Is Type 2 Diabetes a Different Disease in Obese and Nonobese Patients?

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OBJECTIVE — The main purpose of this work was to study the possible differences in insulin secretion in a large group of type 2 diabetic patients in relation to diabetes duration, obesity, and the presence of secondary failure after treatment with oral hypoglycemic agents.

RESEARCH DESIGN AND METHODS — There were 147 nonobese and 215 obese type 2 diabetic subjects, aged 35–80 years, investigated in a cross-sectional descriptive study. Subjects were grouped according to whether glycemic control was good (mean blood glucose <8.5 mmol/l) or poor. β-Cell function was assessed by measuring meal-stimulated insulin and C-peptide concentrations, as the mean of the three postprandial increments above the premeal value.

RESULTS — Basal C-peptide concentrations were significantly higher in obese than nonobese patients of both groups. The mean of meal-stimulated C-peptide concentrations was also significantly higher in obese than nonobese patients with good glycemic control, but not in the secondary failure groups. In nonobese and obese patients considered separately, a significant negative correlation between the mean of daily blood glucose and meal-stimulated C-peptide was observed ($r = -0.705$ and $r = -0.679$, respectively, $P < 0.001$) and the residual β-cell function was significantly correlated with the known duration of diabetes and metabolic control, but not with BMI, in both groups.

CONCLUSIONS — On average, obese diabetic subjects showed higher meal-stimulated C-peptide than nonobese subjects only in well-controlled groups. In both obese and nonobese patients, an inverse association between meal-stimulated insulin secretion and duration of diabetes was observed. In obese patients, as in nonobese patients, the lower β-cell function seems likely to be the major pathogenetic factor in the appearance of secondary failure, while being overweight plays only a minor role, thus showing that type 2 diabetes is the same disease in obese and nonobese patients.

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Type 2 diabetes is a heterogeneous disease characterized by impaired insulin secretion and both hepatic and peripheral insulin resistance (1,2). Furthermore, chronic hyperglycemia decreases insulin sensitivity and insulin release (3,4). Most type 2 diabetic subjects are obese and often have a history of cardiovascular disease.

Diet and oral hypoglycemic agents (OHA) constitute the common treatment for type 2 diabetic patients but, despite full compliance with diet and drug administration and in the absence of any intercurrent illness, 40% of patients display poor glycemic control. After a fairly good initial response to OHA, many patients fail to achieve good metabolic control (secondary failure [SF]), and require an insulin regimen (5–8). Indeed, it is well known that by improving glycemic control it is possible to partially reverse both insulin resistance and the decline of insulin secretion induced by glucose toxicity (9).

Unfortunately, there is little agreement on the criteria used to define SF, particularly with regard to the period of drug efficacy (6 months to 5 years) necessary to distinguish type 2 diabetes from slow-onset or late-onset type 1 diabetes (10,11); moreover, there is no general consensus on what degree of metabolic derangement indicates good or poor glycemic control (12–14). Thus, the decision to initiate insulin therapy remains arbitrary.

It is generally assumed that obese diabetic patients show higher insulin secretion, lower insulin sensitivity, and lower incidence of SF than nonobese patients (15,16). It has recently been demonstrated that a marked reduction in insulin sensitivity and a preserved insulin release characterize obese diabetic patients, while nonobese patients have a reduction in insulin release and normal insulin sensitivity (17,18).

The aim of the present study was to evaluate the role of insulin secretion in type 2 diabetes, in both obese and nonobese subjects, to better characterize the pattern of SF.

RESEARCH DESIGN AND METHODS

— There were 147 (67 men and 80 women) nonobese and 215 (69 men and 146 women) obese type 2 diabetic subjects, aged 35–80 years, studied. Obesity was defined as BMI (kilograms per meters squared) >30 (19). Age at diagnosis of diabetes ranged between 30 and 77 years, and the duration of diabetes ranged between 1 and 38 years. No patient presented with evidence of hepatic or renal dysfunction.

In 40 patients (6 nonobese and 34 obese), diabetes was well controlled by diet alone; 322 patients were on dietetic and OHA treatment (glibenclamide or glibenclamide plus metformin). No patient had previously received insulin therapy. Clinical characteristics of patients are shown in Table 1.

The patients were consecutively recruited from the type 2 outpatients attending the Diabetic Clinic. All subjects were admitted to hospital to keep their clinical conditions steady and were asked to maintain their previous level of physical

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Abbreviations: ANCOVA, analysis of covariance; ANOVA, analysis of variance; ΔCP, postprandial increments of C-peptide; ΔG, postprandial increments of glucose; GC, good control; ΔIRI, postprandial increments of insulin; mG, mean daily value of glucose; OHA, oral hypoglycemic agents; SF, secondary failure.
A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

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Table 1—*Clinical and metabolic characteristics of nonobese and obese type 2 diabetic patients*

	Nonobese	Obese
n	147	215
BMI (kg/m²)	23.6 ± 0.2	32.3 ± 0.4*
Sex (M/F)	67/80	69/146
Age (years)	63.0 ± 1.1	62.4 ± 0.8
Age at onset (years)	50.2 ± 1.0	51.3 ± 0.7
Duration of disease (years)	12.5 ± 0.7	11.1 ± 0.6
Family history of diabetes (%)	61.9	57.7
Symptoms at onset (%)	49.7	48.4
Triglycerides (mmol/l)	1.72 ± 0.09	2.63 ± 0.12*
Total cholesterol (mmol/l)	5.86 ± 0.11	6.20 ± 0.10†
HDL cholesterol (mmol/l)	1.10 ± 0.13	1.08 ± 0.02
Uric acid (μmol/l)	309.4 ± 6.6	351.15 ± 5.9*

Data are means ± SEM. *$P < 0.001$; †$P < 0.02$.

activity and to continue their previous weight-maintaining diets of 1,600–1,800 kcal/day (45% carbohydrate, 35% fat, and 20% protein). Patients were instructed and monitored by a dietitian.

The study was performed in accordance with the Helsinki Declaration, and informed consent was obtained from each subject.

After 7–10 days, the daily blood glucose profile was drawn up to assess the degree of glycemic control. The patients were considered in good control (GC) when the mean blood glucose was <8.5 mmol/l and the glycated hemoglobin (HbA_{1c}) <7%. These threshold values are in agreement with the position statement of the American Diabetes Association (14).

Nonobese and obese groups in good (GC) and bad control (SF) were established. All subjects in the group with poor glycemic control were on OHA at the maximum effective daily dosage (glibenclamide 15 mg and metformin 1,500 mg). "True" secondary drug failure was diagnosed when drugs became ineffective after an initial good response lasting for at least 2 years. Patients with acute illnesses or those who did not comply with diet and treatment were excluded from the study.

The daily profile was drawn up while maintaining the oral hypoglycemic therapy. Blood samples were collected nine times: before and 1 and 2 h after each of the three meals. The mean daily values of glucose (mG) and the mean of the three postprandial increments above the premeal value for glucose (ΔG), C-peptide (ΔCP), and insulin (ΔIRI) were calculated.

Plasma glucose, triglycerides, and total and HDL cholesterol levels were determined using colorimetric methods (Sigma-Aldrich, Milan, Italy). HbA_{1c} was evaluated by affinity column chromatography (Glycogel, Pierce, Rockford, IL): normal subjects 4.5 ± 1.2% (mean ± SD), insulin by coated radioimmunoassay (20), and C-peptide by double-antibody radioimmunoassay (21).

Statistical analysis

Data for continuous variables are expressed as means ± SEM. Because of their normal distribution, the Student's *t* test procedure was used to evaluate unpaired comparisons between nonobese and obese diabetic groups with GC and SF. Incremental values of C-peptide (ΔCP) in the three groups of diabetes duration were compared by means of one-way analysis of variance (ANOVA) and Tukey's *t* posttest. Differences among observed frequencies were determined by nonparametric χ^2 test.

The relationship between two parameter series was examined by the study of linear regression analysis and the strength of the correlation by their coefficient of correlation. Analysis of covariance (ANCOVA) was used to estimate the difference between two regression lines. Finally, multiple regression analysis with the stepwise regression procedure was used to explore the influence of multiple variables in predicting basal and incremental (ΔCP) values of C-peptide. In all analyses performed, a *P* value <0.05 was considered statistically significant.

RESULTS — Obese and nonobese diabetic patients were comparable in terms of age, age at onset of diabetes, duration of disease, prevalence of family history of diabetes, and prevalence of symptoms at the onset of diabetes (Table 1). Obese patients showed higher values of triglycerides, total cholesterol, and uric acid than nonobese patients.

Glycemic control

Obese and nonobese subjects were divided into two groups with good (GC) or poor glycemic control (SF), according to their mG and HbA_{1c}; in SF subjects, postprandial increments in blood glucose (ΔG) were higher than in GC groups (nonobese: 2.90 ± 0.07 vs. 2.33 ± 0.07 mmol/l, $P < 0.001$; obese: 2.83 ± 0.06 vs. 1.96 ± 0.07 mmol/l, $P < 0.001$) (Fig. 1*A*).

In both nonobese and obese patients, basal (nonobese: 0.484 ± 0.017 vs. 0.626 ± 0.016 nmol/l, $P < 0.001$; obese: 0.633 ± 0.017 vs. 0.820 ± 0.018 nmol/l, $P < 0.001$) and ΔCP (nonobese: 0.234 ± 0.009 vs. 0.472 ± 0.011, $P < 0.001$; obese: 0.256 ± 0.010 vs. 0.580 ± 0.012 nmol/l, $P < 0.001$) values and ΔIRI concentrations (nonobese: 0.095 ± 0.003 vs. 0.172 ± 0.005, $P < 0.001$; obese: 0.119 ± 0.004 vs. 0.230 ± 0.006 nmol/l, $P < 0.001$) were significantly lower in SF groups than in GC groups (Fig. 1*B–D*).

Obesity

A comparison between nonobese and obese patients showed that *1*) mG and HbA_{1c} were similar in both groups (nonobese GC vs. obese GC and nonobese SF vs. obese SF, data not shown), whereas ΔG was lower in obese GC than in nonobese GC ($P < 0.02$) and not significantly different in SF groups (Fig. 1*A*); 2) basal C-peptide concentration was significantly higher ($P < 0.001$) in obese than in nonobese patients in both GC and SF groups (Fig. 1*B*); 3) meal-stimulated ΔCP was significantly higher in obese than in nonobese patients only in the groups with GC ($P < 0.001$) (Fig. 1*C*), whereas it was not statistically different in the SF groups; and *4*) basal (nonobese GC: 0.109 ± 0.003 vs. obese GC: 0.153 ± 0.003 nmol/l, $P < 0.001$; nonobese SF: 0.090 ± 0.003 vs. obese SF: 0.129 ± 0.003 nmol/l, $P < 0.001$) and ΔIRI levels were higher in obese than in nonobese patients in both the GC ($P < 0.001$) and SF groups ($P < 0.02$) (Fig. 1*D*). When obese and nonobese patients were considered separately, a significant negative correlation between mG and ΔCP was observed (nonobese: $r = -0.705$, obese: $r = -0.679$, $P < 0.001$) (Fig. 2). ANOVA and ANCOVA performed on the two regression lines showed a similarity in the slopes ($F = 0.73$, NS) and a slight, but significant, difference in the inter-

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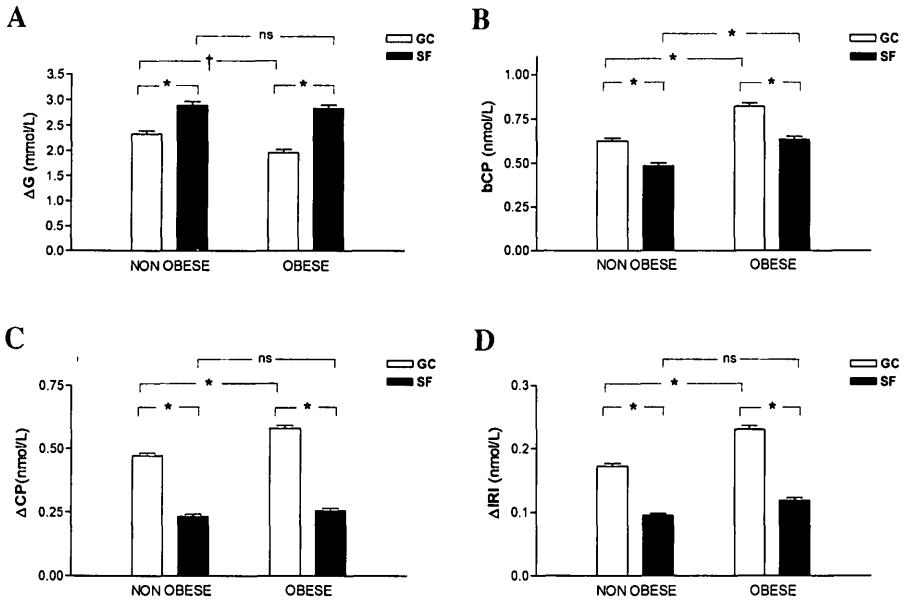

Figure 1—*Mean of postprandial increments of plasma glucose (ΔG) (A), basal C-peptide (bCP) (B), postprandial increments of C-peptide (ΔCP) (C), and postprandial increments of insulin (ΔIRI) (D) in nonobese and obese patients with good (GC) and poor (SF) glycemic control.* *P < *0.001;* †P < *0.02.*

cept points ($F = 7.20$, $P < 0.05$), but overlapping of the single values was very large.

Duration of diabetes

When obese and nonobese were grouped in tertiles according to their duration of disease (1–10, 11–20, and >20 years), ΔCP values showed a progressive decrease over time in all groups. Obese showed higher ΔCP than nonobese patients in the 1st and 2nd tertiles of GC groups and in the 1st tertile of SF groups; no difference was observed between obese and nonobese patients in the 3rd tertile of GC groups or in the 2nd and 3rd tertiles of SF groups (Table 2).

The prevalence of well-controlled patients treated by dietetic means alone was lower in nonobese (4.1%) than in obese patients (16%) ($\chi^2 = 12.2$, $P < 0.001$), and in all but two patients, disease duration was <10 years. The prevalence of true SF was modestly lower in obese than in nonobese patients (56 vs. 62%), but this difference, which was more evident in the first decade of disease (40 vs. 55%), was not statistically significant ($\chi^2 = 3.76$, NS).

In all subjects nonobese and obese) known duration of disease was negatively correlated with ΔCP ($r = -0.652$, $P < 0.001$). This relation was also evaluated separately in nonobese and obese patients grouped according to metabolic control. In well-controlled patients (nonobese GC vs. obese GC), ANOVA and ANCOVA of the two regression lines between duration of disease and ΔCP showed a significant difference in the slopes ($F = 7.14$, $P < 0.05$) and the intercept points ($F = 26.3$, $P < 0.01$) (Fig. 3*A*).

In poorly controlled patients (nonobese SF vs. obese SF), statistical analysis of the two regression lines between duration of disease and ΔCP revealed similar slopes ($F = 1.58$, NS) and a slightly significant difference in the intercept points ($F = 8.18$, $P < 0.05$) (Fig. 3*B*). Multiple regression analysis followed by stepwise procedure showed that *1*) basal C-peptide concentration was mainly influenced by BMI (partial $F = 96.2$) and mG (partial $F = 38.2$) and less by duration of disease (partial $F = 15.6$) and *2*) ΔCP was mainly influenced by mG (partial $F = 216.7$) and duration of disease (partial $F = 160.3$) and less by BMI (partial $F = 27.2$).

CONCLUSIONS — This study involved 362 type 2 diabetic patients with a wide range of metabolic control, duration of disease, and BMI, whose data had been partially reported previously (22). The prevalence of SF was 58.3%, which is a moderately higher value than that reported by others (23,24). It is possible that a very few type 1 diabetic subjects might have been present in our nonobese group, but the negligible number should not affect the data interpretation. Only 40 patients (11.1%) were well controlled by diet alone.

Among our obese patients, a lower prevalence of SF and a higher percentage of dietetic control were observed in comparison with nonobese patients only in the first decade of disease (16 vs. 4.1%). Indeed, in both obese and nonobese groups, after 10 years of disease, the prevalence of SF is similar and the likelihood of achieving GC by diet alone is poor (25). It has been suggested that the progressive exhaustion of insulin production and the consequent decrease in secretion over time is the leading factor in SF (22,25–29). The data, however, are not always concordant (24,30–35).

In our nonobese and obese groups, insulin secretion was inversely associated with duration of diabetes. In GC patients, the slope and the intercept points of the two regression lines (nonobese and obese) were significantly different. This may be interpreted as meaning that insulin hypersecretion in obese patients is, on average, a characteristic of the first years of disease. The progressive exhaustion of β-cell func-

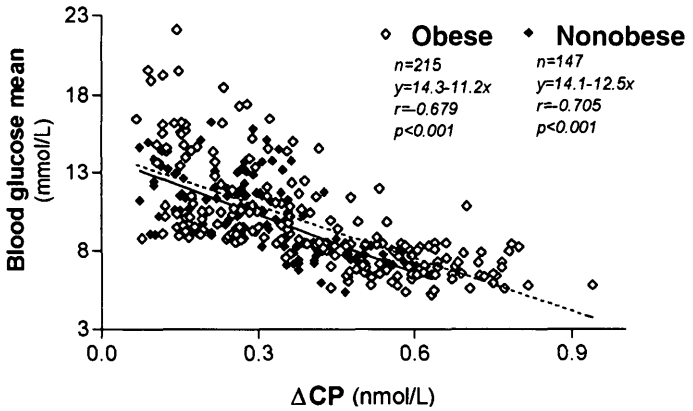

Figure 2—*Relationship between mG and ΔCP in obese (◇) and nonobese (◆) diabetic patients. Regression lines are solid (——) for the nonobese group and dotted (----) for the obese group.*

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Table 2—*Meal-stimulated C-peptide (ΔCP) in nonobese and obese type 2 diabetic patients grouped according to their glycemic control and the known duration of disease*

	Nonobese GC	Obese GC	Nonobese SF	Obese SF
Disease duration (years)				
0–10	0.512 ± 0.016	0.613 ± 0.014*	0.292 ± 0.009	0.347 ± 0.016†
11–20	0.444 ± 0.011	0.507 ± 0.017‡	0.230 ± 0.013	0.228 ± 0.011
>20	0.358 ± 0.014	0.390 ± 0.015	0.138 ± 0.014	0.147 ± 0.008

Data are means ± SEM and are given in nanomoles per liter. *$P < 0.001$; †$P < 0.02$; ‡$P < 0.005$.

tion over time is faster in obese than in nonobese patients. Thus, after 15–20 years of disease, the difference between nonobese and obese patients becomes negligible.

In poorly controlled patients, the two regression lines of nonobese and obese patients were similar. It is conceivable that the progressive reduction in β-cell function occurs over time, at exactly the same rate in both groups, regardless of BMI.

The significant difference between the two regression lines of nonobese GC and obese GC proves that obese patients need higher insulin levels to achieve good glycemic control; however, the insulin response shows considerable heterogeneity, with overlapping between nonobese and obese groups. This finding confirms previous data (36–38). Thus, an unequivocal separation between the two groups was difficult to achieve.

Obesity and type 2 diabetes are characterized by insulin resistance (39). Indeed, it is well known that weight loss improves insulin sensitivity and glycemic control in obese type 2 diabetic patients (40–42). Moreover, it has been reported that, in the spontaneous condition of hyperglycemia, obesity has an additive effect on both hepatic and peripheral insulin resistance of type 2 diabetes (43). Nevertheless, the contribution of obesity to insulin resistance in type 2 diabetes remains a matter of controversy (38,44–46).

It has recently been reported that, during euglycemic-hyperinsulinemic clamp, obesity has a major impact on insulin resistance in nondiabetic subjects, but its effects on insulin resistance in type 2 diabetes patients are more modest. Thus, diabetes per se is the major contributor to insulin resistance in type 2 diabetes, whereas the effect of increasing weight is less significant and is only appreciable when true obesity is superimposed (47).

In addition, there is an impressive body of evidence that demonstrates that the progression of glucose intolerance to overt diabetes is heralded, in obese as well as nonobese subjects, by a decline in insulin secretion, without any worsening of the insulin resistance (48).

In the present study, insulin secretion was on average higher in obese than nonobese patients. When metabolic control was considered, the difference between obese and nonobese patients was still evident in well-controlled groups. By contrast, in poorly controlled groups, obese SF showed higher ΔIRI levels than nonobese SF but similar ΔCP, suggesting decreased hepatic insulin extraction (Fig. 1) (49–52). Therefore, obese SF, when compared with nonobese SF, displayed a similar low insulin secretion and possibly an increased hepatic insulin resistance. In all subjects, however, the daily mean glycemia (mG) was better correlated with meal-stimulated C-peptide (ΔCP) levels (Fig. 2) than with basal C-peptide ($r = 0.529$ vs. $r = 0.335$, both $P < 0.001$); interestingly, BMI was correlated with basal C-peptide ($r = 0.223$, $P < 0.001$) but not with ΔCP.

Indeed, multiple regression analysis demonstrated that ΔCP was mainly dependent on glycemic control (mG) and duration of disease, whereas basal C-peptide was mainly dependent on BMI, and less on duration of disease. The postprandial incremental value of C-peptide appears to be the

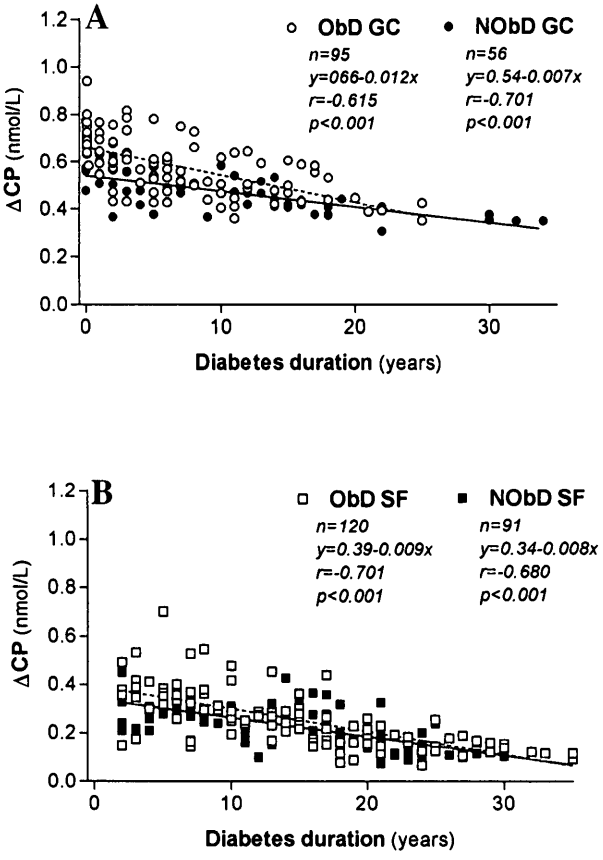

Figure 3—*A: Relationship between ΔCP and known diabetes duration in obese (○) and nonobese (●) diabetic patients with good glycemic control (ObD-GC and NObD-GC). B: Relationship between ΔCP and known diabetes duration in obese (□) and nonobese (■) diabetic patients with poor glycemic control (ObD-SF and NObD-SF). Regression lines are solid (——) for the nonobese group and dotted (----) for the obese group.*

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most important index of metabolic control, and is relatively independent of the overweight condition.

In this study, the residual β-cell function (ΔCP), but not fasting C-peptide, is significantly correlated with the known duration of diabetes in all groups (Fig. 3*A* and *B*). In this regard, the conflicting results reported in the literature may well be due largely to the range of disease duration and BMI and the use of basal C-peptide or peak values of stimulated C-peptide, instead of increments above basal value.

The negative correlation between ΔCP and duration of diabetes underlines, in agreement with other studies (53–55), that β-cell exhaustion constitutes a major pathogenetic factor in SF in both nonobese and obese type 2 diabetic patients. Thus, this suggests that type 2 diabetes is a progressive disease that is no different in obese and nonobese diabetic patients and leads to the need for insulin therapy (56,57).

On the basis of this study, it is possible to conclude that *1*) in GC groups, obese patients displayed higher insulin secretion than nonobese patients, especially in the early years of disease; 2) obesity (BMI) seems more closely related to insulin resistance than to basal C-peptide level; 3) residual β-cell function (ΔCP) modulates metabolic control and is mainly influenced by diabetes duration; and 4) after several years of diabetes, both groups have similar insulin secretion. Thus, the progressive impairment of insulin secretion is the major pathogenetic factor in the onset of SF for both obese and nonobese type 2 diabetic subjects.

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