insulin secretion has shown a down-regulation of beta cell function in increased insulin sensitivity accompanying weight reduction in obesity and following exercise. Acknowledging this inverse relationship between insulin secretion and insulin sensitivity therefore requires estimation of both variables for correct assessment in any individual.

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Insulin sensitivity vs insulin secretion – the hyperbolic relationship

It had already been shown several decades ago that insulin resistance such as in obesity is associated with an increased insulin secretion (1–3). Nevertheless, the close and inverse relationship between insulin secretion and insulin sensitivity has been widely acknowledged only during recent years. An early attempt at finding a mathematical relationship between insulin sensitivity and insulin secretion as defined by the pancreatic sensitivity to glucose was described by Richard Bergman in a bioengineering conference in 1980 (4). Five dogs were maintained on a high carbohydrate diet and over a 2-month period at least three i.v. glucose tolerance tests with frequent sampling (FSIGTs) were performed and analyzed in any single animal. This analysis yielded a measurement of insulin sensitivity (S_I) and the sensitivity to glucose of the first (Φ_1) and second (Φ_2) phase insulin release. By plotting S_I vs Φ_2 , a progressive fall of insulin sensitivity was accompanied by a rise in pancreatic sensitivity, such that their product remained approximately constant

in each animal. That report introduced, without expressly naming it, the concept of a non-linear inverse relationship to describe ‘the apparent physiological regulating system which allows insulin sensitivity and pancreatic sensitivity to move in opposite directions, so that the ability of the intact animal to dispose of glucose remains relatively constant’.

The first application of this analysis of data obtained during an FSIGT in man was introduced again by Bergman and collaborators (5) for characterizing obese subjects in comparison with lean controls. In this landmark paper from 1981, for the first time, the word hyperbola was used in this context and the product between S_I and Φ_2 was termed ‘disposition index’ or ‘disposition factor’. It is worth noting that the disposition index was defined from two parameters obtained by modeling analysis of glucose (6) and insulin (7) of FSIGT data. Regarding insulin secretion the authors adopted the parameter indicating the sensitivity to glucose of the second phase insulin release. They had found indeed a large variability in the estimates of parameter Φ_1 , which represents the first phase sensitivity to glucose, and therefore they were

not confident in using it, despite recognizing the importance of the early phase in the etiology of glucose intolerance.

After Bergman's pioneering work, one of the first attempts to hyperbolically relate insulin sensitivity to secretion was that of Johnston and collaborators that used the hyperbolic regression line found in control subjects as the normality curve to assess whether HLA-identical siblings of type 1 diabetic patients were falling below this curve (8). Also in this study insulin sensitivity was calculated from the FSIGT analyzed with the minimal model technique. In this study, the authors also took into account the first phase insulin response as given by the acute insulin response (mean insulin concentration in the first minutes of the test, AIR_G) and related this measure to S_I obtained from the same experiment. Insulin secretion was therefore assessed directly from the peripheral concentration without exploiting any mathematical model of insulin kinetics. In addition, they also demonstrated the hyperbolic relationship between S_I and the acute response obtained with the arginine test performed on another occasion.

It was the classic paper of Kahn and collaborators (9) that formally identified that the non-linear relationship between sensitivity and secretion is best described by a hyperbolic function. In a large cohort of subjects these authors showed that insulin sensitivity from minimal model-analyzed FSIGTs was related in a hyperbolic manner to fasting insulin, AIR_G , glucose potentiation slope and AIR_{MAX} from the arginine test. The hyperbolic relationship means that the product of insulin sensitivity times insulin secretion is constant for a given degree of glucose tolerance. This product is usually called the disposition index. The hyperbolic relationship also means that a change in one of the variables is mirrored by a reciprocal change in the other variable. Figure 1 illustrates the relationship, the understanding of which is

Figure 1 The hyperbolic relationship between insulin sensitivity and insulin secretion. Glucose tolerance is bad if an individual is located below the hyperbolic line and good if an individual is located on or above the line. Arrows indicate possible therapeutic approaches to move from the bad to the good area by increasing either insulin sensitivity or secretion.

fundamental for an accurate comprehension of the nature of type 2 diabetes.

The use of measurements related to circulating insulin concentration, however, does not necessarily allow information on insulin secretion, since only post-hepatic insulin delivery is considered. The role of hepatic insulin extraction should in fact also be taken into account if we are interested in evaluating the beta cell function: i.e. how the cell directly changes hormone release in response to changes in insulin sensitivity. To this aim, it has been necessary to include in the analysis also C-peptide, which is equimolarly released with insulin but not degraded in the liver. Again, it is possible to evaluate C-peptide in a model-independent manner (area under the curve (AUC) or concentration values at specific time points) or by exploiting particular mathematical models that provide direct indices of beta cell secretion (in terms of absolute values and sensitivities) and hepatic insulin extraction (in terms of percent of the secreted hormone) (10–12). Therefore, as a further development of the use of the hyperbolic relationship, by using S_I from the minimal model of glucose disappearance during regular FSIGTs and beta cell parameters from C-peptide analysis, an index of how capable the beta cell is of adapting its secretion to changes in insulin resistance was derived. This index thus assesses true insulin secretion in relation to insulin sensitivity; it has been called the 'adaptation index' and, together with the classic disposition index, has been used to characterize women in the post-menopausal state (13). Furthermore, in an attempt to estimate the hyperbolic relationship also under other conditions, the insulin response to arginine was related to insulin sensitivity assessed by the euglycemic hyperinsulinemic clamp performed on a separate day, and also under these conditions, a hyperbolic relationship was found (14, 15). Similarly, a hyperbolic relationship was found between the insulin response to arginine and the insulin sensitivity as determined by the glucose-dependent arginine stimulation test (16).

Table 1 summarizes the various indices used for the characterization of the hyperbolic relationship between insulin secretion and insulin sensitivity and the specific variables used for their calculation. For simplicity, the term disposition index has been used in most recent publications, regardless of the variables used for its calculation.

The hyperbolic relationship in experimental animals

The above-mentioned studies have established the hyperbolic relationship between insulin sensitivity and insulin secretion in humans. Since the comprehension of this relationship is fundamental for the understanding of pathogenesis of type 2 diabetes, there is a need to develop experimental tools for studying this

Table 1 Indices for the hyperbolic relationship between insulin secretion and insulin sensitivity and the specific variables used for the calculation.

Name of index	Variable for insulin secretion	Variable for insulin sensitivity	Reference
Disposition factor	Glucose sensitivity of 2nd phase insulin secretion (Φ_2) from FSIGT	Insulin sensitivity index (S_i) from FSIGT	4, 5
Disposition index	Acute insulin response to i.v. glucose (AI_{RG})	Insulin sensitivity index (S_i) from FSIGT	9
Adaptation index	Glucose sensitivity of 1st phase insulin secretion (Φ_1) from FSIGT	Insulin sensitivity (S_i) from FSIGT	12
Insulin effect index	Acute insulin response to i.v. arginine	Insulin sensitivity from euglycemic hyperinsulinemic clamp	13
Disposition index	Acute insulin response to i.v. arginine	Insulin sensitivity from euglycemic hyperinsulinemic clamp	14
Disposition index	Acute insulin response to i.v. arginine	Insulin sensitivity from glucose-dependent arginine stimulation test	15

relationship. In 1998 it was shown that it is possible to use the FSIGT in experiments in mice (17). The technique involves, as in humans, a rapid i.v. injection of glucose which is followed by repeated sampling of blood for analysis of insulin and glucose. The number of samples was reduced in mice, and it was shown that by taking seven samples over 50 min, reliable measures of insulin secretion and insulin sensitivity were obtained after modeling the data with, for example, the S_i value showing a good correlation with the insulin sensitivity as obtained from the euglycemic hyperinsulinemic clamp technique (18). Also in mice, a hyperbolic relationship was evident when plotting insulin sensitivity vs insulin secretion (18, 19) and therefore also in mice it was possible to calculate a disposition index. This has offered a tool for experimental analysis of the mechanisms regulating the interrelationships between insulin action and secretion and for studies of potential treatment modalities in mice (20).

Measurement of insulin sensitivity and insulin secretion

In most studies, the parameters are derived from modeling glucose, insulin and C-peptide kinetics during specific tests. The methodological aspects and the experimental and analytical methods for the correct assessment of insulin sensitivity and secretion have been subjects of several excellent reviews (21–23). Mathematical handling of the fasting levels of glucose and insulin concentration has been used for the calculation of insulin sensitivity and secretion by introducing various indices such as HOMA (homeostasis model assessment) and QUICKI (quantitative insulin sensitivity check index) (24, 25). However, these simplistic approaches do not give any clue to the dynamic state of the relationship between insulin sensitivity and secretion.

The gold standard for measurement of insulin sensitivity is the euglycemic hyperinsulinemic clamp technique (26), which is reproducible and sensitive. A drawback is, however, that this technique yields an

estimate of insulin sensitivity calculated for only one of the infinite couples of the glucose/insulin space. To circumvent this drawback, different levels of insulin concentrations are required and the need for reaching and maintaining different steady states possibly within the same experiment makes it long, cumbersome and impossible to perform routinely. Another drawback is that insulin secretion cannot be evaluated from the euglycemic clamp. When using the clamp, therefore, it is necessary to carry out another experiment, such as a primed hyperglycemic glucose clamp, an i.v. glucose tolerance test (IVGTT), an arginine test or any other experiment where the beta cell is stimulated (not necessarily only by glucose) to release insulin (27).

An experimental procedure that includes determination of both insulin sensitivity and insulin secretion is the IVGTT (28, 29) with frequent sampling at the beginning (i.e. FSIGT). This allows measurement of glucose, insulin and more often also C-peptide during the highly dynamic phase that immediately follows the glucose injection. Advantages and disadvantages of this test as well as the different protocols and the relative performance in humans and experimental animals have been described in detail elsewhere (5, 18, 28, 30, 31). Briefly, advantages are that there is a known dose of glucose in the circulating blood and direct stimulation of the beta cell, without confounding effects of incretins or gastrointestinal hormones, and possible problems related to gastric emptying and to delay in glucose absorption do not interfere with the analysis. Disadvantages are that it is unphysiological, not easy to perform, requires the use of computers and sophisticated programming to be analyzed, and is hard to use in epidemiological studies. Once glucose and insulin concentration data are available for the whole duration of the experiment (from 3 to 4 h in humans to 50 min in mice), mathematical model analysis may be performed to calculate metabolic parameters not directly obtainable from simple combinations of the experimental data. The classic Bergman's minimal model was developed to analyze glucose disappearance during FSIGT in dogs (5). The protocol in humans was then modified with the additional injection/infusion 20 min

after that of glucose of exogenous insulin (28, 32, 33) (initially tolbutamide (34)) that augments the whole dynamics of the experiment, yielding a better identification of the parameters (34). In both cases, regular and modified FSIGT, the solution of a system of differential equations yields S_I , which quantifies the ability of insulin to enhance glucose uptake by insulin-dependent tissues and to inhibit liver glucose production. Regardless of the protocol used, S_I is a robust parameter and turned out to be the same with regular and insulin-modified FSIGTs when performed in the same subjects (29). As regards the analysis of the commonly used, simple and widespread oral glucose tolerance test (OGTT), recently several formulas have been published to calculate insulin sensitivity indices (35–37); their validation in various clinical settings has yet to be established.

There is no consensus on which to assess the reference method of insulin secretion. The simplest one is the calculation of the insulin AUC during the whole test or during specific intervals. This measurement gives an idea of the amount of insulin that acts on the tissues, but cannot add information on the dynamics of the hormone in terms of secretion and clearance. For the FSIGT, it has been proposed to use AIR_G , i.e. the mean insulin concentration above basal during the first peak (in general from 2 to 10 min) (8, 9). Also mathematical modeling has been exploited to describe the main processes (secretion, extraction, clearance) during FSIGT (11, 12).

Another test for evaluating beta cell function is the glucose-dependent arginine stimulation test. This test was first developed by Ward and collaborators in Seattle (38), and was later characterized in detail (39). This test characterizes the acute insulin secretion at three glucose levels and the glucose sensitivity of the beta cell secretion. The technique has also been used in combination with the euglycemic, hyperinsulinemic clamp, to illustrate the hyperbolic relationship of insulin sensitivity vs insulin secretion (14, 15).

In a recent study, it was also examined whether insulin sensitivity could be estimated from the glucose-dependent arginine stimulation test (16). In this test, glucose is infused to raise and maintain glucose levels at 14 mmol/l, and by dividing the amount of glucose infused to reach this value by the resulting insulin level, an indirect measure of insulin sensitivity may be estimated. It was thereby shown that this measure correlated nicely with the measure of insulin sensitivity obtained by the gold standard of the euglycemic, hyperinsulinemic technique (16).

Clinical consequences

By acknowledging the hyperbolic relationship, measuring both insulin action and insulin secretion, plotting them together and evaluating the disposition index, beta cell function is evaluated more accurately than

when analyzed in isolation. The model is illustrated in Fig. 1. It shows that during the development of insulin resistance, insulin secretion is increased. As long as the compensation is adequate, i.e. the disposition index remains normal, the glucose tolerance is normal. When the increase of insulin secretion becomes inadequate in relation to insulin resistance, i.e. when the disposition index drops, glucose intolerance and type 2 diabetes develop. This model thus focuses on the islet beta cell as the important target of defect in the disease.

The model may be illustrated in obesity, which is known to be accompanied by insulin resistance which is compensated by increased insulin secretion. To evaluate whether obese subjects with glucose intolerance have defective islet compensation, insulin sensitivity and insulin secretion were evaluated together in the same individuals by the euglycemic clamp and the glucose-dependent arginine stimulation tests. It was found that those exhibiting glucose intolerance had a lower insulin secretion than those having normal glucose tolerance, in spite of having the same insulin sensitivity (40). Nevertheless, insulin secretion in the obese subjects with impaired glucose tolerance was higher than in non-obese subjects with normal insulin sensitivity and normal glucose tolerance. If insulin secretion had been analyzed in isolation, the conclusion would therefore be that the beta cells were functioning normally. However, when analyzed in relation to the insulin insensitivity, it is obvious that beta cell function is inadequate for the degree of insulin resistance. Another group at risk of developing glucose intolerance are subjects treated with glucocorticoids. An experimental study has shown that the induction of insulin resistance by short-term exogenous administration of dexamethasone is followed by a compensatory increase in insulin secretion (41). In the subjects where the islet compensation was adequate, glycemia remained normal. However, in subjects where the islet compensation was inadequate in relation to the induced insulin resistance, i.e. when the disposition index was reduced, fasting hyperglycemia increased. Also in these subjects, insulin secretion *per se* was increased, thus again illustrating that the defective islet function as the cause of fasting hyperglycemia after dexamethasone would have been overlooked if the two variables had not been analyzed together. Moreover, cross-sectional studies in subjects with impaired glucose tolerance have shown a defective insulin secretion in relation to insulin sensitivity (15) by plotting the two variables together (Fig. 2). The importance of evaluating a defective insulin secretion in relation to insulin resistance for correctly validating pathophysiology of type 2 diabetes is also evident from prospective studies. An important study has been presented in Pima Indians, where insulin secretion and insulin sensitivity have been judged from FSIGTs performed every fifth year in subjects maintaining normal glucose tolerance vs those

Figure 2 Scatterplots of insulin sensitivity (measured by euglycemic, hyperinsulinemic clamp) vs the acute insulin responses to arginine at fasting glucose in 71 women, aged 58 years, with normal glucose tolerance (NGT) (○) vs 37 women, aged 58 years, with impaired glucose tolerance (IGT) (●). The regression line is shown for the hyperbolic fit of the data for the groups with normal glucose tolerance. Original data are reported in (15) where the relationship at higher glucose levels is also illustrated.

progressing through impaired glucose tolerance to type 2 diabetes (42).

A defective insulin secretion in relation to insulin sensitivity, i.e. reduced disposition index, has been shown not only to be associated with impaired glucose tolerance and type 2 diabetes, but also with conditions having increased risk of developing type 2 diabetes. Thus, first-degree relatives of diabetics and women with gestational diabetes or polycystic ovary syndrome have a low disposition index (43). A low disposition index *per se* is also associated with future worsening of glucose tolerance, as demonstrated in a prospective 3-year study (14).

A consequence of the hyperbolic relationship is that increased insulin sensitivity is compensated by reduction, or down-regulation, of beta cell function, which may be a mechanism to avoid hypoglycemic episodes. This has been demonstrated as a reduced insulin response to arginine when insulin sensitivity is increased during weight reduction in severely obese subjects undergoing standardized weight reduction by bariatric surgery (16). That study also demonstrated that the reduction in insulin secretion was quantitatively not as prominent as the increase in insulin sensitivity, which increased the disposition index along with weight reduction. This was followed by improvement of glucose tolerance, in support of the model that glucose tolerance is governed by the hyperbolic relationship between insulin secretion and action. Similarly, in a group of elite sportsmen having extremely high insulin sensitivity, the insulin response to arginine was reduced along a hyperbolic line in comparison with a group of sedentary subjects (44). Hence, both increases and decreases of insulin sensitivity are associated with compensatory reciprocal changes in insulin secretion.

Basic mechanisms

The hyperbola defining the inverse relationship between insulin sensitivity and insulin secretion indicates that it is impossible to judge insulin secretion in a given individual without knowing the ambient insulin sensitivity. Most importantly, the hyperbola has convincingly demonstrated the critical and fundamental importance of beta cell dysfunction for the development of type 2 diabetes, as it was initially proposed in the classic work of Cerasi & Luft in 1967 (45) and exploited in detail by Porte, Kahn and collaborators (43, 46). Now we need to establish the mechanism of the hyperbolic relationship, both in the organism and in the beta cells, i.e. which factors signal to the beta cells to augment insulin secretion when insulin resistance worsens. Several factors are candidates for being such signals. One possible candidate is glucose, which may increase during the development of insulin resistance thereby signaling to the beta cells to increase insulin secretion. However, glucose is probably not a key signal in this respect because glucose levels are usually not increased when insulin resistance develops if the beta cells are functioning adequately. Also, a study has shown that when insulin sensitivity is improved by exercise, a reduced insulin secretion is observed in association with increased, not reduced, glucose levels and another study using nicotinic acid has shown that insulin resistance is followed by increased insulin secretion but a reduced circulating glucose (43). Other candidates would be circulating lipids, because free fatty acids (FFAs) are known to be increased in insulin resistance due to reduced antilipolytic action of insulin, and FFAs might then stimulate insulin secretion (47). However, whether FFAs stimulate insulin secretion at the concentrations seen under these conditions is not known. Another possible candidate for mediating the increased insulin secretion in insulin resistance is the autonomic nervous system (48). It has thus been demonstrated that the hyperinsulinemia in the insulin-resistant *ob/ob* mouse is sensitive to cholinergic blockade and that in insulin-resistant high-fat-fed mice insulin secretion is very sensitive to cholinergic activation (48). This could be explained by increased activity in the vagal nerves due to insulin resistance, and in support of this notion, the circulating levels of pancreatic polypeptide, a marker of cholinergic activation, are increased in insulin-resistant Pima Indians (49). Also other candidates might contribute, however, and recently it has been suggested that circulating levels of the gut incretin, glucagon-like peptide-1 (GLP-1) as well as the expression of GLP-1 receptors in the pancreas were increased in insulin-resistant high-fat-fed dogs (50). Hence, GLP-1 might contribute to hyperinsulinemia in insulin resistance. However, the relative contribution of these tentative candidates is not known, and needs now to be established. Conversely, possible signals from the beta cells

regulating insulin sensitivity need also to be examined. We also need knowledge as to why and when the hyperbolic relationship fails, in order to target physiologically relevant processes when exploring new treatment modalities for type 2 diabetes.

Methodological suggestions

This review underlines that the simultaneous assessment of both insulin secretion and sensitivity is necessary to reach appropriate conclusions. However, a great deal of attention must be placed on the choice of the experimental tests to be performed (27). The most important issue is that the two measurements must be as independent as possible. This may yield some problem when the disposition index has to be determined in large epidemiological studies. In this case, for instance, a widely used method to assess insulin sensitivity is HOMA (24), because it uses only the product of fasting insulin and glucose concentration. The corresponding index of beta cell function also uses basal insulin; thus, the two indices are strictly related being both proportional to the same basal insulin measurement. Their product therefore does not make much sense and should not be used. Other simple estimations of insulin sensitivity for epidemiological studies include the QUICKI calculation (25) still based on fasting glucose and insulin concentrations. These methods exhibited a good correlation with insulin sensitivity as determined by the euglycemic hyperinsulinemic clamp test, but their limitations should be recognized (27, 51).

To have a trustworthy measurement of insulin secretion, it is necessary also in large studies to use dynamic tests, such as the OGTT, which provide independent measurements of beta cell function, for example from the insulinogenic index (52) or from the ratio of the insulin area over the glucose area. For calculating the disposition index, these measurements can be used in conjunction with insulin sensitivity indices such as HOMA or other simple and probably more reliable methods. In particular, the method called OGIS (37) only needs three samples – fasting, 90 min and 2 h – and it has been used successfully for calculating the disposition index (53). The content of information from this simple test should be enough for large-scale studies, with a low cost/benefit ratio. However, the results must be interpreted having in mind all the assumptions and simplifications included in these methods.

In metabolic studies, when the number of subjects is not very high and the investigator needs a clear quantification of the parameters, possibly affected by the least error possible, dynamic tests, such as the euglycemic hyperinsulinemic clamp, the FSIGT, the arginine test or other tests, are mandatory. The burden for the clinical investigator and the discomfort of the subject under

study increase, but the information gathered from these studies is quite large and reliable for the purpose of characterizing in detail the metabolic status of the single individual. Also in these cases attention should be focused on the simultaneous assessment of insulin secretion and sensitivity. For instance, the hyperglycemic glucose clamp yields a measurement of both processes, but insulin secretion, obtained from peripheral insulin concentration, may be intrinsically related to insulin sensitivity, as the same insulin concentration values are used also to assess insulin sensitivity. For medium size metabolic studies, measurement of beta cell function independently from the corresponding ones of insulin sensitivity, such as the first-phase insulin secretion indices from either the hyperglycemic clamp or the arginine test or the FSIGT are therefore advisable. In particular, in the insulin-modified FSIGT (29, 30), insulin secretion is calculated during the first 8–10 min (AI_{RG}), while for the estimation of the parameter S_I the delayed insulin action, i.e. after exogenous insulin administration from 20 min on, plays the major role. Plotting S_I vs AI_{RG} to obtain the disposition index is therefore correct. A methodological problem in metabolic studies in diabetic subjects is the confounding factor of hyperglycemia, which requires standardization and therefore in many cases more than one dynamic test (54).

For more precise measurements of insulin sensitivity in specific tissues, particular experimental protocols involving the use of sophisticated instrumentation must be carried out (among several: forearm arteriovenous differences, nuclear magnetic resonance spectroscopy, positron emission tomography, multiple tracer dilution). For the assessment of pre-hepatic insulin release in the portal vein, measuring also C-peptide is necessary, while molecular biology studies allow the investigation of the fine mechanisms regulating insulin release directly from the beta cell. However, presentation and comments on these last techniques are beyond the aim of this review.

The same approach as in metabolic studies may be instituted for the clinician in an attempt to quantify disposition index in clinical practice. Here, however, an important issue is the reference values of the estimates, because both insulin sensitivity and insulin secretion are heavily influenced by age, ethnicity, body weight, fat distribution and other clinical conditions or treatment, and for accurate determination reference values would be required controlling for these confounders. Until such information is available, the use of a simple dynamic test, such as OGTT, might be sufficient.

Concluding remarks

Accurate estimation of insulin secretion and insulin sensitivity requires determination of both variables because they need to be judged in relationship to

each other. The nature of the relationship in different populations and different clinical groups needs now to be established. We also need a deeper understanding of the basic mechanism relating these two processes to each other and why the compensatory insulin secretion in insulin resistance fails in type 2 diabetes.

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