Prediction of Postprandial Glycemic Exposure

Utility of fasting and 2-h glucose measurements alone and in combination with assessment of body composition, fitness, and strength

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OBJECTIVE — To determine the best predictors of total postprandial glycemic exposure and peak glucose concentrations in nondiabetic humans.

RESEARCH DESIGN AND METHODS — Data from 203 nondiabetic volunteers who ingested a carbohydrate-containing mixed meal were analyzed.

RESULTS — Fasting glucose and insulin concentrations were poor predictors of postprandial glucose area above basal ($R^2 = \sim 0.07$, $P < 0.001$). The correlation was stronger for 2-h glucose concentration ($R^2 = 0.55$, $P < 0.001$) and improved slightly but significantly ($P < 0.001$) with the addition of fasting glucose, insulin, age, sex, and body weight to the model ($r^2 = 0.58$). The 2-h glucose concentration also predicted the peak glucose concentration ($R^2 = 0.37$, $P < 0.001$) with strength of the prediction increasing ($P < 0.001$) modestly with the addition of fasting glucose, insulin, age, sex, and body weight to the model ($R^2 = 0.48$, $P < 0.001$). On the other hand, addition of measures of body function and composition did not improve prediction of total glycemic exposure or peak glucose concentration.

CONCLUSIONS — Isolated measures of fasting or 2-h glucose concentrations alone or in combination with more complex measures of body composition and function are poor predictors of postprandial glycemic exposure or peak glucose concentration. This may explain, at least in part, the weak and at times inconsistent relationship between these parameters and cardiovascular risk.

Diabetes Care 29:2708–2713, 2006

Both fasting and postprandial hyperglycemia are associated with increased cardiovascular risk (1–11). The mechanism(s) of this risk remains an area of active investigation. Short-term studies in animals and humans have shown that elevated glucose concentrations can impair endothelial function, increase oxidative stress, stimulate intracellular signaling, and alter protein structure and function (12–17). Virtually all studies that have evaluated the relationship between postprandial hyperglycemia and cardiovascular complications have measured the glucose concentration 2 h after a glucose challenge (1–11). This time point presumably was chosen because it also is used during a traditional glucose tolerance test to classify individuals according to whether they have diabetes, impaired glucose tolerance, or normal glucose tolerance (18). However, the extent to which measurement of a single value 2 h after a carbohydrate challenge reflects the postprandial glucose area above basal, and thus the total exposure of tissues to elevated glucose concentrations, has received limited attention and therefore is the focus of the present study. Furthermore, because studies suggest that there may be a glucose threshold that when exceeded, albeit briefly, triggers a cascade of events that could ultimately affect cell function (19,20), peak postprandial glucose concentrations also may modulate subsequent cardiovascular risk.

A standard oral glucose tolerance test (OGTT) entails ingestion of 75 g of glucose and measurement of two glucose concentrations: fasting and 2 h after the glucose challenge (18). Accurate assessment of either the total postprandial glycemic exposure or peak postprandial glucose concentrations presumably requires more frequent blood sampling. Thus, such an evaluation is particularly difficult in the setting of clinical practice or as part of a clinical trial. Several studies have suggested that models including fasting glucose concentrations and other readily available demographics (e.g., age) or body composition (e.g., degree of obesity) are able to predict glucose tolerance with sufficient accuracy that it may not be necessary to perform an OGTT as part of population-based screening programs (21,22). We are unaware of similar analyses determining whether these factors alone or in combination with more complex measures of insulin secretion, action, body composition, and function also can accurately predict the postprandial glycemic excursion and peak postprandial glucose concentrations.

The present studies sought to address this question by analyzing data from 203 nondiabetic volunteers who had frequent measurements of glucose and insulin concentrations after ingestion of a carbohy-

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Received for publication 31 May 2006 and accepted in revised form 18 September 2006.
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Abbreviations: AUC, area under the curve; HOMA, homeostasis model assessment; HOMA-B%, HOMA of β-cell function; HOMA-S%, HOMA of insulin sensitivity; OGTT, oral glucose tolerance test.
A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.
DOI: 10.2337/dc06-1118

Table 1—*Volunteer characteristics*

	Elderly men	Young men	Elderly women	Young women
Subjects (*n*)	86	30	59	28
Age (years)	68.6 ± 0.6	23.5 ± 0.6	70.3 ± 0.8	22.3 ± 0.6
BMI (kg/m^2)	27.6 ± 0.3	25.1 ± 0.5	27.3 ± 0.5	24.0 ± 0.5
Percent body fat	27.0 ± 0.6	20.8 ± 1.3	41.8 ± 0.8	31.9 ± 1.3
Lean body mass (kg)	57.4 ± 0.6	59.3 ± 0.9	37.3 ± 0.5	39.4 ± 0.6
Visceral fat (cm^2)	208 ± 10	74 ± 8	117 ± 7.0	37 ± 4
$V_{O_{2max}}$ (ml · kg^{-1} · min^{-1})	27.1 ± 0.6	42.9 ± 1.2	20.0 ± 0.6	34.6 ± 1.1
Double knee extension (lb)	102 ± 3	166 ± 6	70 ± 3	97 ± 4
Isometric knee extension (lb)	98 ± 2	133 ± 5	59 ± 2	84 ± 4
Seated chest press (lb)	119 ± 2	178 ± 6	69 ± 2	88 ± 3

Data are means ± SE.

drate-containing mixed meal, as well as a comprehensive assessment of body composition and function. We began by determining how well fasting glucose alone or in combination with simple demographic factors that can be readily measured in the clinical setting (e.g., age and sex) predicted the postprandial glucose area above basal and peak postprandial glucose concentration. We next added measurement of a single additional glucose concentration at 2 h as is done during a traditional glucose tolerance test. We then included more complex measures of body composition, strength, and aerobic fitness in the model. Finally, in an effort to gain a greater insight into the regulation of postprandial glucose metabolism, we also determined whether the addition of sophisticated measures of insulin secretion and action further improved prediction of postprandial glycemic exposure and peak postprandial glucose concentration. We chose a mixed meal as a challenge because, under the conditions of daily living, people eat food rather than drink 75 g of glucose as is done during an OGTT, and because we were interested in how well a traditional (e.g., American Diabetes Association–recommended) 2-h postprandial glucose measurement reflects the actual postprandial glycemic exposure and/or peak postprandial glucose concentration.

RESEARCH DESIGN AND METHODS

— As described in detail elsewhere (23), 203 healthy nondiabetic subjects underwent a comprehensive assessment of carbohydrate tolerance, body composition, and function (Table 1). Studies were conducted following approval by the Mayo Clinic Institutional Review Board and informed written consent. All subjects consumed a weight maintenance diet (55% carbohydrate, 15% protein, and 30% fat) provided by the General Clinical Research Center kitchen for at least 3 days before study. Subjects were admitted at 1600 on the afternoon before the study and given a standard 10 kcal/kg meal (55% carbohydrate, 15% protein, and 30% fat), which was consumed between 1700 and 1730. No additional food was eaten until the next morning. Subjects did not engage in vigorous exercise following admission. At 0900 (0 time) the following morning, a mixed meal (10 kcal/kg, 45% carbohydrate, 15% protein, and 40% fat) was consumed within 15 min. Blood was sampled from the arterialized venous site at frequent intervals. Plasma glucose concentration was measured using a glucose oxidase method (YSI, Yellow Springs, OH), and plasma insulin was measured using a chemiluminescence assay with reagents obtained from Beckman (Access Assay; Beckman, Chaska, MN). Plasma C-peptide concentrations were measured by radioimmunoassay (Linco Research, St. Louis, MO).

Body composition was measured using dual-energy X-ray absorptiometry (DPX scanner; Lunar, Madison, WI). Visceral fat was measured by a single slice computed tomographic scan at the level of L2/L3 as previously described (24). The $V_{O_{2max}}$ was measured using a standard treadmill stress test. Knee extensor strength was measured by having each participant lift a progressively higher weight using a bilateral leg press machine (Cybex, Medway, MA) until the one-repetition maximum was reached.

Indexes of insulin action and insulin secretion were calculated using the "oral" and C-peptide minimal models (23,25–27) incorporating age-associated changes in C-peptide kinetics as measured by Van Cauter et al. (28). Homeostasis model assessment (HOMA) of insulin sensitivity (HOMA-S%) and β-cell function (HOMA-B%) were estimated using HOMA from fasting serum glucose and insulin using the Oxford HOMA calculator (29).

Values from −30 to 0 min were averaged and considered as basal. Area above basal was calculated using the trapezoidal rule. Parameters of all models were estimated by using the SAAMII software (30) as previously described (14). Statistical analyses were performed using SPSS for Windows (version 11; SPSS, Chicago, IL). Data are presented as means ± SD. Insulin sensitivity index (S_i) was log transformed because it was nonnormally distributed. Pearson or Spearman correlations were performed to describe the pattern of associations between the independent continuous variables and outcome measures. A series of multiple linear

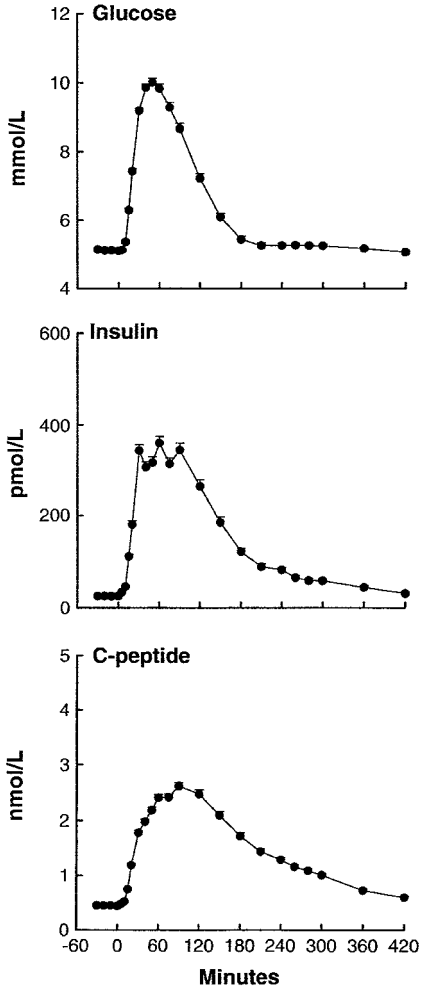

Figure 1—*Plasma glucose, insulin, and C-peptide concentrations observed following ingestion of a mixed meal at time zero.*

Table 2—*Result summary of multiple hierarchical regressions predicting postprandial glucose area above basal*

Model and variable(s)	Pearson correlation	*P*	β	*P*	R^2 (*P*)	R^2 change (*P*)
Model 1						
2-h glucose	0.74	<.001			0.557 (<0.001)	
Model 2						
2-h glucose		<0.001	0.76	<0.001	0.558 (<0.001)	0.001 (NS)
Fasting glucose	0.27	<0.001	−0.02	NS		
Model 3						
2-h glucose			0.74	<0.001		
Fasting glucose			<0.07	NS		
Sex	0.06	NS	<0.07	NS	0.574 (<0.001)	0.015 (<0.05)
Age	0.41	<0.001	0.12	<0.05		
Model 4						
2-h glucose						
Fasting glucose						
Sex						
Age						
Fasting insulin*	0.16	<0.05	0.06	NS	0.574 (<0.001)	0.004 (NS)
HOMA-S%*	−0.11	NS	−0.04	NS	0.575 (<.001)	0.001 (NS)
HOMA-B%*	0.00	NS	0.07	NS	0.575 (<.001)	0.001 (NS)
$V_{O_{2max}}$*	−0.38	<0.001	−0.10	NS	0.576 (<.001)	0.002 (NS)
Knee strength*	−0.26	<0.001	−0.01	NS	0.575 (<.001)	0.001 (NS)
Body weight*	0.15	<0.05	0.13	<0.05	0.583 (<.001)	0.009 (<0.05)
Visceral fat*	0.32	<0.001	0.15	<0.05	0.586 (<.001)	0.012 (<0.05)

*Variable entered separately to the regression.

regression analyses were performed to identify the relationships between the predictors and postprandial glucose area above basal and peak postprandial glucose concentration. Univariate ANOVAs were performed for between-group comparisons.

RESULTS

Plasma glucose, insulin, and C-peptide concentrations

Fasting plasma glucose concentrations averaged 5.1 ± 0.5 mmol/l before meal ingestion. After meal ingestion, glucose concentration increased to a peak of 10.7 ± 1.6 mmol/l at 54.0 ± 18.5 min then fell to 7.2 ± 2.0 mmol/l at 120 min and 5.1 ± 0.6 mmol/l at 420 min, values which no longer differed from basal (Fig. 1).

Fasting plasma insulin and C-peptide concentrations averaged 25.4 ± 11.7 and 0.44 ± 0.14 pmol/l, respectively, before meal ingestion. Plasma insulin and C-peptide concentrations increased following meal ingestion, reaching peak concentrations at ~60 and ~90 min, respectively. Plasma insulin and C-peptide concentrations fell, reaching basal levels by the end of the 7 h of study.

Prediction of postprandial glucose area above basal

To determine how well the fasting and 2-h glucose concentrations (i.e., sampling times used for a traditional glucose tolerance test) predicted the postprandial area above basal, these parameters were entered in a step-wise fashion in a multivariate model. Fasting glucose alone was a poor predictor ($R^2 = 0.07$, $P < 0.001$) of postprandial glucose area under the curve (AUC), whereas 2-h glucose alone was somewhat better ($R^2 = 0.55$, $P < 0.001$). The strength of prediction with a model containing both fasting and 2-h glucose ($R^2 = 0.55$, $P < 0.001$) was not better than that with 2-h glucose alone. Addition of age and sex (i.e., easily obtainable demographic descriptors) slightly but significantly ($P < 0.05$) improved ($R^2 = 0.57$) prediction of glucose AUC, whereas addition of fasting insulin, HOMA-S%, HOMA-B%, $V_{O_{2max}}$, and knee strength did not further improve prediction of glucose AUC ($R^2 = 0.57$); however, body weight ($R^2 = 0.58$) and percent visceral fat ($R^2 = 0.59$) each slightly but significantly improved the model (Table 2).

Minimal model indexes of insulin action (S_iV-log) were a moderate predictor of glucose AUC ($R^2 = 0.30$, $P < 0.001$), whereas insulin secretion ($Phi_{dynamic}$) alone was a very poor predictor of glucose AUC ($R^2 = 0.03$, $P < 0.001$). The strength of the prediction improved somewhat when both were included in the model ($R^2 = 0.37$, $P < 0.001$) and further improved when 2-h glucose concentration also was added ($R^2 = 0.64$, $P < 0.001$).

Prediction of peak postprandial glucose concentration

Fasting ($R^2 = 0.29$, $P < 0.001$) and 2-h glucose ($R^2 = 0.38$, $P < 0.001$) concentrations alone were moderate predictors of the peak postprandial glucose concentration with the prediction improving when both were considered together in the same model ($R^2 = 0.48$, $P < 0.001$). Addition of age, sex, fasting insulin, HOMA-S%, HOMA-B%, $V_{O_{2max}}$, knee strength, and percent fat did not further improve the strength of the prediction. However, addition of visceral fat slightly improved ($P < 0.05$) the prediction of peak postprandial glucose concentration ($R^2 = 0.50$, $P < 0.001$). Indexes of insulin secretion (i.e., $Phi_{dynamic}$, Phi_{static}, Phi_{total}, and Phi_{global}) were modest predictors of peak postprandial glucose concentrations ($R^2 = 0.43$, $P < 0.001$), whereas the contribution of insulin action was small ($R^2 = 0.06$, $P < 0.01$). A model including fast-

Table 3—*Prediction of peak glucose*

Model and variable	Multilinear regression analysis				
	Pearson correlation	*P*	β	*P*	R^2 (adjusted)
Model 1					
2-h glucose	0.615	<0.001			0.38*
Model 2					0.48*
2-h glucose	0.615	<0.001	0.473	<0.001	
Fasting glucose	0.545	<0.001	0.356	<0.001	
Model 3					0.48
2-h glucose	0.615	<0.001	0.462	0.000	
Fasting glucose	0.545	<0.001	0.473	0.015	
Fasting insulin	0.084	NS	−0.270	NS	
Body weight	0.062	NS	−0.038	NS	
Age-sex	0.228	0.001	0.297	NS	
HOMA-S%	−0.100	0.081	−0.096	NS	
HOMA-B%	−0.242	<0.001	0.120	NS	
$V_{O_{2max}}$	−0.317	<0.001	−0.041	NS	
Knee strength	−0.202	0.002	0.155	NS	
Percent fat	0.176	0.007	−0.117	NS	
Model 4					
2-h glucose	0.615	<0.001	0.472	0.000	0.50*
Fasting glucose	0.545	<0.001	0.530	0.006	
Fasting insulin	0.084	NS	−0.327	NS	
Body weight	0.062	NS	−0.007	NS	
Age-sex	0.228	0.001	0.238	NS	
HOMA-S%	−0.100	0.081	−0.095	NS	
HOMA-B%	−0.242	<0.001	0.196	NS	
$V_{O_{2max}}$	−0.317	<0.001	−0.071	NS	
Knee strength	−0.202	0.002	0.183	0.039	
Percent fat	0.176	0.007	−0.006	NS	
Visceral fat	0.152	0.017	−0.239	0.009	

*Indicates R^2 change $P < 0.05$.

ing glucose and 2-h glucose, as well as indexes of insulin secretion, yielded the best prediction of peak postprandial glucose concentration ($R^2 = 0.63$, $P < 0.001$) (Tables 3 and 4).

CONCLUSIONS — The present study examined the extent to which fasting and 2-h postmeal glucose concentrations alone or in combination are able to predict either total postprandial glycemic exposure or the peak postprandial glucose concentration. We report that while knowledge of fasting and 2-h glucose concentrations provides some insight in this regard, even when used together, they at best predict only 50–60% of the variation observed in the actual postprandial glycemic exposure or peak postprandial glucose concentration. While measures of body composition (e.g., percent fat or visceral fat) or function (e.g., $V_{O_{2max}}$ or strength) have been shown to be independent predictors of cardiovascular risk (31,32), they do not enhance the prediction of the degree of postprandial glycemic exposure. Taken together, these data indicate that measurement of fasting or 2-h glucose concentration alone or in combination with measures of body function or composition provide limited information regarding the degree of postprandial hyperglycemia that occurs following ingestion of a mixed meal.

There now is strong evidence that cardiovascular risk increases as fasting and 2-h post–glucose challenge concentrations increase within what was previously considered the normal range (33–35). While the mechanism(s) responsible for this relationship is an area of active investigation, it is likely that the adverse effects, at least in part, are due to greater overall glycemic exposure. This premise is supported by the fact than an increase in HbA_{1c} (an index of 24-h glycemic exposure) also within the "normal" range is associated with increased cardiovascular risk (19). If, indeed, hyperglycemia per se increases vascular risk, a key unresolved question is whether an excessive rise in glucose concentration, such as occurs in some individuals after food ingestion, is more deleterious than the same degree of glycemic exposure produced by a chronic increase in fasting glucose concentrations. The recent observation that therapies that primarily lower postprandial glucose concentrations in people with type 2 diabetes may be associated with less cardiovascular disease than those that primarily lower fasting glucose supports this premise (36–38). Therefore, the knowledge of the total postprandial glycemic area above basal becomes a potentially important therapeutic target even in the absence of overt diabetes. If so, the current data indicate that measurement of fasting or 2-h glucose concentration alone or in combination provide limited insight as to the actual postprandial glycemic exposure.

The glucose profile following meal ingestion is dynamic and influenced by a variety of factors, including meal composition, degree of insulin resistance, and pattern of insulin secretion. We have previously shown that although addition of protein and fat to a mixed meal results in a slight delay in meal appearance in comparison to ingestion to the same amount of glucose alone, the overall glycemic profile is virtually identical, with 2-h glucose concentrations in both instances being close to preprandial levels (39). Similarly, because ingestion of complex carbohydrates blunts the postprandial rate of rise of glucose, the concentrations at 2 h are closer to preprandial level than they are to the postprandial peak. It is therefore not surprising that the current data indicate that knowledge of the 2-h glucose concentration only weakly predicts the actual postprandial glycemic area.

We and others have previously presented data (40,41) indicating that whereas changes in the timing of insulin release primarily alter peak postprandial glucose concentrations, changes in insulin action prolong the duration of hyperglycemia . The current data lend further support to these relationships because the addition of minimal model indexes of insulin secretion (but not action) to fasting and 2-h glucose concentration improved the prediction of the postprandial peak glucose concentration. On the other hand, addition of indexes of insulin action (but not secretion) improved prediction of the total postprandial glycemic exposure. Because body composition, aerobic fitness, strength, and age are all

Table 4—*Prediction of postmeal glucose peak*

	β	R^2 (adjusted)
Model 1		
Fasting glucose	0.540	0.289*
Model 2		
Fasting glucose	0.358	0.474*
2-h glucose	0.470	
Model 3		
Fasting glucose	0.324	0.635*
2-h glucose	0.317	
$Phi_{dynamic}$	−0.536	
Phi_{static}	−1.711	
Phi_{total} meal	0.567	
Phi_{global} meal	1.455	

*Indicates R^2 change $P < 0.05$.

determinants of insulin action, we added these parameters to the multivariate models to determine whether they could serve as surrogates of insulin action, thereby obviating the need for sophisticated models of glucose and insulin metabolism. Unfortunately, the addition of measures of body composition and function minimally improved prediction of the postprandial glycemic area compared with measurement of fasting and 2-h glucose alone. Furthermore, addition of HOMA, a simple, albeit qualitative measure of insulin action, also did not improve the accuracy of the prediction. However, few of the subjects were frankly obese. Because obese subjects are more likely to be more insulin resistant, inclusion of body composition data in the model may improve the prediction of the postprandial glycemia. On the other hand, while use of the "oral" minimal model to measure insulin action in the postprandial state is potentially of considerable theoretical interest, this obviously adds no value if the goal is to simply assess the postprandial glycemic area, because frequent measures of glucose concentration (as well as insulin) are required to calculate insulin action.

The current studies suffer from certain limitations. While a large number of young and elderly men and women were examined, data from middle-aged subjects were not included. However, we doubt if this would alter our conclusions, because the glycemic profiles of healthy middle-aged nondiabetic subjects who ingested the same mixed meal as part of previous studies are virtually identical to those observed in the current studies (42). Glucose concentrations were also not measured continuously. Therefore, we do not know either the true peak postprandial glucose concentration or area above basal. However, because they were measured frequently, particularly during the first 2 h after meal ingestions (i.e., every 10–15 min), we doubt if the errors were substantial. Finally, we do not know if the same relationships apply to in the presence of diabetes or other states of impaired glucose tolerance. Futures studies will be required to address this question.

In summary, the present data indicate that fasting glucose alone or in combination with a 2-h postprandial glucose concentration are poor predictors of either the postprandial glucose area above basal or the peak postprandial glucose concentration. Addition of specific measures of body composition, aerobic fitness, or muscle strength at best minimally improved the strength of the prediction. Therefore, if either excessive total postprandial glycemic exposure or an elevated peak postprandial glucose concentration contribute to the pathogenesis of atherosclerotic vascular disease, then more frequent measurements of glucose following either a glucose challenge or a mixed meal likely will be required to better delineate this relationship.

Acknowledgments— This study was supported by the U.S. Public Health Service (AG 14383, DK 50456, DK29953, EB01975, and RR-00585), the Ministero dell'Università e della Ricerca Scientifica e Tecnologica (MIUR), Italy, and the Mayo Foundation.

R.B. was supported by an American Diabetes Association mentor-based fellowship.

We wish to thank R. Rood for assistance with graphics, M. Davis for assistance in the preparation of the manuscript, and the staff of the Mayo General Clinical Research Center for assistance with performing the studies.

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