living with a depressed person can be distressing, the use of spouses as a control group may have underestimated the differences between diabetic and nondiabetic subjects (3,4). Therefore, further studies comparing overweight type II diabetic subjects with age-, sex-, and weight-matched unrelated individuals would be of interest.

In addition, this study used only the BDI and examined depressive symptomatology but not clinical depression. Previous studies have shown that major depression occurs frequently in adults with type I (insulin-dependent) and type II diabetes, and these depressions tend to run a chronic course (1,5,6). Therefore, it would be interesting to compare diabetic and nondiabetic subjects with multiple measures of depression and to compare the prevalence of both current and lifetime history of depression. This would help determine whether the differences observed in this study represent clinically significant differences.

Finally, it is important to determine the variables related to depressive symptomatology in diabetic individuals and the interrelationship between depression and diabetes therapy. Lustman et al. (1) have suggested that the onset of clinical depression in type II diabetic subjects often precedes the development of diabetes and that depression and diabetes may interact at a basic biologic level. Patients with a history of major depression have poorer glycemic control, but there have been no studies to determine whether improvements in glycemic control, produced by intensive insulin therapy or weight loss in obese type II diabetic subjects, would have an impact on depressive symptomatology or whether treating patients for their depression would improve response to diabetes treatment (5). Such studies are clearly warranted.

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Blood Glucose Area Under the Curve
Methodological Aspects

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To specify the influence of methods used in estimating area under the curve (AUC) and the meaning of total and incremental AUC, 75 glycemic responses to a mixed meal were studied in 75 diabetic patients, 39 with insulin-dependent diabetes mellitus and 36 with non-insulin-dependent diabetes mellitus. AUC was integrated with five computerized methods: polynomial interpolation of third and fourth degree, trapezoidal rule, Simpson's integration, and cubic interpolatory splines. Although these methods gave significantly different results ($P < 0.001$), a strong correlation was found between estimations of AUC with different methods ($r > 0.99$, $P < 0.001$). In addition, variation between methods was ≤2%, whereas the coefficient of variation between subjects was 38%. Total AUC was strongly correlated with basal blood glucose value ($r = 0.90$, $P < 0.001$), whereas incremental and positive AUC were not ($r = 0.12$ and 0.07, respectively, NS). Incremental and positive AUC were strongly correlated with glycemic rise ($r = 0.89$ and 0.93, respectively, $P < 0.001$), whereas total AUC was only slightly so ($r = 0.31$, $P < 0.01$). Incremental and positive AUC gave slightly but significantly different information on glucose response. These results suggest that variations related to the method used in estimating AUC are not clinically relevant and that a simple method such as trapezoidal rule can be used. Total AUC is a descriptive factor related to basal blood glucose value, whereas

incremental and positive AUC more accurately describe glycemic response to foods. *Diabetes Care* 13:172–75, 1990

A recent classification of carbohydrates has been proposed for diet prescription, based on glycemic index of foods, defined as the ratio of area under the curve (AUC) for tested food to AUC for reference food (1–3). However, the glycemic index's accuracy in predicting glycemic response remains unclear, and several questions concerning methodological aspects have been raised (4–6). Trapezoidal rule or planimetry have been used to estimate AUC (7,8), but surprisingly, the methods used are not always clearly described, and no study has proved the reliability of any method and no consensus has been reached. In addition, both total AUC (tAUC) and incremental AUC (iAUC) have been used to study glycemic response, and it is still unclear whether area below baseline (horizontal from basal value) should be subtracted when estimating iAUC (1,2,4,6,8–10). Our purpose was to study the influence of the method used in AUC estimation and to specify the meaning of tAUC and iAUC.

RESEARCH DESIGN AND METHODS

Consecutive diabetic outpatients were included if their standard diet corresponded with the test meal. Patients with hypoglycemia <2.5 mM, ketosis, or hyperglycemia >30 mM were excluded. Glycemic response was studied after a mixed lunch and under their usual treatment in 75 diabetic patients, 39 with insulin-dependent diabetes mellitus (IDDM) (C-peptide <1 ng/ml 6 min after 1 mg glucagon i.v.) and 36 with non-insulin-dependent diabetes mellitus (NIDDM). Composition of the meal was similar for each subject in terms of exchanges but not in terms of glycemic index and included 68 g carbohydrates, 29 g protein, and 32 g lipids for a total of 676 kcal (2825 kJ) (2,4). Blood samples were taken before lunch (basal value) and at 30, 60, 120, and 180 min and were assayed with glucose oxidase.

tAUC was integrated from estimated curves computed with five methods: *1*) polynomial interpolation of third degree (PI^3) with the least-squares method, *2*) polynomial interpolation of fourth degree (PI^4) with Lagrange's interpolating polynomial method, *3*) trapezoidal rule (TR), *4*) cubic interpolatory splines (CIS), and *5*) Simpson's formula (SF) (11–14). iAUC was obtained by subtracting the rectangle corresponding to basal value multiplied by 180 min from tAUC (1,4,9). Because it has been suggested that negative areas (below baseline) should not be subtracted, positive AUC (pAUC) was computed with two steps: *1*) estimations of cutpoints of estimated curve with baseline and *2*) integration of area above baseline (10).

Statistical analysis. Results are expressed as means ± SE. Glycemic rise was defined as the difference between maximal blood glucose level during the test and basal glucose value. Comparisons between methods were made by analysis of variance with repeated measures. Correlations were analyzed with Pearson's linear regression.

RESULTS

Methods used gave significantly different results with the exception of TR and SF (Table 1). Variations of means between methods (on average ≤2%) were lower than between subjects (coefficient of variation 38%). In addition, strong correlations were found between tAUC estimated by different methods (Table 1).

Mean basal glucose value was 13.0 ± 0.7 mM (patients with IDDM, 13.6 ± 1.1; with NIDDM, 12.4 ± 0.6, $P < 0.05$). Mean glucose values were 14.2 ± 0.9 mM at 30 min (15.0 ± 1.0 and 13.2 ± 0.7, respectively, NS), 17.8 ± 1.0 mM at 60 min (20.1 ± 1.2 and 15.5 ± 0.8, $P < 0.01$), 18.2 ± 1.1 mM at 120 min (20.3 ± 1.2 and 16.0 ± 0.9, $P < 0.01$), and 14.8 ± 0.9 mM at 180 min (15.5 ± 1.1 and 14.1 ± 0.7, NS). Glycemic rise was 5.1 ± 0.8 mM (5.1 ± 0.8 and 5.2 ± 0.6, respectively, NS). On average, with TR, tAUC was 2826 ± 123 min · mM (2960 ± 142 and 2692 ± 113, respectively, $P < 0.05$), iAUC was 487 ± 54

TABLE 1
Estimation of total area under the curve with five different methods

	Area under curve (min · mM)	Comparison of means; correlations: coefficient (slope, y-intercept)				
		PI^3	PI^4	TR	CIS	SF
PI^3	2858 ± 125		0.9986 (0.974, 16.3)	0.9996 (0.982, 18.6)	0.9999 (0.995, 9.7)	0.9997 (0.988, 7.7)
PI^4	2799 ± 122	<0.001*		0.9987 (1.006, 8.5)	0.9988 (1.019, −4.7)	0.9996 (1.013, −4.7)
TR	2826 ± 123	<0.001	<0.001		0.9998 (1.012, −7.5)	0.9995 (1.005, −9.3)
CIS	2852 ± 125	<0.001	<0.001	<0.001		0.9998 (0.993, −1.9)
SF	2830 ± 124	<0.001	<0.001	NS	<0.001	

Values are means ± SE. PI^3, polynomial interpolation of third degree; PI^4, polynomial interpolation of fourth degree; TR, trapezoidal rule; CIS, cubic interpolatory spline; SF, Simpson's formula.
*Significance level for between-method comparison of means (analysis of variance with repeated measures).

min · mM (468 ± 85 and 507 ± 66, NS), and pAUC was 553 ± 67 min · mM (592 ± 74 and 514 ± 67, NS). tAUC was significantly correlated with basal value in patients with IDDM ($r = 0.91$, $P < 0.001$) or NIDDM ($r = 0.87$, $P < 0.001$). In the population as a whole, ~80% of variance of tAUC was explained by basal value (Fig. 1). iAUC was not significantly correlated with basal value among patients with IDDM ($r = 0.19$), NIDDM ($r = 0.08$), or in the total population ($r = 0.12$), and pAUC ($r = 0.17$, 0.02, and 0.14, respectively). iAUC and pAUC were correlated with glycemic rise among patients with IDDM ($r = 0.91$, $P < 0.001$, and $r = 0.95$, $P < 0.001$, respectively) or NIDDM ($r = 0.88$, $P < 0.001$, and $r = 0.91$, $P < 0.001$) and in the total population ($r = 0.89$, $P < 0.001$, and $r = 0.93$, $P < 0.001$). tAUC was slightly correlated with glycemic rise ($r = 0.37$, $P < 0.05$; $r = 0.33$, $P < 0.05$; $r = 0.31$, $P < 0.01$, respectively).

Of 75 patients, 14 (12 with IDDM and 2 with NIDDM) had blood glucose levels below baseline at 180 min. On average, iAUC and pAUC were significantly different only among patients with IDDM ($P < 0.05$) but were significantly correlated in both groups (IDDM, $r = 0.83$, $P < 0.001$; NIDDM, $r = 0.96$, $P < 0.001$). Similar results were found when estimating AUC with CIS or PI.

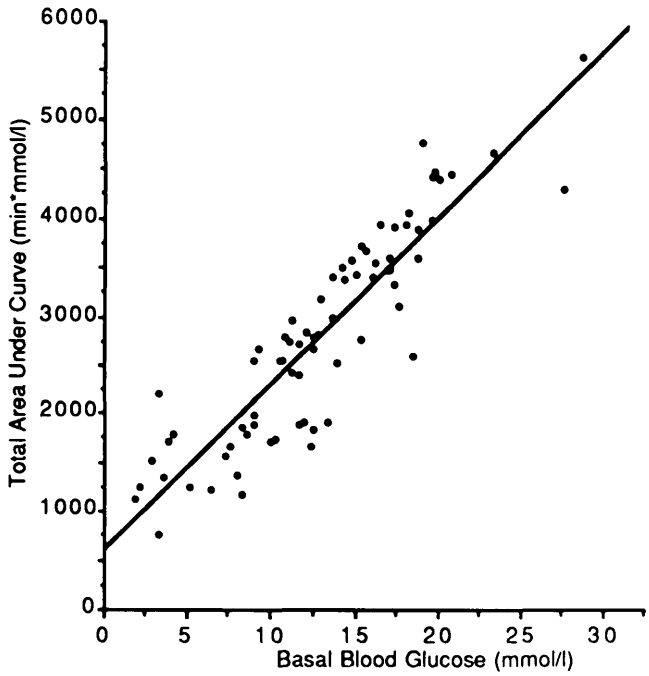

FIG. 1. Correlation between basal blood glucose (BBG) value and total area under the curve (tAUC). Equation of correlation: tAUC = 170 BBG + 614 ($n = 75$, $r = 0.90$, $P < 0.001$).

DISCUSSION

In our study, five different methods were used to compute AUC. Information derived from the methods was different, and some methods could be more convenient than others. With PI[3], sample points were not necessarily included in the estimated curve (11,12). With PI[4], wide oscillations of the estimated curve were observed (11,13). TR and SF are simple composite methods, but the curve aspect is not physiological. The major advantage of CIS is the smoothness of the curve, i.e., the absence of abrupt changes, especially when few sample points are available (11,14). Fourier's or exponential approximations, Chebischev's (minimax) criterion (11), or manual methods such as planimetry (8) were not tested in our study. Selection was based on a broad approach to possible methods and took into account usual sample size and aspect of glycemic response. All methods under study gave strongly correlated results. In addition, between-subject variability was greater than between-method variability, suggesting that differences related to methods were not clinically relevant and that the simplest and easiest method, TR, could be used in estimating AUC.

In our study, iAUC and pAUC were not related to basal glucose value, whereas tAUC was strongly correlated with it. In fact, tAUC clearly depends on basal glucose value and can be expressed as tAUC = iAUC + (180 × basal glucose value). Note that this theoretical expression is close to the observed regression in our population (Fig. 1). On average, iAUC and pAUC were 17 and 20% of tAUC, respectively. Approximately 80% of variance of tAUC was explained by basal glucose value. Conversely, ~80% of variance of iAUC and pAUC was explained by glycemic rise versus <10% of variance of tAUC.

iAUC can be calculated by the method used in this study or by subtracting basal value from sample points before integrating AUC. However, because sample points below baseline can be observed, especially at 180 min, it has been suggested that negative areas (below baseline) should not be subtracted and that points below baseline should be ignored and replaced by zero (10). This method not only suppresses negative area but also increases area above baseline by a triangle, the area of which can be expressed as the product of the area below baseline and the ratio of the difference between glucose level of the previous sample point and basal value to the difference between basal value and glucose level of the sample point below baseline. Because this area can be greater than that below baseline, it is not clear whether points below baseline should be replaced by zero. Conversely, pAUC was computed with information derived from the sample points to find the point where the curve cuts baseline and could be a more reliable estimation of area above baseline. In our study, iAUC and pAUC correlated strongly with each other and with glycemic rise and gave slightly but significantly different information. Because the meaning of negative area remains uncertain, pAUC could be more convenient to study glycemic response (6,10). However, this management of data reduces the information derived from sample points.

In conclusion, our study suggests that TR is a simple and relevant method for estimating AUC. Glycemic rise, iAUC, and pAUC give different information and could be simultaneously used to study glycemic response.

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