Comparison of Insulin Sensitivity and Glucose Effectiveness Determined by the One- and Two-Compartment–Labeled Minimal Model in Late Prepubertal Children and Early Adolescents

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Multiple methods are used to determine insulin sensitivity. Most commonly used in children are euglycemic-hyperinsulinemic clamp and frequently sampled intravenous glucose tolerance (FSIVGTT) with minimal modeling (MinMod). The parameters S_G and S_I of MinMod are related to insulin sensitivity and glucose effectiveness, respectively, but inappropriate modeling of glucose kinetics causes inaccuracies. Glucose tracer use may mitigate such inaccuracies, allowing use of multiple modeling approaches, including a 2-compartment model (2CMM). This study was designed to compare the 1-compartment model (1CMM) and 2CMM in a pediatric population. Twenty-three children were studied 4 times using FSIVGTT with [6,6] D_2 glucose. Glucose effectiveness and insulin sensitivity were calculated by 1CMM (S^*_{G1} and S^*_{I1}) and 2CMM (S^*_{G2} and S^*_{I2}). Indices were reliably estimated in 86 of 87 tests for 1CMM, but only in 49 for 2CMM. S^*_{G1} overestimated S^*_{G2}, but they were positively related. S^*_{I1} and S^*_{12} were not different and were positively related. This suggests that inadequate modeling by the 1CMM has a smaller impact on glucose tolerance indices in children than in adults. Comparison with classical MinMod gave results analogous to those in adults (MinMod S_G was larger than S^*_{G1}, MinMod S_I was smaller than S^*_{I1}). These results demonstrate significant differences in glucose effectiveness, but not insulin sensitivity, as measured by 1CMM and 2CMM in early adolescents. Thus, when insulin sensitivity is the primary interest, the 1CMM is more robust because its parameters are more reliably estimated than those of 2CMM and is the logical choice in pediatric population-based studies.
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MULTIPLE METHODS HAVE been developed to measure insulin sensitivity. In children, the 2 most commonly used are the glucose clamp technique[1-4] and the intravenous glucose tolerance test (IVGTT) with the minimal model (MinMod).[5-7] The glucose clamp technique is labor intensive and, in addition, it cannot distinguish within a single experiment between glucose's ability to stimulate its own uptake and inhibit its own production (glucose effectiveness) and insulin's effect on glucose uptake and production (insulin sensitivity). The frequently sampled IVGTT analyzed with the cold minimal model directly addresses these problems and, if used in conjunction with a tracer, eg, a stable isotope, and the hot minimal model (1CMM), also makes it possible, in principle, to segregate glucose and insulin effects on glucose production from those on disposal.[8,9]

Unfortunately, it has recently been shown that the single compartment description of glucose kinetics embedded both in the MinMod and the 1CMM may be too simplistic for the purpose of assessing insulin sensitivity and glucose effectiveness. This inappropriate modeling, or undermodeling (in which the multicompartmental glucose disappearance mechanism is approximated with a single compartment), causes, in all likelihood, an overestimation of the true value of glucose effectiveness and an underestimation of insulin sensitivity.[10] To overcome these limitations of the original minimal model formulation, a 2-compartment minimal model has been developed and tested in normal adult humans from a labeled IVGTT.[11]

We have previously reported longitudinal data from 23 children followed over 18 months as they progressed through puberty using the stable labeled IVGTT with the 1CMM.[9] The goal of this study was to compare glucose effectiveness and insulin sensitivity from 1CMM (S^*_{G1} and S^*_{I1}) and 2-compartment minimal models (2CMM, S^*_{G2} and S^*_{I2}) in these same children. Glucose effectiveness (S_{G1}) and insulin sensitivity (S_{I1}) indices were also calculated from unlabeled data by using the classic MinMod and compared with the labeled 1CMM indices S^*_{G1} and S^*_{I1}.[12]

MATERIALS AND METHODS

Subjects

Twenty-three children were enrolled in the study. At enrollment, all were Tanner stage 3 or less. Each child was studied 4 times separated by 6-month intervals. Four children withdrew before completing all 4 studies. The mean age, body mass index (BMI), and Tanner stage at the time of each study are shown in Table 1. All subjects were healthy and were on no medications. Informed consent was obtained from the legal guardian and informed assent from the participant. The University of Iowa Institutional Review Board for Human Investigation approved the protocol.

Measures

Plasma glucose concentration was measured using a YSI Model 2300 STAT Glucose Analyzer (Yellow Springs Instruments, Yellow Springs, OH). Plasma insulin was measured by radioimmunoassay in the CORE laboratory of the University of Iowa. Mole percent excess of [6,6] D_2-glucose was measured in the Mass Spectrometry Laboratory of the University of Iowa using a HP series Mass Selective Detector equipped with a HP 5890 series gas chromatograph and a HP 7673 autosampler (Hewlett Packard, Palo Alto, CA). The calibration curve was used for determining the ratio of D_2 to $D_2 + D_0$ (D_o nondeuterated glucose) and was linear over the range of 0.87% to 20.84%.

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Table 1. Mean Age, BMI, and Tanner Stage at the Time of Each Study

Study	Age (yr)	BMI (kg/m^2)	Tanner Stage
1	10.7 ± 1.6	18.6 ± 4.0	1.7 ± 0.7
2	11.3 ± 1.6	18.7 ± 4.4	2.2 ± 1.0
3	11.8 ± 0.3	19.0 ± 4.6	2.8 ± 1.1
4	12.7 ± 0.3	19.7 ± 1.0	3.2 ± 0.22

NOTE. Values are mean ± SD.

Protocol

Each subject was admitted 4 times at 6-month intervals to the Clinical Research Center (CRC) at The University of Iowa. Subjects were admitted at 8 PM and fasted overnight. Subjects were instructed by the CRC dietitian to consume at high carbohydrate diet for 72 hours before study admission. Two intravenous catheters were placed in the antecubital fossa of both arms before starting the study. One catheter was used for sampling while the second intravenous catheter was used for infusion of 25% dextrose in water with 13.3% ± 2.7% [6-6]D_2-glucose. Three milliliter blood samples were taken at −10, 0, 2, 4, 6, 8, 12, 14, 16, 19, 22, 27, 32, 42, 52, 62, 72, 82, 92, 102, 122, 142, 162, and 182 minutes relative to a glucose bolus for measurement of plasma glucose, insulin, and [6,6]D_2-glucose concentrations.

Models and Identification

Glucose effectiveness and insulin sensitivity were determined from labeled glucose by the hot 1CMM[8,9] and 2CMM[11] as previously described. The 1CMM model equations in their uniquely identifiable parameterization are given by:

$$\dot{Q}^*(t) = -[S^*_{G1} + X^*(t)]Q^*(t) \qquad Q^*(0) = D^*$$

$$\dot{X}^*(t) = -p^*_2\{X(t) - S^*_{I1}[I(t) - I_b]\} \qquad X^*(0) = 0 \quad (1)$$

$$G^*(t) = Q^*(t)/V^*$$

where D* is the labeled glucose dose (mg/kg^{-1} body weight), Q*(t) (mg/kg^{-1}) is tracer glucose mass in plasma, G*(t) (mg/dl^{-1}) is tracer glucose concentration, I(t) (U mL^{-1}) is insulin concentration and I^0 is its basal value, X*(t) is tracer-quantified insulin action (min^{-1}) and V* (dL/kg^{-1}) is the glucose distribution volume; the asterisk * denotes tracer-related variables and parameters. The indices S^*_{G1} (min^{-1}) and S^*_{I1} (min^{-1} per U/mL^{-1}) reflect only glucose disposal processes: S^*_{G1} measures the ability of glucose per se, at basal insulin, to stimulate glucose rate of disappearance, and S^*_{I1} measures the ability of insulin to enhance glucose disposal. It is worth noting that in the 1CMM glucose effectiveness S^*_{G1} also coincides with (and thus measures) fractional glucose clearance at basal insulin. Values from the hot 1CMM, traditionally expressed in fractional units, were multiplied by the plasma glucose volume of distribution (another parameter in the model) to make them comparable to values from 2CMM, which are in units comparable to those of the glucose clamp.[11] The 2CMM equations are given by:

$$\dot{Q}^*_1(t) = -[k_{01}(t) + k_{21}]Q^*_1(t) + k_{12}Q^*_2(t) \qquad Q^*_1(0) = D^*$$

$$\dot{Q}^*_2(t) = k_{21}Q^*_1(t) - [k_{02} + X^*(t) + k_{12}]Q^*_2(t) \qquad Q^*_2(0) = 0 \quad (2)$$

$$\dot{X}^*(t) = -p^*_2X^*(t) + p^*_3[I(t) - I_b] \qquad X^*(0) = 0$$

$$G^*(t) = \frac{Q^*_1(t)}{V^*_1}.$$

Model parameters are V^*_1, k_{21}, k_{12}, k_{02}, p^*_2, and p^*_3; k_{01} (t) is the time-varying rate of glucose utilization from the accessible compartment.[1] Indices of glucose effectiveness, plasma glucose clearance rate, and insulin sensitivity can be derived directly from these parameters and are reported here for sake of completeness: glucose effectiveness, S^*_{G2}, is:

$$S^*_{G2} = V^*_1\left(\frac{4k_{21}k_{02}}{k_{02} + k_{12}} - \frac{Rd_0}{G_0V^*_1}\right) \qquad (mL/min^{-1}/kg^{-1}). \quad (6)$$

(Rd_0 is assumed to be 1.0 mg/min^{-1}/kg^{-1})[13] and insulin sensitivity, S^*_{I2}, is:

$$S^*_{I2} = V^*_1\frac{p^*_3K_{21}K_{12}}{p^*_2(k_{02} + k_{12})^2} \qquad (mL/min^{-1}/kg^{-1}/\mu U/mL^{-1}). \quad (7)$$

Lastly, unlabeled indices of glucose effectiveness and insulin sensitivity S_{G1} and S_{I1} were estimated from the available total glucose plasma concentration data by the classic MinMod approach.[12] The model is described by the following equations:

$$\dot{Q}(t) = -[S_{G1} + X(t)]Q(t) + S_{G1}Q_b \qquad G(0) = D/V + G_b$$

$$\dot{X}(t) = -p_2\{X(t) - S_{I1}[I(t) - I_b]\} \qquad X(0) = 0 \quad (8)$$

$$G(t) = Q(t)/V$$

in which D is the total glucose dose (mg/kg^{-1} body weight), Q(t) (mg/kg^{-1}) is total glucose mass in plasma, G(t) (mg/dL^{-1}) is glucose concentration, I(t) (U/mL^{-1}) is insulin concentration, $G_b = Q_b/V$ and I_b are their basal values, X(t) is insulin action (min^{-1}) and V (dL/kg^{-1}) is the glucose distribution volume. Insulin concentration acts as a known (without error) input in the second equation, and model parameters are estimated by fitting the model response, G(t), to glucose concentration data. The model has 4 uniquely identifiable parameters: S_{G1} (min^{-1}), S_{I1} (min^{-1} μU/mL^{-1}), p_2 (min^{-1}) and V. S_{G1} and S_{I1} are the minimal model indices of glucose effectiveness and insulin sensitivity, respectively, and reflect the effect of glucose and insulin on both glucose disposal and production. In particular, S_{G1} measures the ability of glucose per se at basal insulin, to stimulate glucose disposal and to inhibit glucose production. Similarly, S_{I1} measures the ability of insulin to enhance glucose disposal and inhibit glucose production.

The minimal models were all numerically identified by weighted nonlinear least squares (fitting the predicted variable G*(t) to the labeled glucose time course for 1CMM and 2CMM, and fitting G(t) to the total glucose time course for the MinMod assuming a Gaussian, zero mean measurement noise with known variance. Assessment of their performance was based on quantitative criteria including pattern of residuals, ie, difference between data and model prediction, and precision of parameter estimates (expressed as coefficient of variation, ie, the ratio of the standard error of the estimate and the estimate) obtained from the inverse of the Fisher information matrix of the experiment.[14,15] Values for S^*_{I1}, S^*_{G1}, S^*_{I2}, S^*_{G2}, S_I, S_G were considered reliable if their coefficient of variation from the model was less than 100%.[11] Parameter estimation was performed with the SAAM II software (University of Washington and SAAM Institute, Seattle, WA).[16]

Statistics

Paired *t* tests were used to detect differences between the measures of insulin sensitivity and glucose effectiveness for each study. Linear regression analysis was used to assess relationships between variables. Results are expressed as mean ± SE.

RESULTS

Model Comparison

Of the total of 87 studies performed in the 23 children, glucose effectiveness and insulin sensitivity values from the 1CMM could be determined reliably for 86 of the labeled

Table 2. Mean insulin sensitivity ($\times 10^2$/mL^2/kg^{-1}/mn^{-1}/μU^{-1}) at Each Study Session

Study	S^*_{I1}	S^*_{I2}	P S^*_{I1} v S^*_{I2}	r S^*_{I1} v S^*_{I2}	S_{I1}	P S^*_{I1} v S_{I1}	R S^*_{I1} v S_{I1}
1	10.6 ± 1.2	11.5 ± 1.8	.49	.72	7.6 ± 1.4	.001	.56
(N = 13)				P = .009			P = .057
2	12.2 ± 0.23	11.4 ± 2.6	.16	.98	6.0 ± 0.9	<.001	.46
(N = 14)				P = .001			P = .098
3	11.1 ± 4.3	16.6 ± 7.4	.29	.64	4.3 ± 0.9	.034	.099
(N = 11)				P = .023			P = .76
4	6.0 ± 0.8	7.1 ± 1.8	.54	.50	5.3 ± 0.8	.426	.44
(N = 11)				P = .12			P = .18

glucose profiles. For the 2CMM, glucose effectiveness and insulin sensitivity could be determined for 49 of 87 studies. The unlabeled indices S_{G1} and S_{I1} were reliably determined for 85 of the 87 total glucose profiles (Tables 2 and 3).

1CMM and MinMod. S^*_{I1} was significantly greater than S_{I1} for all sessions, except the fourth (Table 2). S^*_{G1} was less than S_{G1} for all sessions (Table 3). S_{I1} tended to be positively related to S^*_{I1} in the first 2 study sessions, but the overall correlation was poor (r = .20). S_{G1} was not related to S^*_{G1} in the first 3 sessions, but was significantly positively correlated in the fourth session. Interestingly, it was or tended to be related to S^*_{I1} in all sessions, but the fourth (session 1, r = .44, P = .057; session 2, r = .80, $P < .001$; session 3, r = .51, P = .026). The lack of correlation between cold and hot glucose effectiveness is not surprising and has been reported previously in adults.[10]

Indices for 1CMM in Tables 2 and 3 are reported in clearance units to make them comparable to those of 2CMM and to those derived with the glucose clamp technique.[10,11] For sake of comparison with the literature, it is worth reporting glucose effectiveness and insulin sensitivity also in the more commonly used units of min^{-1} and min^{-1} per μUmL^{-1} (Table 4).

1CMM and 2CMM. Tables 2 and 3 also show the mean values of glucose effectiveness and insulin sensitivity for each study session from labeled glucose values by each method. In those subjects in whom insulin sensitivity could be reliably determined using both the labeled 1CMM and 2CMM, S^*_{I1} did not differ from S^*_{I2} for any of the 4 sessions. S^*_{I1} and S^*_{I2} were closely related as well ($S^*_{I2} = 0.79 + 1.1S^*_{I1}$, r = .70, $P < .001$) across all 4 sessions. Their similarity is further reflected by the fact that the y-intercept was not significantly different from zero (P = .72) and the slope was not significantly different from 1 (P = .64). For glucose effectiveness, S^*_{G1} was higher than S^*_{G2}, and the 2 were significantly positively correlated for each study session and globally ($S^*_{G2} = -0.48 + 0.90S^*_{I1}$, r = .82, $P < .001$). The y-intercept tended to be different from zero (P = .080). The slope was not different from 1 (P = .28). These strong correlations indicate a strong relationship between insulin sensitivity and glucose effectiveness estimated with the 1CMM and 2CMM.

Puberty and 2CMM

Analysis of variance with Tanner stage and sex as grouping factors and BMI as a covariate demonstrated that S^*_{G2} (Fig 1) significantly differed between the sexes ($F_{1\text{-}20}$ = 4.34, P = .05), but did not differ between Tanner stages. BMI was a near significant covariate ($F_{1\text{-}20}$ = 3.69, P = .069). None of the differences between the sexes at a given Tanner stage were significant. For S^*_{I2}, there was a near significant sex effect ($F_{1\text{-}20}$ = 3.28, P = .085) and again a near significant effect of BMI ($F_{1\text{-}20}$ = 3.97, P = .060). Again, none of the individual Tanner stage effects were significant. Subjects are included only once at any given Tanner stage.

DISCUSSION

These results demonstrate that the labeled glucose 1CMM and 2CMM give similar results for insulin sensitivity estimation in early adolescent children; glucose effectiveness estimates are strongly correlated, but numerically different. Moreover, despite the fact that glucose effectiveness and insulin sensitivity indices from the labeled glucose 1CMM and 2CMM are closely related to the comparable parameters from the other model, the 2CMM was resolvable only in approximately 56% of the studies as compared with approximately 99% for 1CMM.

The fact that 2CMM was more difficult to resolve in children than in adults is in all likelihood due to their relatively faster

Table 3. Mean Glucose Effectiveness (mL/kg^{-1}/min^{-1}) at Each Study Session

Study	S^*_{G1}	S^*_{G2}	P S^*_{G1} v S^*_{G2}	r S^*_{G1} v S^*_{G2}	S_{G1}	P S^*_{G1} v S_{G1}	R S^*_{G1} v S_{G1}
1	2.79 ± 0.19	2.09 ± 0.25	.002	.69	5.69 ± 0.57	<.001	.28
(N = 13)				P = .009			P = .21
2	2.54 ± 0.23	1.72 ± 0.24	<.001	.90	6.21 ± 0.59	<.001	−.033
(N = 14)				P = .001			P = .91
3	3.20 ± 0.36	2.45 ± 0.40	.011	.79	6.40 ± 0.78	<.001	.36
(N = 11)				P = .002			P = .25
4	2.70 ± 0.28	1.92 ± 0.28	.001	.84	4.59 ± 0.63	.003	.68
(N = 11)				P = .001			P = .022

Table 4. S^*_{G1}, S_{G1} (min^{-1}) and S^*_{I1} and S_{I1} ($\times 10^{-4}$ mL/μU min) in Traditional Units

Study	S^*_{G1}	S_{G1}	S^*_{I1}	S_{I1}
1	1.55 ± 0.11	3.97 ± 0.61	5.98 ± 0.84	4.78 ± 0.75
2	1.37 ± 0.11	4.22 ± 0.40	6.73 ± 1.10	4.03 ± 0.61
3	1.73 ± 0.17	4.88 ± 0.86	5.71 ± 2.05	2.76 ± 0.58
4	1.67 ± 0.14	3.08 ± 0.41	3.90 ± 0.53	3.52 ± 0.53

kinetics (ie, total plasma glucose is usually back to basal after the glucose insult by 120 minutes). In fact, in the 56% cases in which 2CMM was resolvable, the rate constants k_{21}, k_{12}, and K_{02} were much higher than those obtained in adults,[11] ie, one often sees a collapsed version of the 2CMM in these study participants. Thus, 2CMM in children may be less advantageous than in adults, in particular, for insulin sensitivity (Table 3), but caution and further studies are needed for glucose effectiveness (Table 2), where differences emerge. The 1CMM was practically always resolvable in children: when insulin sensitivity is the objective of the study, this suggests that the labeled 1CMM is the logical model of choice for population-based studies in children. This observation reinforces the results of Sunehag et al[17] where only the 1CMM was used since a less abundant sampling schedule (15 *v* 22 samples of the present study) was used. However, this does not necessarily mean that undermodeling of glucose kinetics plays a minor role in this study population, but simply that the presence of the second compartment is less apparent in the data, thus making this additional model complexity not well resolvable. A different FSIVGTT experimental design or a more refined approach based on Bayesian prior statistics may help address some of these issues.[18]

Our results comparing glucose effectiveness and insulin sensitivity from labeled 1CMM and 2CMM are similar to those found in adults in most respects.[11] Our comparisons only apply to those situations in which both values from both models could be reliably predicted, and it is unclear how the missing data might alter the relationships between the 2 models. In our subjects, the labeled 1CMM overestimates glucose effectiveness likely for the same reasons discussed by Caumo et al[10] and thus indicates that glucose may have a greater effect on is own disposal than it actually has. S^*_{G1} reflects glucose uptake mainly from the last portion of the test when glucose is low and where single compartment kinetics are valid, but does not reflect uptake from the earlier portion of the test where glucose may interfere with its own uptake as described by the 2CMM. No difference was found between insulin sensitivity indices from labeled 1CMM and 2CMM. Where this study does differ is that we found a good correlation between S^*_{G1} and S^*_{G2}, as well as between S^*_{I1} and S^*_{I2} with slopes not different from 1 for each variable.

Our results comparing glucose effectiveness and insulin sensitivity from the labeled 1CMM and the MinMod (total glucose) are similar to others as reviewed in Caumo et al.[10] This comparison demonstrates that some of the inadequacies of 1CMM previously described in adults are present in early adolescents also. Of particular interest is that S_{I1} is lower than S^*_{I1} a fact, which logically should be reversed, because the latter reflects insulin action on just the periphery, while the former reflects both its stimulatory effect on disposal and its inhibiting effect on production. The underestimation in S_{I1} is compensated for by the overestimation of S_{G1}. The fact that insulin sensitivity plays a role in determining S_{G1} is demonstrated by the correlation between S_{G1} and S^*_{I1}, but not between S_{G1} and S^*_{G1}.

Lastly, our results using the same data with 2CMM support

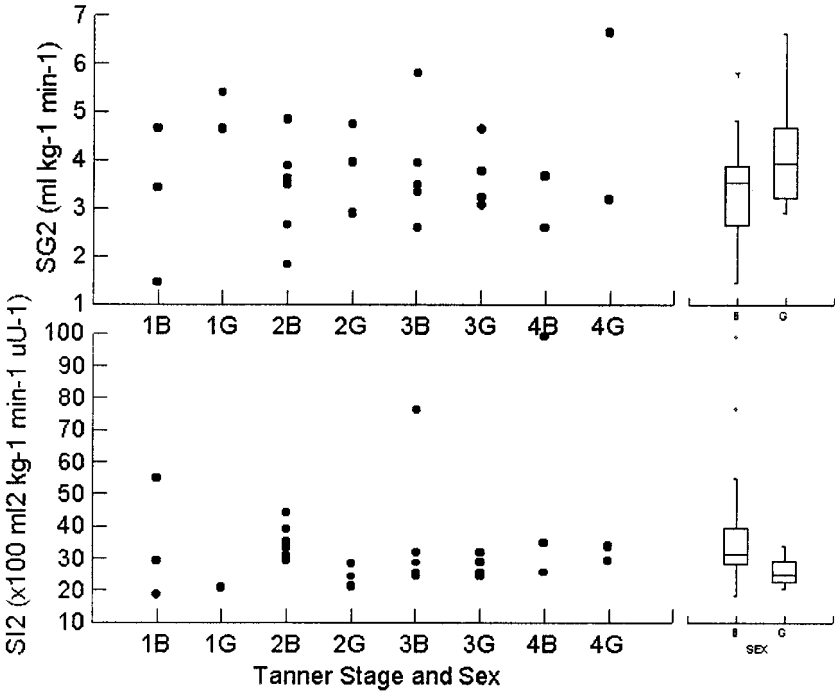

Fig 1. BMI adjusted (A) S^*_{G2} and (B) S^*_{I2} from the 2CMM divided by Tanner stage and sex. Subjects are included only once at any given Tanner stage. Graph at right combines values for all Tanner stages according to sex. Center line is median. Box represents values in the second and third quartiles (25th to 75th percentile) and whiskers are 1.5 times inter quartile range. $P = .05$ for S^*_{G2} difference between sexes and $P = .085$ for S^*_{I2}.

our previously reported results from the 1CMM[9] regarding puberty. We again found that girls have a higher glucose effectiveness and lower insulin sensitivity than boys. In addition, we found no differences between Tanner stages for either BMI adjusted S^*_{G2} or S^*_{I2}.

These results thus demonstrate that the stable labeled FSIVGTT can be used in children for determination of glucose tolerance indices. As glucose kinetics in children appear to be faster than in adults, this makes the intercompartmental exchange parameters of the more sophisticated 2CMM also more difficult to resolve. It is known that results from labeled 1CMM overestimate glucose effectiveness: however, because the labeled 1CMM is practically always resolvable from the data and results from 1CMM and 2CMM are closely correlated for glucose effectiveness and nearly identical for insulin sensitivity indices, the 1CMM is the logical model of choice for population-based studies in children.

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REFERENCES

1. Amiel SA, Sherwin RS, Simonson DC, et al: Impaired insulin action in puberty: A contributing factor to poor glycemic control in adolescents with diabetes. N Engl J Med 315:215-219, 1986

2. Bloch CA, Clemons P, Sperling MA: Puberty decreases insulin sensitivity. J Pediatr 110:481-487, 1987

3. Caprio S, Plewe G, Diamond MP, et al: Increased insulin secretion in puberty: A compensatory response to reductions in insulin sensitivity. J Pediatr 114:963-967, 1989

4. Amiel SA, Caprio, Sherwin RS, et al: Insulin resistance of puberty: A defect restricted to peripheral glucose metabolism. J Clin Endocrinol Metab 72:277-282, 1991

5. Cutfield WS, Bergman RN, Menon RK, et al: The modified minimal model: Application to measurement of insulin sensitivity in children. J Clin Endocrinol Metab 70:1644-1650, 1990

6. Cook JS, Hoffman RP, Stene MA, et al: Effects of maturational stage on insulin sensitivity during puberty. J Clin Endocrinol Metab 77:725-730, 1993

7. Travers SH, Jeffers BW, Bloch CA, et al: Gender and Tanner stage differences in body composition and insulin sensitivity in early pubertal children. J Clin Endocrinol Metab 80:172-178, 1995

8. Avogaro A, Bristow JD, Bier DM, et al: Stable-label intravenous glucose tolerance test minimal model. Diabetes 38:1048-1055, 1989

9. Hoffman RP, Vicini P, Sivitz WI, et al: Pubertal adolescent male-female differences in insulin sensitivity and glucose effectiveness determined by the one compartmental minimal model. Pediatr Res 48:384-388, 2000

10. Caumo A, Vicini P, Zachwieja JJ, et al: Undermodeling affects minimal model indexes: Insights from a two-compartment model. Am J Physiol 276:E1171-1193, 1999

11. Vicini P, Caumo A, Cobelli C: The hot IVGTT two compartment minimal model: Indexes of glucose effectiveness and insulin sensitivity. Am J Physiol 36:E1024-E1032, 1997

12. Bergman RN, Ider YZ, Bowden CR, et al: Quantitative estimation of insulin sensitivity. Am J Physiol 236-E667-E677, 1979

13. Caumo A, Cobelli C: Hepatic glucose production during the labelled IVGTT: Estimation by deconvolution with a new minimal model. Am J Physiol 264:E829-841, 1993

14. Carson ER, Cobelli C, Finkelstein L: The Mathematical Modeling of Metabolic and Endocrine Systems. New York, NY, Wiley, 1983

15. Cobelli C, Foster D, Toffolo G: Tracer Kinetics in Biomedical Research: From Data to Model. New York, NY, Kluwer Academic/Plenum, 2000

16. Barret PHR, Bell BM, Cobelli C et al: SAAM II: Simulation, analysis and modeling software for tracer and pharmacokinetic studies. Metabolism 47:484-492, 1998

17. Sunehag AL, Treuth MS, Toffolo G, et al: Glucose production, gluconeogenesis, and insulin sensitivity in children and adolescents: An evaluation of their reproducibility. Pediatr Res 50:115-123, 2001

18. Facchini F, Humphreys MH, Jeppesen J, et al: Measurements of insulin-mediated glucose disposal are stable overtime. J Clin Endocrinol Metab 84:1567-69, 1999

19. Cobelli C, Caumo A, Omenetto M: Minimal model SG overestimation and SI underestimation: Improved accuracy by a Bayesian two-compartment model. Am J Physiol 277:E481-488, 1999