On the Pathogenesis of Maturity-onset Diabetes

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Diabetes mellitus most probably is a syndrome resulting from different genetic as well as environmental causes. By far the most common type of diabetes is the one which, at least in the beginning, is non-insulin requiring and non-ketosis prone, sometimes called maturity-onset or type 2 diabetes. Most often it is diagnosed in adults and elderly subjects. It has been amply demonstrated that genetic factors play a decisive role in the development of this type of diabetes. It is generally accepted that the disease develops stepwise from a genetically determined initial stage (prediabetes), to chemical diabetes with decreased glucose tolerance only, and finally to manifest diabetes. This course can be slow or more rapid depending on the weight of those factors that usually precipitate this type of diabetes: overweight, age, stress, drugs, etc.

THE PROBLEM

It is still not clear which is the primary derangement in the development of maturity-onset diabetes. For many years, we have advocated the idea that the decisive factor is an impairment of insulin response of the beta-cell to glucose stimulation.[1] Other authors, mainly Reaven and co-workers, are strong supporters for the view that the primary defect is a decreased sensitivity of the tissues to insulin.[2,3] The finding of elevated insulin response to oral glucose in subjects with what was called a borderline oral glucose tolerance test (OGTT) was considered to support this idea.

The study presented here was aimed at elucidating the controversy regarding the primary derangement in maturity-onset diabetes.

THE STUDY

The following groups of subjects were studied: (for details, see Efendić et al.[4]): healthy subjects (N = 164); slight impairment of OGTT, normal IVGTT (N = 23); moderate impairment of OGTT, normal IVGTT (N = 29); decreased OGTT, normal IVGTT (N = 10); impaired OGTT and IVGTT (N = 10); and mild maturity-onset diabetes (N = 13).

TABLE 1
Criteria for oral glucose tolerance test (OGTT)

Group	Venous blood glucose concentration (mM/L)			
	Fasting	1 h		2 h
Normal	<5.2	<7.8	and	<6.4
Borderline-1	<5.2	7.8–8.8	and/or	6.4–6.6
Borderline-2	<5.2	≥8.9	or	≥6.7
Decreased	<5.2	≥8.9	and	≥6.7

In all subjects, oral as well as i.v. glucose tolerance tests were performed. In addition, insulin responses to the oral glucose load and to glucose infusion were evaluated.

The criteria used for the evaluation of the OGTT are given in Table 1. Thus, normal subjects had a fasting blood glucose below 5.2 mmol/L and 1 and 2-h values less than 7.8 and 6.4, respectively. OGTT was considered decreased

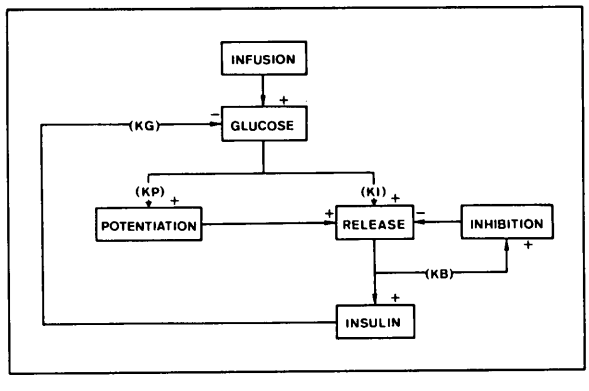

FIG. 1. Hypothetical model for the glucose-insulin interplay during GIT. A plus or minus indicates whether an increase or decrease occurs. Within brackets are parameters that measure the magnitudes of the various effects (KI, KB, KP, KG).

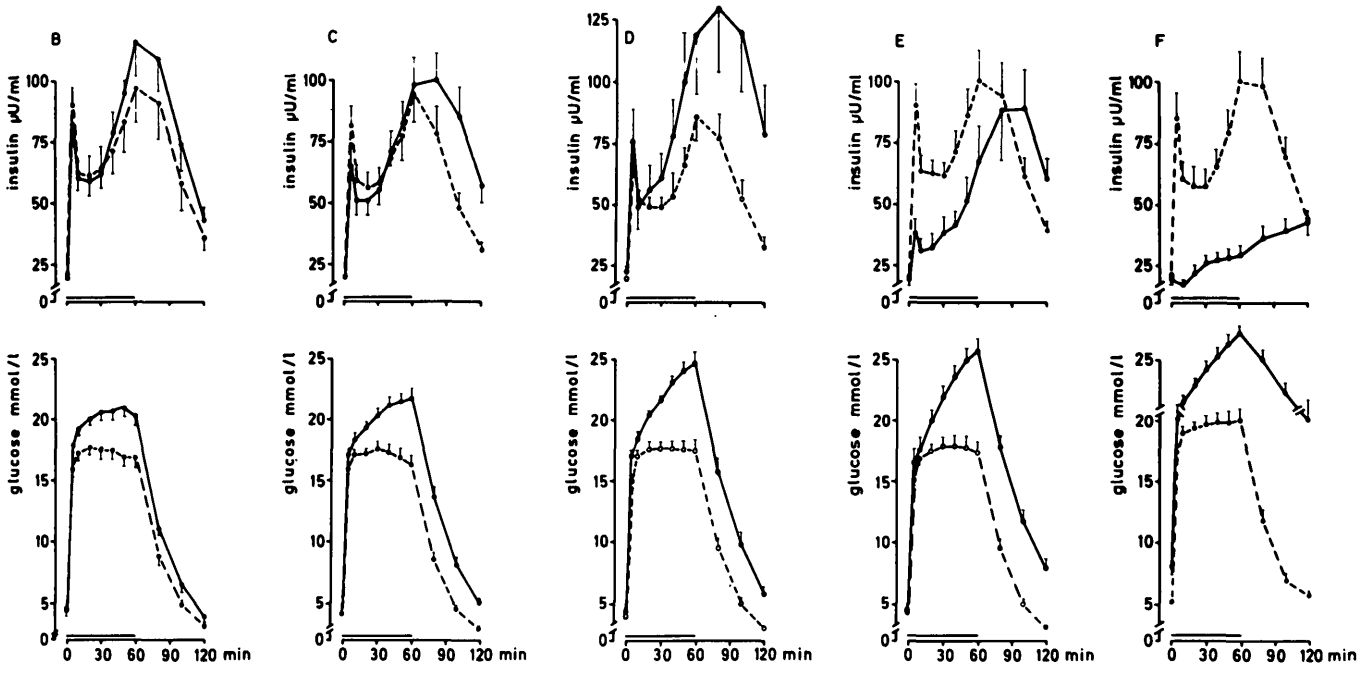

FIG. 2. Insulin and glucose responses (solid lines) to the glucose infusion test (GIT) in subjects with impaired OGTT and normal IVGTT (B, C, D), in subjects with decreased IVGTT (E), and in mild maturity-onset diabetic subjects (F). Broken lines denote the findings in sex-, weight-, and age-matched control subjects.

when the 1 and 2-h values were equal to or higher than 8.9 and 6.7 mmol/L. OGTT was called "borderline" when the 1 and 2-h values were between those of the normal subjects and those with decreased OGTT.

Insulin response to GIT was analyzed by parameter identification in a mathematical model (Figure 1).[5] This assumes that glucose stimulates insulin release by two mechanisms. First, it initiates insulin release by an immediate action (pa-

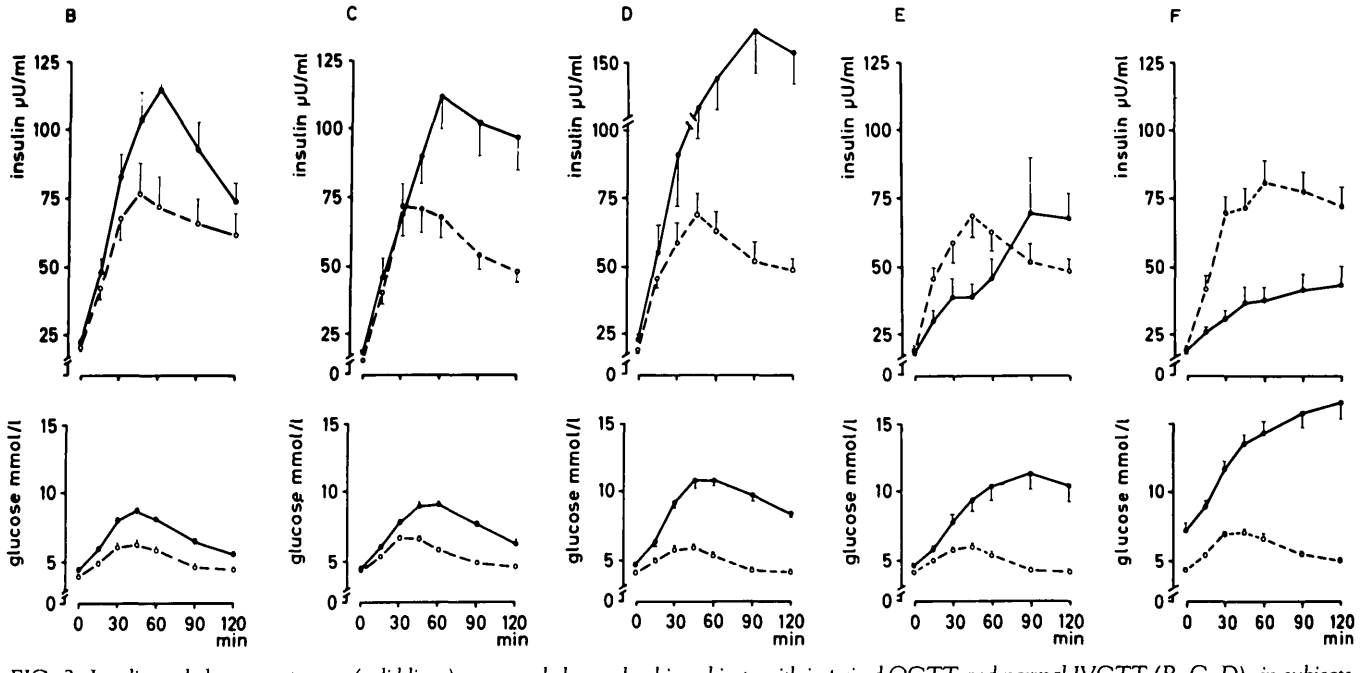

FIG. 3. Insulin and glucose responses (solid lines) to an oral glucose load in subjects with impaired OGTT and normal IVGTT (B, C, D), in subjects with decreased IVGTT (E), and in mild maturity-onset diabetic subjects (F). Broken lines denote the findings in sex-, weight-, and age-matched control subjects.

TABLE 2
IVGTT, basal glucose and insulin, insulin response to GIT, and insulin sensitivity in subjects with glucose intolerance and matched controls*

Groups of subjects	N	Sex ratio (F/M)	Age (yr)	Body weight (% of ideal)	IVGTT (K value)	Fasting values		Computer parameters			
						Glucose (mM/L)	Insulin (μU/ml)	KI	IP	KG	KP
B. Normal IVGTT, borderline-1 OGTT	23	8/15	42.1 ± 2.5	94.9 ± 1.5	1.80 ± 0.13	4.3 ± 0.1	21 ± 1	0.71 ± 0.12	58 ± 8	46.6 ± 4.6	2.3 ± 0.4
Controls†	23		43.0 ± 2.4	94.9 ± 1.4	2.26 ± 0.20	4.2 ± 0.1	21 ± 1	1.01 ± 0.21	61 ± 6	63.1 ± 5.7	2.1 ± 0.4
	P‡										
C. Normal IVGTT, borderline-2 OGTT	29	14/15	40.1 ± 2.3	94.5 ± 1.8	1.56 ± 0.09	4.4 ± 0.1	22 ± 1	0.53 ± 0.10	44 ± 8	41.3 ± 4.8	3.1 ± 0.6
Controls†	29		39.8 ± 2.3	94.9 ± 1.6	2.29 ± 0.21	4.0 ± 0.1	20 ± 1	0.76 ± 0.12	60 ± 8	72.0 ± 7.6	1.9 ± 0.3
	P‡				<0.001			<0.05		<0.01	
D. Normal IVGTT, decreased OGTT	10	3/7	44.1 ± 3.7	100.3 ± 3.1	1.54 ± 0.22	4.5 ± 0.1	23 ± 2	0.64 ± 0.25	41 ± 9	30.9 ± 6.0	3.4 ± 0.6
Controls†	20	6/14	44.4 ± 3.4	98.9 ± 2.3	2.13 ± 0.24	4.1 ± 0.1	19 ± 1	0.62 ± 0.01	48 ± 5	63.5 ± 6.3	1.7 ± 0.3
	P‡				<0.05					<0.01	<0.01
E. Decreased IVGTT, impaired OGTT	10	3/7	45.5 ± 4.9	91.8 ± 3.2	0.93 ± 0.04	4.5 ± 0.1	19 ± 2	0.12 ± 0.03	12 ± 3	23.8 ± 3.6	4.3 ± 1.2
Controls†	20	6/14	44.4 ± 3.4	92.2 ± 1.6	2.18 ± 0.23	4.2 ± 0.1	21 ± 1	1.09 ± 0.18	71 ± 10	56.4 ± 8.4	2.2 ± 0.4
	P‡				<0.001			<0.001	<0.001	<0.01	
F. Mild manifest diabetes	13	5/8	44.0 ± 4.2	96.8 ± 2.6	0.67 ± 0.04	7.3 ± 0.5	19 ± 1	0.10 ± 0.05	7 ± 2	24.3 ± 4.9	2.6 ± 1.0
Controls†	26	10/16	45.0 ± 3.1	94.5 ± 1.6	1.89 ± 0.12	4.2 ± 0.1	20 ± 1	0.91 ± 0.7	63 ± 10	57.2 ± 8.3	2.2 ± 0.4
	P‡				<0.001	<0.001		<0.001	<0.001	<0.01	

* Results are expressed as $\bar{X}$ ± SEM (mean ± standard error of the mean).
† Control subjects were selected from a group of 164 subjects (group A) with normal fasting blood glucose, OGTT, and IVGTT.
‡ Significance was calculated according to Mann-Whitney's test.

rameter KI) and, second, it generates a time-dependent potentiating mechanism (parameter KP), which amplifies the former action. The computer analysis of GIT allows the identification of a further parameter, KG, determining the sensitivity of the tissues for insulin. From the hypothetical insulin release curve given by the mathematical model, an insulin value at 10 min was calculated, called IP, reflecting the response to a standard glucose stimulation.

Figure 2 demonstrates insulin responses to the glucose infusion in our different groups of subjects. Glucose was administered from 0 to 60 min (500 mg/kg as a bolus followed by 20 mg/kg/min). It can be seen that in group E (decreased IVGTT and impaired OGTT) as well as in group F (mild manifest diabetes) both early and late insulin responses to GIT were suppressed. On the other hand, in groups B, C, and D (normal IVGTT but impaired OGTT) early insulin response, at least in absolute terms, was not decreased. Moreover, late insulin response was enhanced.

Insulin responses to the oral glucose load in groups B–F and their controls are demonstrated in Figure 3. Analogous to the findings in the GIT, insulin release was suppressed in groups E and F, whereas in groups B, C, and D early insulin release was of the same magnitude as in the normal subjects but the late release was markedly enhanced.

Table 2 summarizes the results of the computer analyses of GIT in all groups. As for insulin release, the computer findings confirm the impression gained from the curves for insulin and glucose during GIT (Figure 2). Thus, in groups B, C, and D (impaired OGTT and normal IVGTT) early insulin responses (KI and IP) were not different from those of the control groups. On the other hand, insulin sensitivity (KG) was lower than in the controls. The potentiatory mechanism (KP) was elevated in groups C and D but significantly so only in D. In groups E and F, insulin response (KI and IP) as well as insulin sensitivity (KG) was decreased, while KP remained unchanged.

In essence, the computer analyses revealed that decreased insulin sensitivity characterizes all stages of glucose intolerance. Furthermore, when IVGTT is decreased, both early and late insulin release are lowered. Thus, groups B, C, and D demonstrated decreased insulin sensitivity but, in absolute terms, unaltered insulin release. To get a better insight into the dynamics of insulin release in these groups, we compared the insulin release in groups C and D with that of control groups with the same degree of insulin insensitivity but with normal OGTT. As seen in Table 3, insulin release was considerably and significantly higher in the controls than in groups C and D.

These findings are illustrated in Figure 4. The left panel denotes group C and the right one group D. It is obvious that both early and late insulin responses were decreased in groups C and D compared with control groups with the same degree of insulin insensitivity.

In conclusion, the data presented suggest that all stages of glucose intolerance are accompanied by a decreased ability of glucose to initiate insulin release as well as by decreased insulin sensitivity. These two derangements seem to be partially

TABLE 3
Comparison of groups C and D with controls matched for KG*

Groups of subjects	N	Sex ratio (F/M)	Age (yr)	Body weight (% of ideal)	IVGTT (K value)	Fasting values		Computer parameters			
						Glucose (mM/L)	Insulin (μU/ml)	KI	IP	KG	KP
C. Normal IVGTT, borderline-2 OGTT	29	14/15	40.1 ± 2.3	94.5 ± 1.8	1.56 ± 0.09	4.4 ± 0.1	22 ± 1	0.53 ± 0.10	44 ± 8	41.3 ± 4.8	3.1 ± 0.6
Controls†	29		40.0 ± 2.4	94.9 ± 1.6	2.13 ± 0.17	4.2 ± 0.1	22 ± 1	0.86 ± 0.12	74 ± 9	41.3 ± 4.6	2.3 ± 0.5
	P‡				<0.01			<0.01	<0.001		
D. Normal IVGTT, decreased OGTT	10	3/7	44.1 ± 3.7	100.3 ± 3.1	1.54 ± 0.22	4.5 ± 0.1	23 ± 1	0.64 ± 0.25	41 ± 9	30.9 ± 6.0	3.4 ± 0.6
Controls†	10		45.8 ± 4.2	95.2 ± 2.8	2.17 ± 0.20	4.1 ± 0.1	20 ± 2	0.96 ± 0.19	81 ± 11	32.0 ± 5.7	2.7 ± 0.8
	P‡				<0.05			<0.05			

* Results are expressed as $\bar{X}$ ± SEM (mean ± standard error of mean).
† Control subjects were selected from a group of 164 subjects (group A) with normal fasting blood glucose, OGTT, and IVGTT.
‡ Significance was calculated according to Mann-Whitney's test.

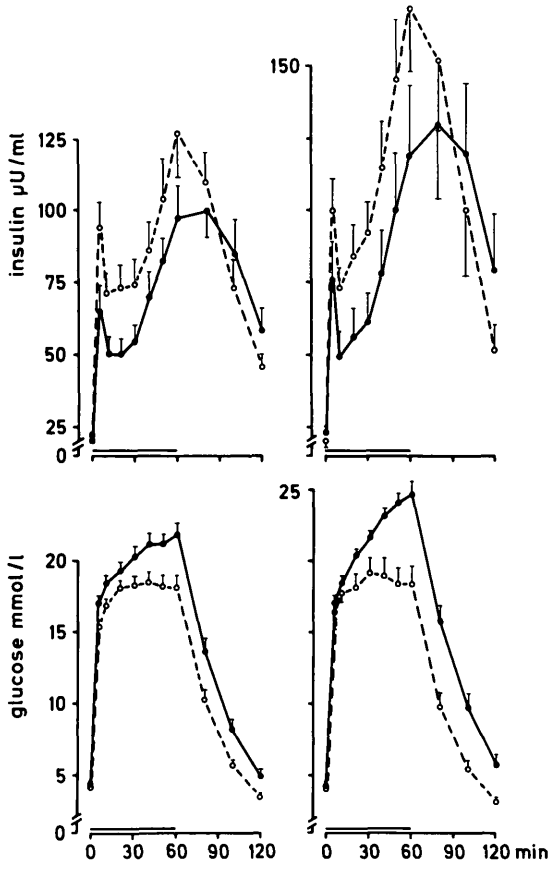

FIG. 4. Insulin and glucose responses to the glucose infusion test (GIT) in subjects with impaired (left panel, group C) and decreased OGTT (right panel, group D) but with normal IVGTT (solid lines). Broken lines denote the responses in control groups matched for insulin sensitivity (KG).

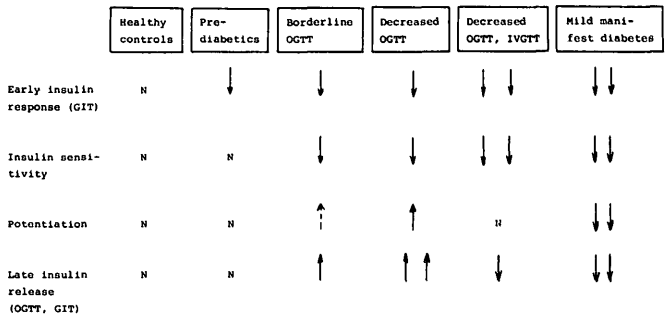

FIG. 5. Hypothesis: development of type 2 diabetes.

compensated for by enhancement of the capacity of glucose to potentiate insulin release in subjects with decreased OGTT but still normal IVGTT.

The impaired insulin release in subjects with decreased IVGTT was recognized previously, and considered by us to be the major reason for the development of glucose intolerance.[1] Since we always used IVGTT to define glucose intolerance, the finding of grossly impaired insulin release to i.v. glucose was one of the cornerstones in our hypothesis that the failure of the beta-cells to respond adequately to glucose was a genetic marker of non-insulin-dependent diabetes.

On the other hand, the increased insulin levels—in absolute terms—during the late phase of an *oral* glucose challenge, together with decreased insulin sensitivity in subjects with decreased OGTT, were previously recognized by other authors.[2,3] Accordingly, they suggested decreased insulin sensitivity as a primary derangement in the development of the disease.

Most likely, non-insulin-dependent diabetes is an inherited disease that develops from a prediabetic state via a stage of glucose intolerance to manifest diabetes.[6] This process might be a slow or a fast one. Our groups of subjects, selected on the basis of arbitrary criteria and representing different degrees of glucose intolerance, might reflect the natural history of this type of diabetes. However, it is still possible that there are types of non-insulin-dependent diabetes with different pathogenesis, e.g., one primarily characterized by major impairment of insulin release and another with marked decrease in insulin sensitivity as a principal derangement.

Our present working hypothesis for the development of type 2 diabetes, in most instances, is summarized in Figure 5. The earliest phase of the disease would be the prediabetic stage, characterized by an inherited low insulin response to glucose. The next stage, characterized by borderline or decreased OGTT, would be precipitated by the appearance of decreased insulin sensitivity. The latter derangement is, at least partially, compensated for by enhancement of the ability of glucose to potentiate insulin release. The interaction of these two processes—decreased insulin sensitivity and increased potentiation—is reflected by the enhancement of the late phase of insulin release, at least in absolute terms. Progression of the impairment of insulin release and/or of decreased insulin sensitivity, together with the loss of the compensatory potentiating mechanism, results in decreased IVGTT or manifest diabetes.

CONCLUSIONS

Insulin response to glucose and insulin sensitivity were determined in groups of subjects with different degrees of glucose intolerance. They were selected on the basis of fasting blood glucose concentration and oral (OGTT) and intravenous (IVGTT) glucose tolerance tests. They were matched as to body weight, age, and sex with control subjects with normal OGTT and IVGTT. The initiatory (parameters KI and IP) and potentiatory (KP) effects of glucose on insulin release as well as the sensitivity to endogenous insulin (KG) were measured by computer analysis of the glucose and insulin curves during a standardized glucose infusion test (GIT).

Subjects with impaired OGTT but normal IVGTT dem-

onstrated decreased KG and increased KP, while KI and IP were normal. However, KI and IP were considerably lower than in a matched group of control subjects with the same decrease in KG but with normal OGTT and IVGTT. In subjects with impairment of both OGTT and IVGTT, KI, IP, and KG were decreased whereas KP was normal.

The data suggest that decreased ability of glucose to initiate insulin release as well as decreased insulin sensitivity accompany all stages of glucose intolerance. In subjects with decreased OGTT but normal IVGTT, these derangements are partially compensated for by increased capacity of glucose to potentiate insulin release. These findings have been combined into a working hypothesis for the development of most instances of maturity-onset diabetes.

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