Maintenance of Basal Insulin Secretion in Severe Non-Insulin-Dependent Diabetes

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It has been postulated that glucose regulation is secondary to maintenance of normal basal insulin secretion. Serum glucose, insulin, and C-peptide levels were measured at fasting in 209 consecutive non-insulin-dependent diabetic patients and after glucose stimulation in 193 patients. The basal serum insulin C-peptide levels were not significantly different in control subjects (mean 22 ± 8.8 μU/ml) and in patients with varying severity of diabetes (mean 24 ± 9.6 μU/ml) except in the most severely diabetic group [fasting serum glucose >350 mg/dl (19.4 mmol/L), mean 19 ± 7 μU/ml]. In 39 patients who developed ketonuria *without acidosis* during follow-up, the mean basal serum insulin was 22 μU/ml during the episode of ketonuria, 21 μU/ml during the glucose tolerance test, and 25 μU/ml after glucose stimulation (statistically nonsignificant differences). Our data suggest that hyperglycemia compensates for β-cell impairment so that basal insulin secretion usually stays above the threshold for ketoacidosis unless there is marked β-cell impairment. Patients who fail to increase insulin in response to nutrient challenge are at risk of developing ketosis. DIABETES CARE 1986; 9:232–35.

Basal secretion of insulin in diabetes is maintained by hyperglycemia. Thus, it has been proposed that glucose regulation is of secondary importance to the maintenance of basal insulin secretion.[1] This hypothesis accounts for the normal basal insulin levels in non-insulin-dependent diabetes mellitus (NIDDM) despite severe islet cell impairment and low intraindividual variation of basal serum glucose levels.[1] NIDDM is common in Saudi Arabia,[2] but it is rarely treated with insulin, even when severe. We have therefore had the opportunity to observe and measure serum insulin levels in a large number of patients with severe NIDDM. Our observations support the above hypothesis and suggest that basal insulin levels are maintained just above the threshold for development of ketosis.

SUBJECTS AND METHODS

Two hundred sixty-five Middle Eastern (240 Saudi-Arabian) patients with diabetes (National Diabetes Data Group criteria)[3] and 12 patients with glucose intolerance[3] were referred to the diabetes clinic of our hospital during the 3-yr period from April 1981 to March 1984.

Fifty-six patients (14 insulin-dependent and 42 non-insulin-dependent) had received insulin in the past and were excluded. Fasting serum glucose (FSG), insulin, C-peptide, and hemoglobin A_1 levels were recorded for all 221 patients who had not received insulin. An oral glucose tolerance test using 75 g glucose, with measurement of serum glucose, insulin, and C peptide at 0, 45, 90, and 120 min, was done in 193 of these patients and 35 control subjects (23 Middle Eastern volunteers and 12 laboratory technicians). These tests were done in the morning on ambulant patients who had discontinued oral hypoglycemic drugs 2 wk before, and no patient was taking corticosteroids, β-blockers, or diuretic drugs.

Analytic methods. Serum glucose was measured by a standard automated technique (SMAC, Technicon, Tarrytown, New York) with an adaption of the hexokinase glucose-phosphate dehydrogenase method. Serum insulin was measured by radioimmunoassay by use of a double-antibody technique with a kit supplied by Amersham (Arlington Heights, IL). Serum C peptide was measured by radioimmunoassay by a double-antibody technique with a kit supplied by Mallingkrodt Diagnostica (St. Louis, MO). Hemoglobin A_1 was measured by differential elution of total hemoglobin A_1 and other fast hemoglobins with a kit supplied by Isolab (Akron, OH).

All measurements were carried out by two laboratory technicians. The interassay coefficients of variation based on 20 consecutive batches are shown in Table 1.

Patients attended each follow-up visit in a fasting state. Serum glucose, C peptide, insulin, and urine glucose and ketones (by use of Ketostix, Ames, Elkhart, IN) were measured, and the information was entered on standard forms.

TABLE 1
Quality control of laboratory measurements

Serum	Coefficient of variation			
	Low target value		High target value	
Glucose (mg/dl)	78	(1.14%)		
Insulin (μU/ml)	10	(19.00%)	112	(7.7%)
C peptide (ng/ml)	1.1	(15.00%)	2.8	(10.6%)
Hemoglobin A_1 (%)	6.9	(6.60%)	16.1	(5.9%)

Coefficient of variation is shown in parentheses.

All patients with positive Ketostix had serum acetoacetate/acetone tested by Ketostix[4] and serum electrolytes determined. Ketoacidosis was diagnosed if the serum was positive for ketones, the serum bicarbonate was <22 mmol/L, and the anion gap was >12. The number of episodes of ketonuria that occurred before treatment with oral hypoglycemic drugs or insulin was recorded as a ratio of the total number of urine tests (clinic visits) performed in those patients. The post-stimulation serum insulin levels in the ketonuric patients were those at 1½ h after ingestion of glucose during the glucose tolerance test (N = 24), or in cases in which a glucose tolerance test was not done, 1½ h after eating breakfast (N = 9). The data were entered in a statistical software program produced for the Radio Shack computer (Tandy, Rydalmere, NSW, Australia). The Student's *t* test was used for comparison of the means and Pearsons simple correlation coefficient for correlation.

RESULTS

The age, body mass index, hemoglobin A_1, serum glucose, insulin, and C-peptide measurements (excluding those from four patients who developed ketoacidosis) are shown in Table 2 and Figure 1, grouped by FSG intervals. Serum insulin and C-peptide levels after glucose stimulation were not significantly different at 1½ h compared with 2 h and were higher than the levels at 45 min in all but nine cases. The results

TABLE 2
Results of serum glucose, C peptide, and insulin (basal and 1.5 h after 75 g glucose), grouped by basal serum glucose intervals

Basal serum glucose (mg/dl)	N‡	Age (yr)	BMI§ (kg/m²)	HbA_1‖ (%)	Glucose (mg/dl)		Serum insulin (μU/ml)		C peptide (ng/ml)		No. with ketonuria
					Basal	1.5 h	Basal	1.5 h	Basal	1.5 h	
	35	32	25.6	6.1	95	149	22	91	1.8	6.8	
Control		(5)	(4.8)	(.65)	(9)	(36)	(8.8)	(51)	(.86)	(2.6)	
				•	•	•		•		•	
Glucose	12	38	28	7.5	117	227	24	147	2.6	9.1	
intolerant		(8)	(4)	(1.0)	(16)	(54)	(10)	(51)	(1.6)	(2.1)	
Diabetic											
				•	•	•		•		•	
<140	26	45	27.7	8.1	121	277	23	107	2.9	6.9	0
		(14)	(2.8)	(1.1)	(13)	(45)	(9.6)	(58)	(1.5)	(1.8)	
				•							
140–199	38	49	27.6	10.1	169	349	26	65	2.7	5.1	0
		(10)	(4.9)	(1.5)	(16)	(52)	(11)	(34)	(0.8)	(1.9)	
				•	•	•				•	
200–249	25	42	27.7	11.4	223	410	27	54	2.6	4.0	1
		(8)	(5.0)	(2.0)	(14)	(50)	(8)	(24)	(1.0)	(1.6)	(4%)
					•	•		†		†	
250–299	35	40	27.5	12.1	275	463	24	41	2.4	3.6	5
		(9)	(5.9)	(1.6)	(13)	(45)	(6)	(17)	(1.4)	(1.5)	(14%)
				•	•	•				†	
300–349	46	44	26.8	13.4	326	520	25	35	2.2	2.7	14
	(36)	(10)	(3.9)	(1.7)	(14)	(61)	(8)	(15)	(0.9)	(1.6)	(30%)
			•	•	•	•	•	•			
>350	39	44	23.6	15.2	425	594	19	21	2.1	2.2	19
	(21)	(14)	(4.2)	(1.4)	(65)	(88)	(7)	(9)	(1.0)	(0.7)	(54%)
Ketonuric	39	43	23.1	14.9	398	576	21	25	2.0	2.3	39
group	(33)	(13)	(4.0)	(1.7)	(71)	(69)	(6.9)	(7.0)	(1.1)	(1.2)	
All diabetic	181		26.8	12.0	266	427	24	55	2.4	4.2	39
subjects			(4.8)	(2.7)	(104)	(113)	(9.6)	(43)	(1.1)	(2.4)	

Standard deviations in parentheses.
Significant differences: Student's *t* test for vertical pairs of means, $*P < .01$; $†P < .05$.
‡N, number of 1.5-h measurements performed in parentheses.
§BMI, body mass index; ‖HbA_1, hemoglobin A_1.

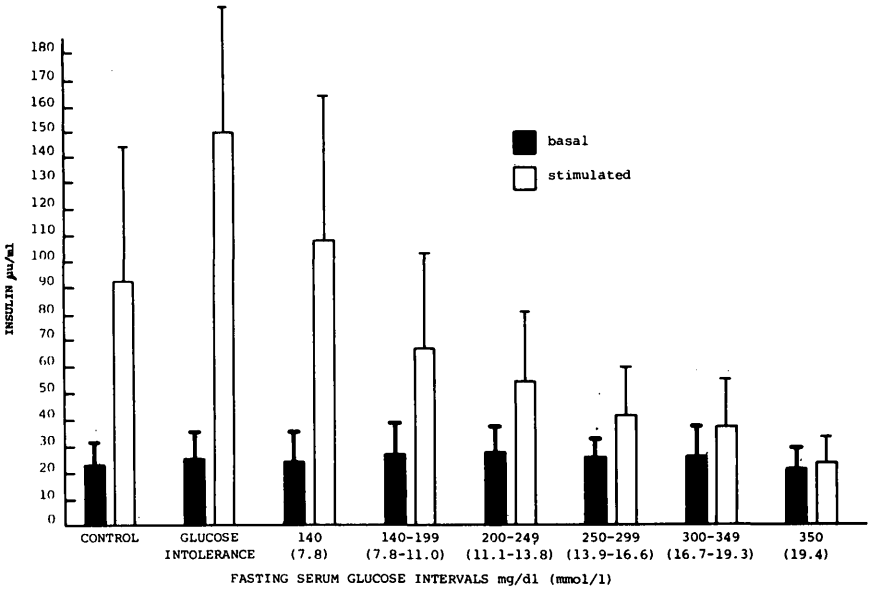

FIG. 1. Basal and poststimulation (90 min after 75 g oral glucose) serum insulin standard deviations in 205 diabetic patients, 12 patients with glucose intolerance, and 35 control subjects.

show that the basal serum insulin and C-peptide levels were similar in the groups of patients with increasing severity of diabetes, the patients with glucose intolerance, and the control subjects. Basal serum insulin levels showed no significant difference, except in the group of patients with the most severe diabetes [FSG >350 mg/dl (19.4 mmol/L)]. Mean poststimulation insulin levels decreased with increasing severity of diabetes. In patients with FSG >350 mg/dl (19.4 mmol/L), poststimulation levels were not significantly different from basal levels.

Correlation coefficients (Table 3) show lower-order negative correlations of basal serum glucose with basal insulin and C peptide compared with higher-order correlations with poststimulation serum glucose, insulin, and hemoglobin A_1.

Four patients developed ketoacidosis and 39 patients developed 47 episodes of ketonuria without acidosis during a total of 135 clinic visits before treatment (mean 3.5 clinic visits). The serum ketone test was negative in all but 2 of these 39 patients with ketonuria. Data on serum glucose and insulin both during the episode of ketonuria and during the glucose tolerance test are shown in Table 4. The mean basal fasting insulin level during the episode of ketonuria was 22 μU/ml and not significantly different from the basal serum insulin level (21 μU/ml) during the glucose tolerance test. The mean poststimulation serum insulin level determined in 30 of 39 ketonuric patients was 25 μU/ml, which was not significantly different from the mean basal insulin level.

TABLE 3
Correlation coefficients in 181 diabetic patients

Independent variable	Dependent variable	Pearsons correlation coefficient
Fasting serum glucose	Fasting serum insulin	−.17*
	Fasting serum C peptide	−.25*
	Poststimulation serum insulin	−.56*
	Peak serum glucose	.88
	Hemoglobin A_1	.80*
	Duration since diagnosis	.017
Fasting serum insulin	Fasting serum C peptide	.4*
	Hemoglobin A_1	−.12*
	Body mass index	.20*

*$P < .01$.

DISCUSSION

Stimulated secretion of insulin is considerably more impaired than basal secretion in NIDDM.[5] Our data show decreasing insulin and C-peptide secretion in response to glucose challenge as diabetes increased in severity (based on FSG levels) and insignificant secretion of insulin in response to glucose when FSG levels exceeded 350 mg/dl (19.4 mmol/L). Despite this failure of stimulated secretion, basal insulin levels were maintained at normal levels (similar to control levels) until the FSG was >350 mg/dl (19.4 mmol/L).

Ketonuria did not occur in patients with FSG <240 mg/

TABLE 4
Data from 39 patients who developed one or more episodes of ketonuria without ketoacidosis

No. with ketonuria at first visit	14/39 (36%)
No. episodes ketonuria/no. clinic visits	47/135 (35%)
Mean (fasting) serum glucose during ketonuria	376 mg/dl (99 SD)
Mean fasting serum insulin during ketonuria	22 μU/ml (6.0 SD)
Mean fasting serum insulin during glucose tolerance test	21 μU/ml (6.9 SD)
Mean poststimulation* serum insulin (N = 33)	25 μU/ml (7 SD)

*Poststimulation: serum insulin 90 min after 75 g oral glucose (N = 24) or 90 min after breakfast (N = 9).

dl (13.3 mmol/L) and was uncommon at levels <300 mg/dl (16.7 mmol/L) in the absence of infection or other stress. When ketonuria did develop, it was intermittent, with the majority of the urine tests negative for ketones; this finding suggests that the insulin levels were near the threshold for ketosis prevention. The mean serum basal insulin levels in the 39 patients who developed ketonuria were not significantly different from those of diabetic patients who did not have ketonuria. This finding suggests that under basal conditions, serum insulin is maintained at levels that are just adequate to prevent ketosis. The mean stimulated serum insulin level, 25 μU/ml in the ketonuric group, was not significantly different from the basal serum insulin level of the diabetic patients without ketonuria. This suggests that these patients were unable to increase insulin secretion significantly in response to hyperglycemia: the islets were maximally stimulated in maintaining normal basal insulin secretion. These patients would presumably be unable to elevate basal insulin levels further during periods of increased insulin resistance, e.g., during stress.[4]

Most physicians accept the concept that insulin controls serum glucose, i.e., the principal objective is maintenance of normoglycemia, and insulin is the means to this end. Turner and Holman[1] proposed the opposite: the principal objective is the maintenance of normal basal insulin levels, and hyperglycemia is the means whereby this is accomplished. Our data add confirmation to this hypothesis. During fasting, glucose principally regulates insulin (not the reverse)[1,6] and modulates insulin secretion in response to nonglucose secretagogues,[6] in keeping with its important actions other than nutrient disposal, e.g., tissue growth,[7] transmembrane potassium flux,[8] and the prevention of excessive catabolism. Considerably less insulin secretion and lower serum insulin levels are required for lipolysis, ketogenesis, and several other important functions than for transport of glucose into cells.[8,9] Our observations extend those of Turner and Holman in showing that ketosis occurs only when "normal" basal insulin levels (~22 μU/ml in our laboratory assay) cannot be maintained by the glycemic stimulus. The considerable individual variation in the basal serum insulin levels at which ketonuria occurred in our patients is probably due to differences in insulin sensitivity. In fact, the basal serum insulin level is considered to be a good index of insulin resistance[10,11] and correlates well with obesity,[11] although only a low-order correlation ($r = .2$) was present in our patients.

A practical implication of these observations is that patients who fail to show an increase in insulin secretion after glucose stimulation are at high risk of developing ketonuria. Our diabetic patients, even with fasting serum glucose levels >300 mg/dl (16.7 mmol/L), were surprisingly well and often asymptomatic during follow-up provided that basal insulin levels were sufficient to prevent ketosis.[1]

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