Food insulin index: Physiologic basis for predicting insulin demand evoked by composite meals

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Food insulin index: physiologic basis for predicting insulin demand evoked by composite meals[1–3]

Jiansong Bao, Vanessa de Jong, Fiona Atkinson, Peter Petocz, and Jennie C Brand-Miller

ABSTRACT

Background: Diets that provoke less insulin secretion may be helpful in the prevention and management of diabetes. A physiologic basis for ranking foods according to insulin "demand" could therefore assist further research.

Objective: We assessed the utility of a food insulin index (FII) that was based on testing isoenergetic portions of single foods (1000 kJ) in predicting the insulin demand evoked by composite meals.

Design: Healthy subjects ($n = 10$ or 11 for each meal) consumed 13 different isoenergetic (2000 kJ) mixed meals of varying macronutrient content. Insulin demand predicted by the FII of the component foods or by carbohydrate counting and glycemic load was compared with observed insulin responses.

Results: Observed insulin responses (area under the curve relative to white bread: 100) varied over a 3-fold range (from 35 ± 5 to 116 ± 26) and were strongly correlated with insulin demand predicted by the FII of the component foods ($r = 0.78$, $P = 0.0016$). The calculated glycemic load ($r = 0.68$, $P = 0.01$) but not the carbohydrate content of the meals ($r = 0.53$, $P = 0.064$) also predicted insulin demand.

Conclusions: The relative insulin demand evoked by mixed meals is best predicted by a physiologic index based on actual insulin responses to isoenergetic portions of single foods. In the context of composite meals of similar energy value, but varying macronutrient content, carbohydrate counting was of limited value. *Am J Clin Nutr* 2009;90:986–92.

INTRODUCTION

A physiologic basis for classifying all foods according to their postprandial insulin response is of both theoretical and practical significance. In individuals at risk of developing type 2 diabetes, diets that provoke excessive insulin secretion may increase oxidative stress and accelerate the course of β cell failure (1). In overweight subjects, high-carbohydrate diets are associated with postprandial hyperinsulinemia and less favorable cardiovascular risk factors than diets containing less carbohydrate (2). Conversely, diets with a lower glycemic index (GI) or glycemic load (GL) elicit lower postprandial insulin responses and produce better clinical outcomes compared with diets with higher GI or GL (3–5).

An insulin index of foods may also facilitate the day-to-day management of type 1 diabetes. Currently, insulin dose is estimated by carbohydrate counting, but there is potential for it to be more precisely predicted by a greater understanding of the relative "insulin demand" evoked by different foods. Together, carbohydrate counting and knowledge of the GI of foods provide the most accurate prediction of likely insulin response (6, 7). However, because GI methodology does not permit the testing of foods with little or no carbohydrate, it cannot provide a guide to the relative insulin response of a large majority of foods in food databases, including high-protein foods such as meat, fish, poultry, eggs, and cheese and high-fat foods such butter and olive oil. Although carbohydrate is the primary stimulus for insulin secretion, it is not the only one. Protein-rich foods also elicit a significant insulin response and, when combined with carbohydrate, act synergistically to raise insulin concentrations and reduce glycemia (8). Similarly, addition of fat to a carbohydrate-rich meal reduces postprandial glycemia but not the insulin response (9, 10). Several insulinotropic factors are known to potentiate the stimulatory effect of glucose and mediate postprandial insulin secretion. These factors include specific amino acids and fatty acids and gastrointestinal hormones such as gastric inhibitory polypeptide, glucagon-like peptide 1, glucagon, and cholecystokinin (10, 11).

In previous research, we compared insulin responses to isoenergetic portions of foods with the use of a 1000-kJ portion as the basis of comparison (12). A food insulin index (FII) was calculated for 38 foods with the use of the observed insulinemic response (area under the curve; AUC) relative to the reference food, white bread (=100). The aim of the present study was to develop the FII database further and to determine whether the concept was able to predict insulin responses to mixed meals composed of variable amounts of foods whose individual FII had been previously determined. We hypothesized that postprandial insulin responses to mixed meals would be more accurately predicted by the weighted average FII of the individual foods than by their carbohydrate content or GL (carbohydrate content × GI).

SUBJECTS AND METHODS

Subjects

Healthy subjects ($n = 21$, including 13 men), with a mean ($\pm$SD) age of 24 ± 2.5 y and body mass index (BMI; in kg/m^2) of 22.8 ± 1.5, were recruited from the student population of the University of Sydney. All met the inclusion criteria: non-smoking, aged 18–40 y, stable body weight, BMI of 19–25, normal glucose tolerance, no prescription medication other than oral contraceptives, no known food allergy, regular physical activity, normal dietary habits, and no history of eating disorders. The protocol was approved by the Human Research Ethics Committee of the University of Sydney, and subjects gave written informed consent. Subject recruitment took place in 2 stages: from July to October 2005 and from July to October 2006.

Test meals

In total, 13 isoenergetic mixed meals were tested in 2000-kJ portions. Because of the large number of meals, 6 meals were tested by group 1 ($n = 11$) and 7 meals by group 2 ($n = 10$). The meals represented breakfasts, lunches, dinners, and snacks in Western diets, varying widely in macronutrient composition and calculated GI and GL (**Table 1**). Nutrient content was calculated from manufacturers' data and Australian food composition tables (Foodworks Professional, 2005; Xyris Software, Highgate Hill, Australia). Protein ranged from 7 to 52 g (6–44% of energy), fat from 3 to 30 g (6–56% of energy), and carbohydrate from 29 to 92 g (25–78% of energy). GL varied over a 5-fold range, from 10 to 51. The GL of each test meal was calculated as the sum of the GL of the component foods:

$$GL = \frac{1}{100} \sum_{a=1}^{n} GI_a \times CHO_a \qquad (1)$$

where n was the number of foods in the meal, GI_a was the GI of the ath food, and CHO_a was the available carbohydrate (in g) in the ath food. A reliable GI was assigned to each carbohydrate food on the basis of published (13) and unpublished data. The FII of component foods were taken from previously published tables (12) and our own unpublished data following the same testing protocol. The predicted insulin demand (relative to white bread) of each mixed meal was calculated as:

$$\text{Predicted insulin demand} = \sum_{a=1}^{n} FII_a \times Energy_a \qquad (2)$$

where n was the number of foods in the meal, FII_a was the FII of the ath component food in the test meal and Energy$_a$ (in %) was the percentage of energy contributed by the ath food. The predicted insulin demand of the mixed meals relative to white bread (= 100) varied over a 5-fold range from 22 to 101 (Table 1).

Experimental procedures

Test meals were consumed in random order, and the reference meal of white bread was tested at the beginning and end of the study. Testing sessions were separated by at least one day. Subjects were instructed to refrain from unusual physical activity, alcohol, and legumes on the previous day and to eat a high-carbohydrate, low-fat meal the night before a test. On the test morning, subjects reported to the laboratory after a 10–12-h fast. After warming the hand in hot water, 2 baseline finger blood samples ($\approx$0.7 mL $\times$ 2) were obtained 5 min apart. Each meal was then consumed with 250 mL water at a comfortable pace within 14 min. Additional blood samples were taken 15, 30, 45, 60, 90, and 120 min after the commencement of eating. Subjects remained seated throughout and were not permitted to eat or drink until the end of session.

Blood samples were collected in anticoagulant-coated tubes (Eppendorf tubes, grade II; Sigma Chemical Company, Castle Hill, Australia) containing 10 IU heparin sodium salt and centrifuged immediately (1 min at $10,000 \times g$ at room temperature). The plasma layer was pipetted into a labeled tube and stored at $-20°C$ until analysis. Plasma insulin was measured by antibody-coated tube radioimmunoassay (Diagnostic Products Corporation, Los Angeles, CA). The within- and between-assay CVs were 3.0% and 3.5%, respectively. All samples in one group study were analyzed within the same run.

Data analysis

The incremental insulin AUC over 120 min for each meal was calculated according to the trapezoidal rule with the fasting concentration as the baseline (14). Area below the fasting concentration was ignored. For each subject, an individual relative insulin response (in %) was calculated by dividing the insulin AUC value for the test meal by his or her average insulin AUC value for white bread (tested twice) and expressed as a percentage. The mean ($\pm$SEM) percentage for 10 or 11 subjects was the reported observed response to the meal. Statistically significant differences among the meals were determined by repeated-measures analysis of variance with the use of SPSS for Windows, version 15.0 (SPSS, Chicago, IL). Simple (univariate) analysis was used to test the significance of associations between the observed insulin responses, predicted insulin demand, calculated GL, and macronutrient content of the meals. $P < 0.05$ (2-tailed) was considered as statistically significant and $P < 0.01$ as highly significant.

RESULTS

As expected, the insulin responses to the meals varied over a wide range with significant differences between the meals (**Figure 1**A; $P < 0.001$). The AUC relative to white bread (= 100) ranged from 35 ± 5 to 116 ± 26 (Figure 1B) and was strongly correlated with calculated insulin demand predicted by the FII of the component foods ($r = 0.78$, $P = 0.0016$; **Figure 2**A). The calculated GL of the mixed meals was also strongly correlated with the observed insulin response ($r = 0.68$, $P = 0.01$; Figure 2B). In contrast, carbohydrate content was not a significant predictor of the average response ($r = 0.53$, $P = 0.064$; Figure 2C).

We also examined the relation between the observed insulin response and other nutrients in the meal. Fat content was inversely related ($r = -0.60$, $P = 0.03$; Figure 2D), but protein ($r = -0.04$, $P = 0.88$; Figure 2E) and fiber ($r = -0.46$, $P = 0.116$; Figure 2F) showed no relation.

DISCUSSION

This study shows that the degree of postprandial hyperinsulinemia elicited by realistic mixed meals is best predicted by

TABLE 1
Macronutrient composition, calculated glycemic load (GL), and food insulin index (FII) values for the test meals and the reference white bread[1]

Food categories	Serving size	Energy	Portion of energy	Protein	Fat	Fiber	AvCHO	GI	GL	FII
	g	kJ	%	g	g	g	g			
White bread[2]	193	2000	100	19.4	4.8	3.8	93.4	70	65	100
Group 1 meals										
Breakfast meals										
M1										
Grain bread[3]	77.7	786	39.3	12.0	5.4	4.2	23.2	36	—	71
Peanut butter[4]	25.0	668	33.4	5.8	13.4	2.9	4.4	14	—	15
Full-fat milk[5]	200	546	27.3	6.8	7.2	0.0	9.6	31	—	33
Total meal	302.7	2000	100	24.6	26.0	7.1	37.2	32	12	42
M2										
Honeydew melon	100	140	7	0.7	0.3	1.0	6.5	62	—	127
Banana	98	353	17.7	1.7	0.1	2.2	19.6	52	—	81
Yogurt[6]	300	1167	58.3	15.9	2.7	0.0	44.1	31	—	115
Apple juice[7]	200	340	17	0.2	0.0	0.0	20.2	39	—	64
Total meal	698	2000	100	18.5	3.1	3.2	90.4	40	36	101
Snacks										
M3										
Walnuts[8]	44	1276	63.8	7.2	29.6	4.0	1.6	N/A[9]	—	7
Raisins[10]	28.3	396	19.8	0.7	0.1	1.2	22.6	64	—	42
Carrot juice[11]	250	328	16.4	2.0	0.3	0.8	13.5	47	—	56
Total meal	322.3	2000	100	9.9	30.0	6.0	37.7	55	21	22
M4										
Raspberry jam[12]	30	351	17.6	0.0	0.0	0.0	20.4	51	—	85
Croissant	85	1304	65.2	7.1	15.0	0.0	36.4	67	—	79
Ice tea[13]	214	345	17.2	0.0	0.0	0.0	20.6	59	—	95
Total meal	329	2000	100	7.1	15.0	0.0	77.4	61	47	83
Lunch meals										
M5										
Roast chicken	75	662	33.1	20.2	8.6	0.0	0.0	N/A	—	23
Avocado	40	356	17.8	0.8	9.0	0.6	0.2	N/A	—	6
Grain bread	97.1	982	49.1	15.1	6.8	5.3	28.9	36	—	71
Total meal	212.1	2000	100	36.1	24.4	5.9	29.1	36	10	44
Dinner meals										
M6										
Tuna[14]	110	815	40.8	19.6	12.3	0.0	1.8	N/A	—	22
White rice[15]	221.7	981	49.0	4.3	0.0	0.0	52.4	75	—	79
Corn[16]	45	204	10.2	1.3	0.7	0.0	8.7	47	—	53
Total meal	376.7	2000	100	25.2	13	0.0	62.9	69	43	53
Group 2 meals										
Breakfast meals										
M7										
All-Bran cereal[17]	245	1500	75	17.2	4.6	21.2	61.0	30		32
Apple juice	294	500	25	0.3	0.0	0.0	29.7	39		64
Total meal	539	2000	100	17.5	4.6	21.2	90.7	33	30	40
M8										
Poached eggs	159	1000	50	19.6	17.8	0.0	0.5	N/A	—	31
Whole-meal bread[18]	101	1000	50	7.6	2.6	6.6	38.9	68	—	96
Total meal	260	2000	100	27.2	20.4	6.6	39.4	67	26	64
Snack meals										
M9										
Banana	279	1000	50	4.8	0.3	6.2	55.5	52	—	81
Full-fat milk	352	1000	50	12.0	13.7	0.0	16.5	31	—	33
Total meal	631	2000	100	16.8	14.0	6.2	72.0	47	34	57
M10										
Cookies[19]	49	1000	50	2.7	10.4	0.0	17.3	62	—	92
Ice cream[20]	123	1000	50	6.5	12.3	0.0	27.1	50	—	89
Total meal	172	2000	100	9.2	22.7	0.0	44.4	55	24	91

(Continued)

TABLE 1 (*Continued*)

Food categories	Serving size	Energy	Portion of energy	Protein	Fat	Fiber	AvCHO	GI	GL	FII
	g	*kJ*	*%*	*g*	*g*	*g*	*g*			
Lunch meals										
M11										
Pizza[21]	90	1000	50	12.4	7.6	0.0	30.2	60	—	64
Coca-Cola[22]	583	1000	50	0.0	0.0	0.0	61.8	53	—	60
Total meal	673	2000	100	12.5	7.6	0.0	92.0	55	51	62
Dinner meals										
M12										
Pasta[23]	201	1000	50	7.8	8.0	3.5	45.6	44	—	40
Lentils[24]	253	1000	50	19.4	4.6	11.4	17.7	37	—	58
Total meal	454	2000	100	27.2	12.6	14.9	63.3	42	27	49
M13										
Beef steak	158	1000	50	42.0	7.7	0.0	0.0	N/A	—	51
Boiled potatoes[25]	368	1000	50	10.0	1.0	9.2	39.8	77	—	121
Total meal	526	2000	100	52.0	8.7	9.2	39.8	77	31	86

[1] Glycemic index (GI) and GL values of the mixed meals were calculated with the use of GIs of individual food components and available carbohydrate content. The FII value of each test meal in this table represented the predicted insulin response relative to white bread, which was calculated by the formula described in Subjects and Methods. AvCHO, available carbohydrate; M, meal; N/A, not applicable.

[2] Fresh-sliced wheat-flour bread; Sunblest Tip Top Bakeries, Enfield, Australia.

[3] Burgen Soy Lin bread; George Weston Foods, Chatswood, Australia; the grain bread contains whole-grain kibble wheat (4%), kibble soy (8%), and linseed (8%).

[4] Kraft, smooth; Kraft Foods (Australia) Ltd, Fishermans Bend, Australia.

[5] Dairy Farmers, Lidcombe, Australia.

[6] Ski D'lite low-fat strawberry; Dairy Farmers.

[7] Berri apple juice; Berrivale Orchards Ltd, Docklands, Australia.

[8] Lucky California walnuts; Select Harvests Food Products Pty Ltd, Thomastown, Australia.

[9] GI of the component food is negligible because of the small amount of carbohydrate contained.

[10] Sunbeam Foods, Irymple, Australia.

[11] Extracted from fresh, raw carrots.

[12] Cottees, Southbank, Australia.

[13] TAISUN lemon ice tea; Narkena Pty Ltd, Sefton, Australia.

[14] Coles Tuna Chunks in Oil; Coles, Sydney, Australia.

[15] SunRice White; SunRice, Leeton, Australia.

[16] McCain Super Juicy frozen corn; McCain Foods (Australia) Pty Ltd, Wendouree, Australia.

[17] Wheat-bran cereal, served with 125 mL low-fat milk; Kellogg Pty Ltd, Melbourne, Australia.

[18] Fresh-sliced bread made from whole-meal wheat flour; Riga Bakeries, Sydney, Australia.

[19] Chocolate-chip cookies; Arnott's Biscuits Ltd, Newcastle, Australia.

[20] Vanilla ice cream; Dairy Farmers.

[21] Pizza base: white-flour pizza base (McCain Foods); tomato paste (Leggo tomato paste; JR Simplot, Mentone, Australia); cheese: shredded mozzarella cheese (Perfect Italiano; Fonterra Pty Ltd, Mount Waverley, Australia).

[22] Coca-Cola Amatil (Australia) Pty Ltd, Northmead, Australia.

[23] Pasta: white spiral pasta; San Remo Pasta Company, Wetherill Park, Australia.

[24] Lentils: served in a basic tomato sauce. Ingredients: 15 mL olive oil, 350 g dried green lentils, 410 g canned tomatoes, 120 g onion, 1 clove garlic, 1 teaspoon pepper.

[25] Russet potatoes, peeled and boiled for 20 min before serving.

a novel classification based on ranking the insulin responses to individual foods (ie, the FII). Surprisingly, in the current context, carbohydrate, fiber, and protein content were found to be relatively poor predictors of the overall insulin response, whereas GL (the product of the available carbohydrate content and the GI of the component foods) and fat content were significant predictors, although less so than the FII. The findings suggest that if the database were sufficiently large, the FII classification could provide a more accurate alternative to carbohydrate content for estimating insulin demand of different meals and diets. This classification may be useful in nutritional epidemiology because diets associated with high-insulin demand have been hypothesized to increase the risk of diabetes, obesity, and cardiovascular disease (15, 16). A system of ranking of foods based on relative insulin demand could also have application in the clinical management of diabetes.

The present study has both strengths and limitations. The mixed meals were designed to represent typical Western diets, and we selected component foods with a wide range of FIIs with the expectation that the range of insulin responses among the mixed meals would also be high. Although the predicted insulin demand varied over a 5-fold range (from 22 to 101), actual insulin responses ranged only 3-fold (from 35 to 116). The meal with the lowest predicted demand (M3: a snack of walnuts, raisins, and carrot juice) produced a somewhat higher than expected insulin response, although nonetheless the lowest of all 13 meals.
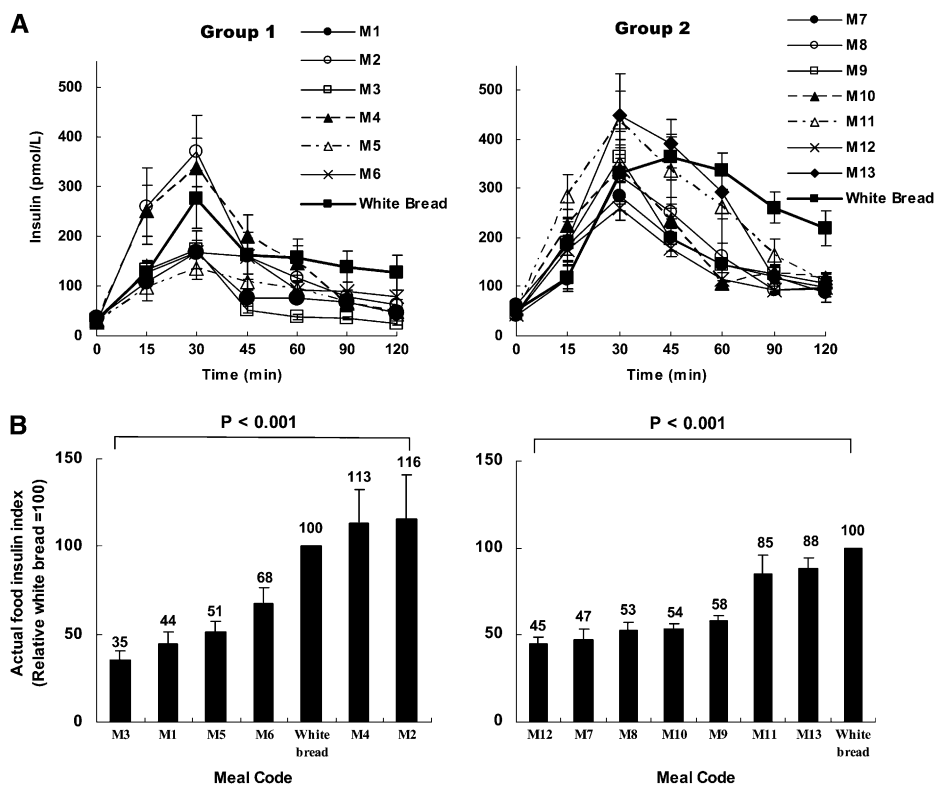
FIGURE 1. Mean (±SEM) insulin responses (area under the insulin curve) (A) and actual food insulin index (B) values (relative to white bread = 100) evoked by 13 mixed meals compared with an isoenergetic white bread reference meal. Because of the large number of meals, 6 meals were tested by 11 subjects in group 1 and 7 meals by 10 subjects in group 2. Repeated-measures analysis of variance was used to determine significant differences. M, meal.

Similarly, the meal with the highest predicted demand (M2: a breakfast of honeydew melon, banana, and yogurt) produced a response a little higher than expected, but the highest response in practice. Our study also shows that some meals with widely disparate carbohydrate content had similar insulin responses (both observed and predicted). For example, M12 and M1 had comparable FIIs (observed 45 and 44, predicted 49 and 42, respectively), yet their carbohydrate content varied markedly (63 and 37 g, respectively). If carbohydrate counting was used to predict the bolus insulin dose in type 1 diabetes, then the dose for these meals would vary accordingly. In contrast, the FII suggests the meals generate the same insulin demand. Nonetheless, the study's limitations should also be noted: the small number of meals, some with contrived portion sizes and relatively low fiber content. The statistical power is therefore low, and it would not be appropriate to dismiss available carbohydrates and fiber as related to insulin response.

The advantage of a classification system in which a reference food is used is that data can be derived from testing different groups of people. In the present study, the 2 groups of subjects clearly show differences in insulin secretion, the first group showing an average insulin response to white bread which is approximately half that of the second group (mean ± SEM AUC: 14,350 ± 2260 compared with 30,700 ± 3100 pmol × min/L, respectively). However, this large between-subject variation was diminished when the subjects' individual responses were indexed to a reference food. Moreover, testing the reference food twice reduces the effect of day-to-day variability within individuals. Hence, these sources of variation within and between

subjects can be managed sufficiently to be able to show true differences among foods and meals in their capacity to stimulate insulin secretion. However, our choice of subjects may also be a significant limitation because any ranking of foods according to insulin demand in lean, young healthy subjects may not be directly applicable to the diabetic population or the general population. Worsening insulin resistance in overweight subjects and impairment in β cell function in diabetic individuals will reduce the capacity to respond appropriately to everyday meals and therefore reduce the range of responses seen. Nonetheless, our findings could be applicable in the early stages of development of disease when β cell function is adequate.

Currently, carbohydrate counting is commonly recommended for matching insulin dosage to insulin demand in individuals with type 1 diabetes, although the emphasis on carbohydrate counting varies between clinics, and many dietitians consider that it is too simplistic. In the present study, mixed meals with similar carbohydrate content produced widely disparate insulin responses. For example, meal M13 (beef steak and potatoes) with ≈40 g carbohydrate produced twice the insulin response of meal M1 (grain bread, peanut butter, and milk) despite a similar amount of carbohydrate (≈37 g). Although the addition of protein or fat to a carbohydrate-rich meal is known to evoke additional or synergistic insulin secretion and to contribute to the reduction in glycemia (8, 17, 18), these variables are often not considered in the day-to-day management of diabetes. Because the FII classification allows all the factors influencing insulin demand to be integrated into a single result, it may be an attractive component in the very complex treatment of type 1 diabetes.
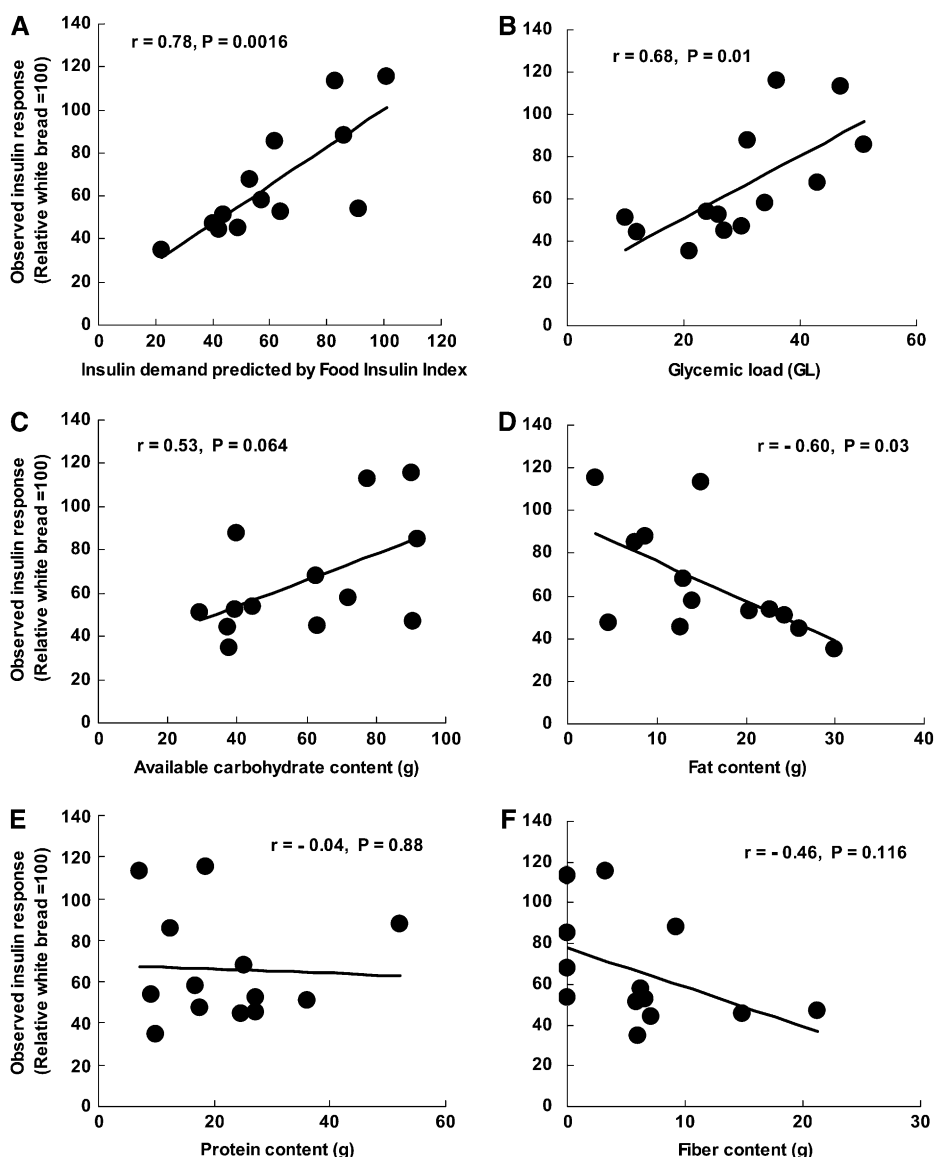
FIGURE 2. A–F: Univariate correlations between observed insulin responses (relative to white bread = 100) and insulin demand as predicted by food insulin index of component foods, glycemic load, or macronutrients of the 13 mixed meals.

Interestingly, in the present study, the fat content of the mixed meal showed a significant inverse relation ($r = -0.60$) with observed insulin responses and was a more reliable predictor of insulin demand than the amount of carbohydrate. This finding is consistent with our previous study of 38 single foods (12). The explanation may be the reciprocal relation between fat and the sum of the other 2 macronutrients, protein and carbohydrate. Although carbohydrate is the primary stimulus for insulin secretion, insulinotropic amino acids and bioactive peptides are also potent stimulators of insulin release (11, 19, 20). Because protein stimulates insulin secretion, particularly when combined with carbohydrate (8, 20), the meals with the highest protein and carbohydrate content (and hence lowest fat content) produce the highest insulin responses.

Further research is needed to validate the FII concept and to show its usefulness. The ability of FII to predict the diet-disease relation in epidemiologic research vis-á-vis other nutrients, GI, and GL will be a major test of its usefulness. Although the database currently has 120 single foods, including the most common sources of energy in Western diets (12) (J Bao, F Atkinson, JC Brand-Miller, unpublished data, 2007), further expansion is required. Dose-response and day-long investigations extending from breakfast to the evening meal are needed. To confirm the food rankings in a broader population, studies in overweight and obese subjects and in individuals with impaired glucose tolerance and impaired insulin secretion, including type 2 diabetes, should be undertaken. Although it is possible that worsening defects in insulin secretion may obviate the ability to detect differences among foods, the concept itself may still be relevant in the management of those conditions.

In summary, the relative insulin demand evoked by mixed meals consumed by lean young healthy subjects is best predicted by a physiologic index based on integrating insulin responses to isoenergetic portions of single foods. In the context of composite meals of similar energy value but varying macronutrient content, carbohydrate counting had limited value.

The authors' responsibilities were as follows—JCB-M: conceived the study and interpreted the data; JB and VdJ: conducted the study, prepared the meals, and collected the data; JB and JCB-M: wrote the manuscript; FA: designed the experiment, adjusted the composition of the meals, and assisted with the writing of the manuscript; and JCB-M, JB, and PP: analyzed the data.

JCB-M is a co-author of *The New Glucose Revolution* book series (Hodder and Stoughton, London; Marlowe and Co, New York; Hodder Headline, Sydney and elsewhere) and director of a nonprofit, glycemic index (GI)–based, food endorsement program in Australia. JCB-M and FA manage the University of Sydney GI testing service. None of the other authors had a conflict of interest.

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