

Fasting-based Estimates of Insulin Sensitivity in Overweight and Obesity: A Critical Appraisal

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Abstract

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Objective: To identify simple methods to estimate the degree of insulin resistance.

Research Methods and Procedures: The performance of a wide range of fasting-based index estimates of insulin sensitivity was compared by receiver operating characteristic analysis (area under curves and their 95% confidence intervals) against the M value from euglycemic insulin clamp studies collected in the San Antonio (non-Hispanic whites and Hispanic residents of San Antonio, TX) and European Group for the Study of Insulin Resistance (non-diabetic white Europeans) databases ($n = 638$).

Results: Insulin resistance differed substantially between lean ($BMI < 25 \text{ kg/m}^2$), overweight or obese ($BMI \geq 25 \text{ kg/m}^2$), and type 2 diabetic individuals. Estimates of insulin resistance were, therefore, assessed in each group separately. In the overweight and obese subgroup ($n = 302$), the receiver operating characteristic performance of fasting-based indices varied from 0.72 (0.62 to 0.82), in the case of the insulin/glucose ratio, to 0.80 (0.72 to 0.88) in the case of Belfiore free fatty acids. One superior method could not be identified; the confidence intervals overlapped, and no statistically significant differences emerged. All indices performed better when using the whole study population, with

fasting plasma insulin, homeostatic model assessment, insulin/glucose ratio, quantitative insulin sensitivity check index, glucose/insulin ratio, Belfiore glycemia, revised quantitative insulin sensitivity check index, McAuley index, and Belfiore free fatty acids showing area under curves of 0.83, 0.90, 0.66, 0.90, 0.66, 0.90, 0.85, 0.83, and 0.86, respectively, because of the inclusion of very insulin sensitive (lean) and very insulin resistant cases (diabetic subjects).

Discussion: In conclusion, a superior fasting-based index estimate to distinguish between the presence and absence of insulin resistance in overweight and obesity could not be identified despite the use of the large datasets.

Key words: insulin resistance, insulin sensitivity, glucose clamp technique, metabolic syndrome, diabetes mellitus

Introduction

Type 2 diabetes and cardiovascular disease share common antecedents such as abdominal obesity, hypertension, lipid disturbances, and a procoagulant state. The clustering of these antecedents has been viewed as a syndrome (commonly called metabolic syndrome) in which insulin resistance plays a pivotal role (1–3). Insulin resistance, the reciprocal of insulin sensitivity, e.g., a diminished effectiveness of insulin in lowering blood sugar levels, is present long before the individual metabolic syndrome components become clinically manifest (4,5). Insulin resistance, which predicts and precedes type 2 diabetes and may be directly linked with atherosclerosis and cardiovascular disease (6–8), is modifiable by lifestyle interventions and pharmacologically (9,10). Correctly identifying patients with insulin resistance may, therefore, be clinically useful for prevention.

The main determinants of insulin resistance are insulin-mediated glucose clearance in peripheral tissues and insulin-mediated suppression of hepatic glucose output; moreover, different tissues of the body may have different sensitivity to the action of insulin. Accurate measurements of insulin resistance are, therefore, time-consuming and

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Table 1. Characteristics of the study population ($n = 638$) selected from the San Antonio and EGIR databases

	Whole study population (M:F = 384:254)	Overweight and obesity (M:F = 184:118)
Age (years)	47 (18 to 80)	47 (20 to 77)
BMI (kg/m ²)	26 (18 to 55)	28 (25 to 55)
Waist-to-hip ratio	0.92 (0.59 to 1.18)	0.94 (0.59 to 1.17)
FPG (mM)	5.2 (3.7 to 16.5)	5.2 (3.9 to 6.5)
FPI (pM)	60 (10 to 404)	70 (17 to 235)
Fasting FFA (μ M)	569 (106 to 1652)	550 (106 to 1473)
Fasting triglycerides (mM)	1.13 (0.06 to 13.5)	1.48 (0.06 to 13.5)
M_{LBM} (μ mol/min/kg LBM)	43.6 (5.4 to 117.1)	40.4 (10.2 to 117)

Data are expressed as median and range. EGIR, European Group for the study of Insulin Resistance; FPG, fasting plasma glucose; FPI, fasting plasma insulin; FFA, free fatty acid; M_{LBM} , mean glucose infusion rate at steady state normalized per kilogram lean body weight.

expensive, unsuitable for clinical practice and population studies (11). Consequently, a number of more attractive simple methods or tests have been developed. Previous reviews on these methods have been narrative (12–14) or provided limited information on test validity because of selection of subjects (with a wide range of insulin resistance), smaller population samples than the present one, or the use of correlation coefficients (15–20), which is misleading according to Bland and Altman (21).

In this study, we compared the performance of a wide range of fasting-based index estimates of insulin sensitivity by using receiver operating characteristics (ROCs)¹ functions, which yield practical information on test validity such as sensitivity and specificity. We used euglycemic insulin clamp data, the gold standard method to measure insulin sensitivity, of the San Antonio and European Group for the Study of Insulin Resistance (EGIR) study cohorts, including men and women, lean and obese, and normal glucose tolerance and diabetes.

Research Methods and Procedures

We analyzed data from the EGIR database (which is comprised of non-diabetic white Europeans) and the San Antonio Metabolism Study cohort (which includes non-Hispanic whites and Hispanic residents of San Antonio, TX) obtained with the use of the euglycemic insulin clamp technique (with an infusion rate of 240 pmol/min per meter

squared for 2 hours). Details on the study cohort, the protocol, experimental, and analytical methods have been published previously (22–27). Approval of the protocol by the local Ethics Committee and informed consent from all subjects was obtained before the studies at each geographic center. For the purpose of this study, insulin sensitivity was taken to be the steady-state total body insulin-mediated glucose disposal rate (M_{LBM}), expressed as μ mol per minute per kilogram of fat-free (or lean body) mass. Blood samples were collected in the fasting state for the measurement of fasting plasma glucose (FPG), fasting plasma insulin (FPI), fasting plasma triglyceride, and fasting free fatty acids (FFAs). Plasma glucose was measured by the glucose oxidase method. Plasma insulin concentrations were measured by radioimmunoassay. Serum lipid levels were assayed by standard enzymatic assays. Plasma FFA concentrations were assayed spectrophotometrically. Fat mass [hence lean body mass (LBM)] was measured by different techniques: underwater weighing, electrical bioimpedance, and tracer water. The results were generally in agreement, but for homogeneity, it was decided to use the sex-specific Hume formula throughout. An assorted set of simple index estimates of insulin sensitivity was calculated, derived from glucose, insulin, FFAs, and triglycerides, which all can be derived from a single fasting blood sample (8,13,15–17,28–32). Only subjects with complete data for BMI, M_{LBM} , glucose, insulin, FFAs, and triglycerides were analyzed ($n = 638$).

Data are given as medians and their range, because most distributions were skewed. Spearman correlation coefficients were used to express the strength of the relation of the index estimates of insulin sensitivity to the M_{LBM} value from the clamp. To compare the performance of single indices, ROC curves were constructed. ROC curves char-

¹ Nonstandard abbreviations: ROC, receiver operating characteristic; EGIR, European Group for the study of Insulin Resistance; M_{LBM} , mean glucose infusion rate at steady state normalized per kilogram lean body weight; FPG, fasting plasma glucose; FPI, fasting plasma insulin; FFA, free fatty acid; LBM, lean body mass; AUC, area under the curve; HOMA_{IR}, homeostatic model assessment of insulin resistance; I/G, fasting insulin to fasting glucose ratio; GLY, glycemia; QUICKI, quantitative insulin-sensitivity check index.

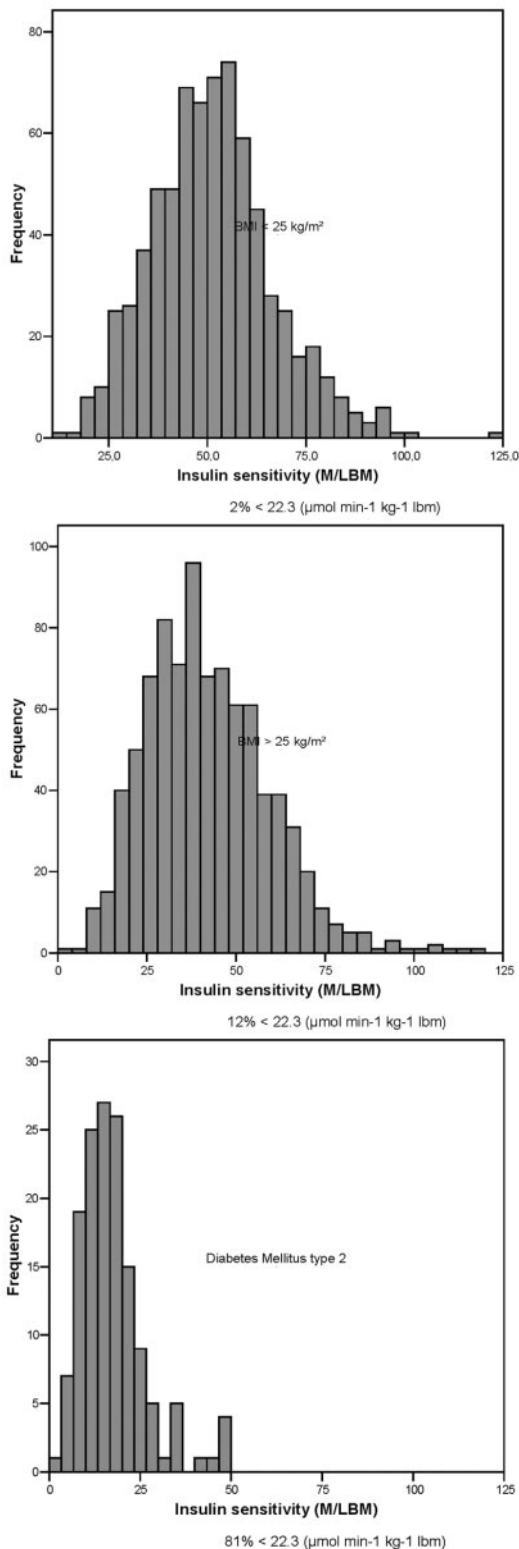


Figure 1: Histograms of insulin sensitivity (M/LBM) in lean (BMI < 25 kg/m²), overweight and obese subjects (BMI ≥ 25 kg/m²), and type 2 diabetic subjects. An M/LBM value <22.3 μmol/min per kilogram LBM is found in 2%, 12%, and 81% in the lean, overweight and obese, and diabetes populations, respectively.

acterize the relationship between the true-positive ratio (sensitivity) and the false-positive ratio (1 – specificity). The sensitivity of a test is the probability (0% to 100%) that a test is positive for subjects with insulin resistance or the proportion of cases picked out by the test, relative to all cases that actually are insulin resistant. The points on the curves represent different values of the aggregate score. Curves of tests that perform well aggregate toward the top left corner of the square. The area under the ROC curve (AUC) quantifies the diagnostic value of the test: the greater the AUC, the better the performance of the test. It varies between 0.5, when the test is no better than chance in correctly categorizing the two groups, and 1.0, when its predictive value is perfect (33–35). ROC curves were calculated for indices of insulin resistance [FPI, homeostatic model assessment (HOMA_{IR}), fasting insulin to fasting glucose ratio (I/G)] and indices of insulin sensitivity [quantitative insulin sensitivity check index (QUICKI), the G/I ratio, Belfiore glycemia (GLY), revised QUICKI, McAuley, Belfiore FFA] separately. To compare different indices of insulin sensitivity with each other, a cut-off value of M_{LBM}, derived from the euglycemic insulin clamp, was used to define “the presence or absence” of insulin resistance: 22.3 μmol/min/kg_{lbm} (corresponding to the sixth percentile of the EGIR population). Analyses were performed with the SPSS-PC software package, version 11.0.1 (SPSS, Chicago, IL).

Results

Table 1 shows the characteristics of the study population selected from the EGIR and San Antonio study cohorts. In general, insulin sensitivity was highest in normal weight subjects (BMI < 25 kg/m²), intermediate in overweight or obese subjects (BMI ≥ 25 kg/m²), and lowest in type 2 diabetic subjects, but showed a wide variation in each group (Figure 1). For example, an M_{LBM} value <22.3 μmol/min/kg_{lbm} was found in 2% of the normal weight subjects, 12% of the overweight/obese subjects, and 81% of diabetic patients. Table 2 shows the correlation coefficient (r) between each of the fasting-based indices of insulin sensitivity (with its formula and reference) and the clamp M_{LBM} in different subgroups. As expected, because all methods were devised to estimate the same quantity, all coefficients were significant. However, the magnitude of coefficients varied considerably in different subgroups, being smaller in lean subjects (36) and diabetic subjects compared with overweight/obese subjects. The performance of the different indices against clamp-derived M_{LBM} was tested by ROC analysis by defining insulin resistance as an M_{LBM} value <22.3 μmol/min/kg_{lbm}. We reasoned that a fasting-based index of insulin sensitivity would be useful as a diagnostic tool if it had sufficient discriminating power in overweight and obesity, where insulin resistance is neither infrequent (as in lean subjects) nor very common (as in diabetic pa-

Table 2. Spearman correlation coefficients between fasting-based index estimates of insulin sensitivity and directly measured insulin sensitivity from the euglycemic insulin clamp

Simple measure (ref.)	Formula	BMI	BMI	Diabetes	Whole study population
		<25 kg/m ² (n = 247)	≥25 kg/m ² (n = 302)		
FPI (8, 28)	Fasting plasma insulin	-0.35	-0.48	-0.35	-0.59
HOMA _{IR} (13, 29)	Insulin × glucose/22.5	-0.33	-0.47	-0.35	-0.63
QUICKI (30)	1/[log (insulin) + log (glucose)]	0.33	0.47	0.35	0.63
G/I ratio (31)	Glucose-to-insulin ratio	0.36	0.47	0.28	0.43
I/G ratio (16)	Insulin-to-glucose ratio	-0.36	-0.47	-0.28	-0.43
Belfiore GLY (17)	2/[(insulin × glucose) + 1]	0.33	-0.47	0.35	0.63
Revised QUICKI (15)	1/[log(glucose) + log(insulin) + log(NEFA)]	0.39	0.39	0.43	0.57
McAuley index (32)	e ^[2.63 - 0.28 ln(insulin) - 0.31 ln(triglycerides)]	0.22	0.47	0.27	0.56
Belfiore FFA (17)	2/[(insulin × NEFA) + 1]	0.38	0.37	0.41	0.55

Spearman’s correlation coefficients are all statistically significant (*p* < 0.001). FPI, fasting plasma insulin; HOMA_{IR}, homeostatic model assessment of insulin resistance; QUICKI, Quantitative Insulin Sensitivity Check Index; G/I, glucose-to-insulin ratio; I/G, insulin-to-glucose ratio; Belfiore GLY, Belfiore (IS_{Igly}_basal); NEFA, non-esterified fatty acids; Revised QUICKI, QUICKI with additional NEFA concentration; Belfiore FFA, Belfiore (IS_{Iffa}_basal).

tients). Figure 2 shows the ROC curves, and Table 3 shows their AUCs and 95% confidence intervals for all indices. They ranged from 0.72 (0.62 to 0.82), in the case of I/G and G/I, to 0.80 (0.72 to 0.88) in the case of the Belfiore FFA; a statistical difference between the curves could not be established. In contrast, applying ROC analysis to the whole dataset (including lean, overweight/obese, and diabetic subjects) resulted in a better performance of HOMA_{IR}, QUICKI, Belfiore GLY, Belfiore FFA, Revised QUICKI, FPI, and McAuley compared with the I/G and G/I, with AUCs ranging from 0.66 (0.60 to 0.72) to 0.90 (0.86 to 0.93; Table 3). Finally, the performance of the FPI or HOMA_{IR} did not improve after logarithmic transformation (data not shown) (19,37), and a different performance of HOMA_{IR} in non-Hispanic whites vs. non-whites could also not be established (data not shown). Varying the cut-off for M_{LBM} between 12.3 and 27.3 μmol/min/kg_{l_{bm}} did not appreciably change the pattern of results.

Discussion

In this analysis, one superior fasting-based index estimate of insulin sensitivity could not be identified for overweight and obesity despite the use of a large sample. Previous studies have identified a variety of tests as superior (15–20,29–32,38). These reports were based on correlation coefficients (15,17–20,29,30), which has been methodologically criticized (21), and on selected subjects and smaller samples than the present cohort (31,32) (*n* = 55, 178); other reports were based on the ability to predict diabetes (16,38), which is highly relevant but not the same as insulin resistance.

The usefulness of an index of insulin sensitivity as a diagnostic tool depends on its relevance, practicality, reproducibility, and validity (39). Identifying subjects with insulin resistance seemed most relevant in overweight and obesity. In this population, a large number of subjects are at risk for diabetes and cardiovascular disease and may benefit from intervention. Identifying subjects with insulin resistance is also relevant to ongoing research on the role of insulin sensitivity in the pathogenesis of type 2 diabetes and cardiovascular disease; its precise role is not fully understood. Prospective studies on the pathogenesis of diabetes with accurate measurements of insulin sensitivity are few (38,40), and, thus far, none has assessed the predictivity of insulin resistance for cardiovascular disease. Consequently, cut-off values for prediction of diabetes and/or cardiovascular disease derived from accurate measurements of insulin sensitivity are lacking.

In this study, we hypothesized that an index estimate of insulin sensitivity is practical if it is simple and easily applicable in daily practice. We, therefore, selected only indices based on biochemical parameters (insulin, glucose, triglycerides, FFAs) that can be measured in a single fasting blood sample.

The reproducibility of the indices described in this study depends on the intra-individual variation of insulin, glucose, triglycerides, or FFA concentrations. In particular, fasting plasma insulin is a component of all formulas. The intra-individual variation of insulin has recently been analyzed by Mooy et al. and found to be predominantly determined by biological variation, whereas analytical variation made

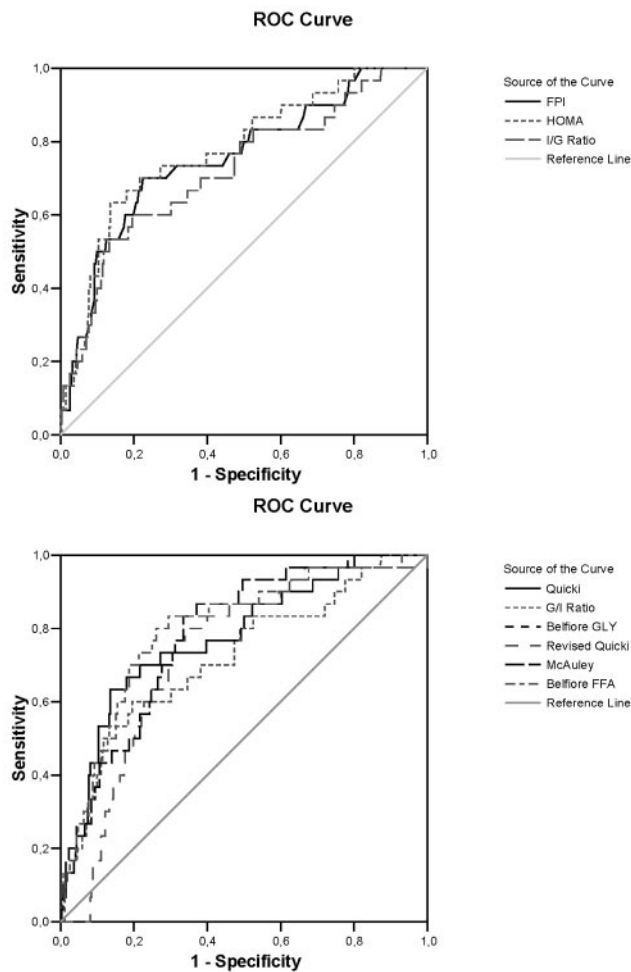


Figure 2: ROC curves of fasting-based index estimates of insulin sensitivity in overweight and obesity.

only a minor contribution. Fasting plasma insulin had a 95% random test–retest difference (2 standard deviation of the test–retest differences/median level of individual average score) of $\sim 60\%$, whereas it was 15% for fasting plasma glucose (41). According to another report (42), intra-individual variation of lipids was also predominantly determined by biological variability and was greatest for triglycerides. Furthermore, there is marked interlaboratory variance in the measurement of insulin, which may result in up to 3-fold variation in measured insulin concentrations (43).

Finally, findings on the validity of the fasting-based indices of insulin sensitivity in this study are robust and based on data from different centers (the multicenter EGIR and San Antonio study cohorts). In contrast to most previous reviews (15–20,29,30) but not all (31,32,38), ROC curves and their 95% confidence intervals were calculated to provide information on the test validity. We could not establish superiority for any index of insulin sensitivity in over-

weight and obesity. Thus, a statistical difference in performance between FFI (insulin) and, for example, revised QUICKI (a formula that contains an insulin, a glucose, and a FFA term) could not be established. If one should use, for example, an FFI level of 53 pM as a screening tool to detect insulin resistance, 90% of the overweight and obese subjects with an $M_{LBM} < 22.3 \mu\text{mol}/\text{min}/\text{kg}_{\text{lbm}}$ would be detected, but 67% of them would have M_{LBM} values $> 22.3 \mu\text{mol}/\text{min}/\text{kg}_{\text{lbm}}$ (i.e., a specificity of 33%). Raising this FFI cut-off to 117 pM would result in a sensitivity of 50% and a specificity of 90%.

It could be argued that some fasting-based index estimates performed better in the whole study population (Table 3). This is expected because the inclusion of very insulin sensitive (lean subjects) and very insulin-resistant subjects expands the range toward more extreme values. These subgroups, however, are easily distinguishable based on anthropometrics and plasma glucose values.

The use of both insulin and glucose values in prediction formulas has been defended by the glucose allostasis hypothesis: stability through change by physiological adaptation to chronic stress (insulin resistance) (44). The close relationship between FFA and triglycerides and insulin resistance is supported by recent work on data from the EGIR cohort (27), despite the fact that neither FFAs nor triglycerides improved the performance of the formulas in the overweight and obese subpopulation.

However, hyperinsulinemia is not synonymous with insulin resistance (25). Hyperinsulinemia in obesity is the result of both compensatory (to insulin resistance) and primary (central) hypersecretion of insulin. The risk for type 2 diabetes and cardiovascular disease associated with a predominantly hypersecretory vs. a predominantly insulin-resistant obese phenotype may, therefore, be different. Thus, improving the performance of fasting-based index estimates of insulin resistance by repeat fasting blood sampling and use of mean insulin levels is inherently limited. Limitations of this study, of insulin assay or estimate of LBM, may temper the individual performance of fasting-based indices on the one hand, but may also provide a more realistic insight into the performance in daily practice on the other hand. It is unlikely that the results are influenced by these limitations because they affected all estimates equally.

In conclusion, the validity of a wide variety of fasting-based index estimates of insulin sensitivity based on formulas including insulin, glucose, FFAs, or triglycerides has been studied. These index estimates showed sensitivities varying between 90% and 50%, with associated specificities ranging between 30% and 90%. A superior index to distinguish between the presence and absence of insulin resistance in overweight or obesity could not be identified, despite the use of large datasets.

Table 3. Area under the curves (AUCs) and their 95% confidence intervals (CIs) of fasting-based index estimates of insulin sensitivity in overweight/obese (BMI \geq 25 kg/m²) and the whole study population (lean, overweight/obese, and diabetic individuals)

	Overweight and obesity			Whole study population		
	AUCs	95% CIs		AUCs	95% CIs	
FPI	0.75	0.66	0.85	0.83	0.78	0.87
HOMA _{IR}	0.78	0.69	0.87	0.90	0.86	0.93
I/G ratio	0.72	0.62	0.82	0.66	0.60	0.72
QUICKI	0.78	0.69	0.87	0.90	0.86	0.93
G/I ratio	0.72	0.62	0.82	0.66	0.60	0.72
Belfiore GLY	0.78	0.69	0.87	0.90	0.86	0.93
Revised QUICKI	0.73	0.65	0.82	0.85	0.82	0.89
McAuley	0.79	0.71	0.86	0.83	0.79	0.87
Belfiore FFA	0.80	0.72	0.88	0.86	0.83	0.90

Insulin resistance was defined as an M_{LBM} value $<22.3 \mu\text{mol}/\text{min}/\text{kg}$ LBM. FPI, fasting plasma insulin; HOMA_{IR}, homeostatic model assessment of insulin resistance; I/G, insulin-to-glucose ratio; QUICKI, Quantitative Insulin Sensitivity Check Index; G/I, glucose-to-insulin ratio; Belfiore GLY, Belfiore (ISIgly_{basal}); Revised QUICKI, QUICKI with additional non-esterified fatty acids concentration; Belfiore FFA, Belfiore (ISIfa_{basal}).

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