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Comparison of Equivalence and Determination of Diagnostic Utility of Min-Mod and Clamp Methods for Insulin Resistance in Diabetes Free Subjects

A Meta-Analysis

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The gold standard for quantifying insulin sensitivity (IS) is the hyperinsulinemic–euglycemic clamp (Clamp) with a cut-off point of 5×10^{-2} (dL/min)/(μU/mL) or less to indicate insulin resistance. Bergman's minimal model (Min-Mod) is also being used to estimate IS, but there are doubts as to its equivalence with Clamp. The objective of the present study is to determine if Clamp and the tolbutamide and insulin techniques of Min-Mod are equivalent. Meta-analysis based on a bibliographic search from 1970 until the present was made for the MeSH terms: *insulin resistance, hyperglycemic–clamp, euglycemic–clamp, Min-Mod, minimal model approach*. Concordance was determined with both simple and intraclass correlation and Bland and Altman's concordance limits using *R*. Three of the 109 articles found were included. The concordance limits indicate that Clamp and Min-Mod are not equivalent, which could result in diagnostic errors if the accepted cut-off point is used for both methods. Given this lack of equivalence, a ROC analysis was performed and new diagnostic cut-off points of 2.4 and 4.6×10^{-2} (dL/min)/(μU/mL) for insulin and tolbutamide techniques of Min-Mod, respectively, are proposed, with adequate sensitivity, specificity, and predictive value. These values should be prospectively validated.

Key Words: Insulin resistance; measurements; minimal model; clamp; meta-analysis.

Introduction

Clinical insulin resistance (IR) is defined as the lack of expected biological action by tissues in the utilization of glucose *(1)*. Since the 1970s, this metabolic alteration has been quantified in humans with the hyperinsulinemic–euglucemic and hyperglycemic clamps (Clamp), which have been accepted as the "gold standards" for measuring glucose consumption in living organisms *(2)*. The cut-off point for diagnosis of IR with these methods is 5×10^{-2} (dL/min)/(μU/mL). Values >6 are considered as normal and values <2 indicate severe IR *(3)*. The process is highly labor intensive and requires an exclusive metabolic hospital unit with highly trained personnel resulting in elevated costs.

Bergman's Minimum Model (Min-Mod), a computerized statistical program, analyzes serum insulin and glucose during a glucose tolerance test *(4)*. Min-Mod has been proposed as an alternative to Clamp for clinical studies as it is more accessible. As such, it ought to have equivalent precision and reproducibility *(5,6)*. The initial technique for the application of Min-Mod has been modified to include fewer blood samples and the use of tolbutamide IV *(7,8)*, or insulin IV at 20 min *(7)* in the validation of Min-Mod and Clamp equivalences *(9,10)*. These changes to the original procedure make it necessary to reevaluate the utilization of Min-Mod and its variants as equivalents to Clamp.

The objective of the present work is (1) to determine if there is equivalence between Clamp and the tolbutamide, and insulin variants of Min-Mod in non-diabetic subjects, and (2) to determine the best diagnostic cut-off point for Min-Mod in the case that the methods are not equivalent.

Results

Nine articles included comparisons between Clamp and Min-Mod. Three included data or graphics in the indicated units and were used in the analysis:

1. Tolbutamide variant: Data published in Bergman and Saad studies 6 and 7.

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Table 1
Summary of ISI's Values for Clamp and Min-Mod Tolbutamide Variant in Units × 10^{-2} (dL/min)/(μU/mL) (n = 45) *(6,7)*

	Clamp	Min-Mod
Mean	5.0	4.6
Median	5.0	4.5
SD	2.2	2.6
Shapiro–Wilks	0.97 (p = 0.35)	0.93 (p < 0.01)

Table 2
Summary of ISI's Values for Clamp and Min-Mod Insulin Variant in Units in × 10^{-2} (dL/min)/(μU/mL) (n = 46) *(7,8)*

	Clamp	Min-Mod
Mean	5.7	2.9
Median	5.7	2.7
SD	2.3	1.4
Shapiro–Wilks	0.95 (p = 0.7)	0.92 (p < 0.01)

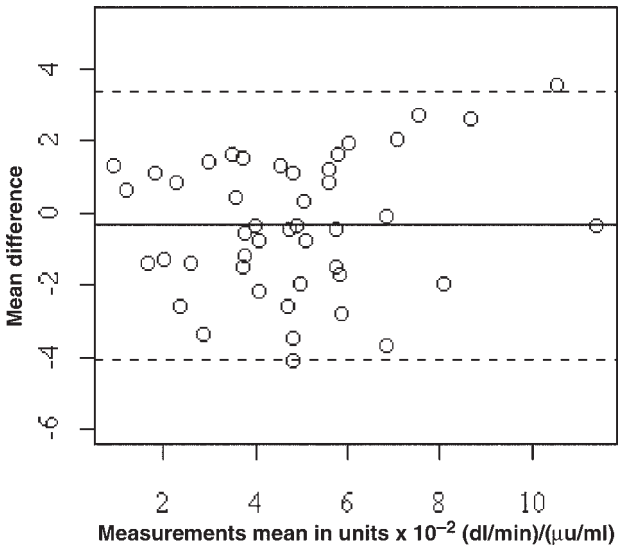

Fig. 1. BA plot of the differences between the values reported by ISI Clamp and ISI tolbutamide variant Min-Mod, with a mean difference of –0.35 and a standard deviation of 1.9.

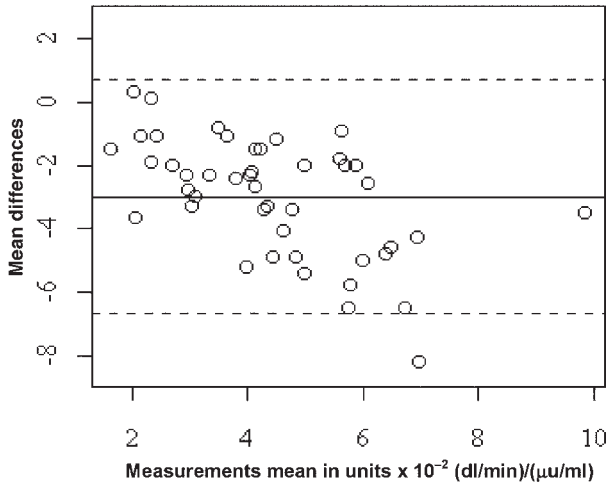

Fig. 2. BA plot of the differences between the values reported by ISI Clamp and ISI insulin variant Min-Mod with a mean difference of –2.97 and a standard deviation of 1.85.

2. Insulin variant: Data were obtained from tables and graphics used in studies 7 and 8 (n = 46).

Given the no normality of the Min-Mod ISI in the tolbutamide variant (see Table 1), Spearman's Rho was used, 0.653. The $ICC_{3,1}$ was 0.7 (CI: 0.58 to 0.81). Figure 1 is a BA plot of the differences between the values reported by both methods which had a difference of –0.349 with a standard deviation of 1.9. The concordance limit, the mean minus/plus two standard deviations, where –4.072 and 3.374.

The mean difference is near 0 and was interpreted as demonstrating equivalence between the methods. However, the differences show substantial variation reflected by the wide concordance limits. It should be noted that the differences between Min-Mod and Clamp can be up to 7.4 units × 10^{-2} (dL/min)/(μU/mL) for the same subject.

Again, with the no normality of the Min-Mod ISI in the Insulin variant (see Table 2), Spearman's Rho was used, 0.61. The $ICC_{3,1}$ was 0.25 (CI: –0.1 to 0.57). Figure 2 is a BA plot of the differences reported by both methods that had a mean of –2.966 and a standard deviation of 1.85. The concordance limits where –5.573 and 0.741. The mean difference was different from 0 and was interpreted as demonstrating a lack of equivalence between the methods. The differences between Min-Mod and Clamp with the insulin variant are similar to those obtained with the tolbutamide variant and can be up to 7.3 units × 10^{-2} (dL/min)/(μU/mL) for the same subject.

Linear regressions were calculated for Clamp ISI (y) with respect to the tolbutamide variant ISI (x), the insulin variant ISI (x), and Clamp ISI (x). The residuals were normal for the three regressions. The tolbutamide ISI (x) and insulin ISI (x) slope were tested for equality with the Clamp ISI (x) slope following Kleinbaum *(11)*. There is no evidence that the tolbutamide ISI regression slope is different from the Clamp ISI regression slope (p = 0.29), but the insulin ISI regression slope is different from the Clamp ISI regression slope (p < 0.0001) (Fig. 3).

The established cut-off point for the "gold standard," Clamp, is 5 × 10^{-2} (dL/min)/(μU/mL). Given the lack of

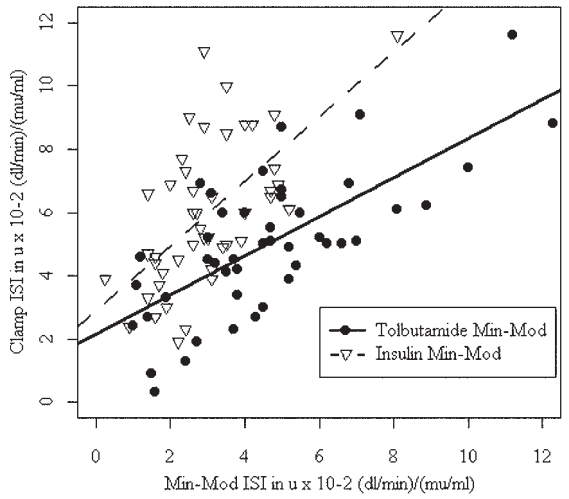

Fig. 3. Linear regression slopes for Clamp ISI (y) with respect to the tolbutamide variant ISI (x), and the insulin variant ISI (x).

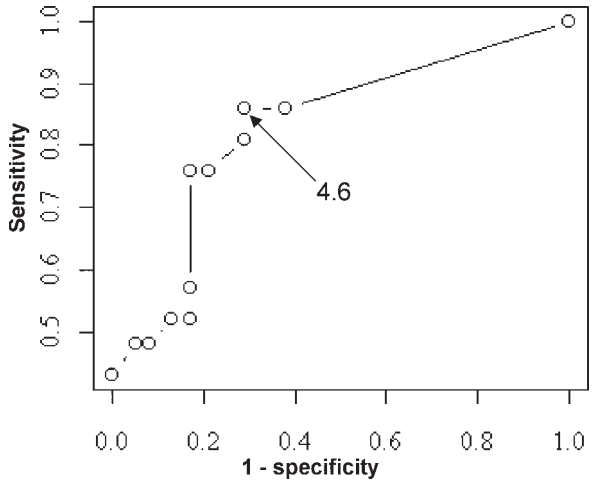

Fig. 4. ROC curve for diagnosis of insulin resistance ISI with Min-Mod variant tolbutamide, diagnostic cut-off point for Clamp 5×10^{-2} (dL/mg)/(μU/mL).

equivalence between the Clamp and the two Min-Mod variants as a diagnostic test *(12)*, a ROC curve *(13)* was used to define the cut-off point which best differentiated between insulin resistant and normal individuals with the two Min-Mod variants (Figs. 4 and 5).

Discussion

The analysis shows that the ISIs obtained by Clamp and Min-Mod variants are not equivalent given that the ICC for the tolbutamide variant was 0.70 and for the insulin variant was 0.25. ICCs ≥ 0.75 demonstrate concordance *(14)*. The BA plots showed that a patient's ISI values using Min-Mod can vary 7.4×10^{-2} (dL/min)/(μU/mL) (tolbutamide variant) and 7.3×10^{-2} (dL/min)/(μU/mL) (insulin variant) from the values reported by Clamp. This is of fundamental importance given that the measurements from Clamp classify patients as insulin resistant if the ISI is $<5 \times 10^{-2}$ (dL/min)/

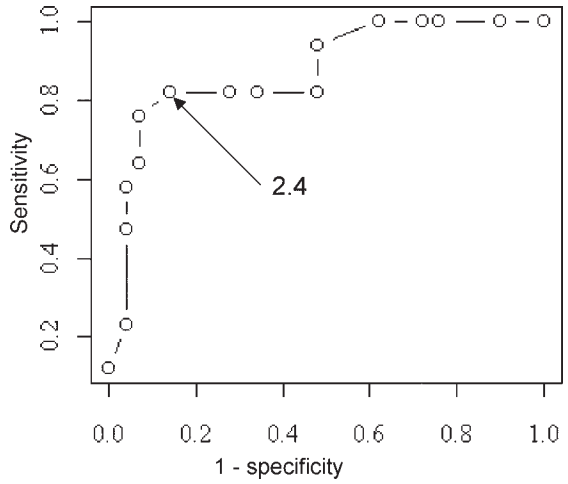

Fig. 5. ROC curve for diagnosis of insulin resistance ISI with Min-Mod variant insulin. Diagnostic cut-off point for Clamp 5×10^{-2} (dL/mg)/(μU/mL).

(μU/mL) *(15)*. It should be noted that the variation is greater than the cut-off value. Thus, lack of equivalence between the procedures can cause a subject to be classified as insulin resistant by Min-Mod, while the same subject is classified as normal by Clamp [values $>5 \times 10^{-2}$ (dL/min)/(μU/mL)]. This phenomenon has been reported previously *(16,17)*.

This lack of equivalence can be at least partially explained by the fact that Clamp estimates insulin sensitivity by measuring glucose disappearance in a pharmacokinetic single compartment model, while Min-Mod utilizes a two-compartment model *(18,19)*. It should be noted that Clamp is performed in a metabolic unit with artificially controlled conditions, while Min-Mod is performed in an uncontrolled environment. Another factor explaining the lack of equivalence is the fact that Clamp only utilizes external insulin and Min-Mod also uses the subject's insulin secretion stimulated by glucose challenge.

The correlation coefficients demonstrate that both methods measure the same biological phenomena; however, the measurement values are not equivalent. On the other hand, information exists that validates both the theoretical and clinical basis of analysis of the glucose tolerance and insulin curve with Min-Mod. With the objective of evaluating if the lack of equivalence between the results of the methods suggests the inability of the ISI values obtained by Min-Mod to recognize patients with insulin resistance, ROC curves were utilized for each technique to evaluate their diagnostic utility and to obtain new cut-off points for the diagnosis of insulin resistance that correspond with the Clamp's cut-off point. For the tolbutamide variant, the best cut-off point is 4.6×10^{-2} (dL/min)/(μU/mL) with a sensitivity of 0.86 (95% CI 0.65–0.95), specificity of 0.71 (95% CI 0.51–0.85), positive predictive value of 0.72 (95% CI 0.52–0.86), and negative predictive value of 0.85 (95% CI 0.64–0.95). The test has a diagnostic accuracy in accord to Altman of 0.69 *(20)*.

Table 3
Sensitivity and Specificity ROC Curve Values for Min-Mod Insulin Variant in Units of $\times 10^{-2}$ (dL/min)/(μU/mL)

Cut off point	Sensitivity	Specificity
5.6 +	1	0
3.2	0.94	0.52
3.0	0.82	0.52
2.8	0.82	0.66
2.6	0.82	0.72
2.4	0.82	0.86
2.2	0.76	0.93
2.0	0.64	0.93
1.8	0.58	0.96
1.6	0.47	0.96
1.4	0.23	0.96
1.2	0.12	1

For the insulin variant the best cut-off point is 2.4×10^{-2} (dL/min)/(μU/mL) with a sensitivity of 0.82 (95% CI 0.59–0.94), specificity of 0.86 (95% CI 0.69–0.94), positive predictive value of 0.77 (95% CI 0.54–0.91), negative predictive value of 0.89 (95% CI 0.73–0.96), and a diagnostic accuracy of 0.87; which all of them are acceptable. However, if 2 to 3.2×10^{-2} (dL/min)/(μU/mL) is used as the cut-off value for diagnosis, the sensitivity increases to 0.93 and the specificity to 0.94 (see Table 3). Therefore, it is proposed that values between these two points should be considered as indicating a probable metabolic alteration, while values <2 should be considered as indicating a positive diagnosis.

While the tolbutamide variant values more closely resemble the values obtained from Clamp, the unavailability of this medication for IV application makes its utilization difficult in clinical practice. The insulin variant uses commercial insulin that is readily available for IV application.

Prospective studies are necessary to validate the suggested cut-off points for ISI by Min-Mod in healthy non-obese persons.

It is recommended that the cut-off points for values obtained by Clamp should not be used with Min-Mod variants. This practice has demonstrated problems in the IR definition and diagnosis. Furthermore, a strict statistical reevaluation of all new indices for the ISI measurement is recommended.

Insulin resistance and lack of insulin secretion are two physiopathogenic factors associated with the clinical development of diabetes mellitus *(21)*. The Min-Mod is a readily available, correctly validated, and highly precise method that permits diagnosis of the alteration in the clinical environment.

Materials and Methods

We found 109 articles in a bibliographic search for the MeSH terms: *insulin resistance, hyperglycemic–clamp, euglycemic–clamp, Min-Mod, and minimal model approach*, using Medline, Educational Resources Information Center (ERIC), and National Technical Information Service (NTIS) databases. The criteria for including an article in the meta-analysis were as follows:

1. Include the comparison of the insulin sensitivity index (ISI) measurements between Clamp and Min-Mod variants (nine articles).
2. Include the raw values or usable graphs for every individual studied (five articles).
3. Use only non-diabetic subject values.
4. Use the same scale or scales for the techniques that could be transformed to the same scale (three articles).

The included articles were classified as "tolbutamide technique" for those that used IV tolbutamide and "insulin technique" for those that used IV insulin as part of the procedure. Min-Mod variants with 12 and 22 samples were treated as equivalent. In agreement with Bergman's recommendation, the selected measurement scale was units $\times 10^{-2}$ (dL/min)/(μU/mL) which was obtained by multiplying the ISI generated by Clamp by the corporal surface and by multiplying the ISI generated in Min-Mod by the subject's glucose distribution volume *(7)*.

Statistical Analysis

The statistical analysis was performed with R version 1.6.0 (June 15, 2000) *(22)*. Normality was tested with the Shapiro–Wilk procedure. Clamp and Min-Mod ISI associations were determined with concordance tests and the Pearson and Spearman correlation coefficients.

The concordance determinations applied were the intraclass correlation coefficient ($ICC_{3,1}$) *(14,23,24)*, which corrects possible correlation coefficient skew and is recommended by Kramer and Feinstein *(25)* if the residuals are normal and it produces similar values to the Lin's Concordance Correlation Coefficient *(26,27)* . Also, the Bland–Altman (BA) concordance plot *(28)* which graphically show the differences between the measurements of the two methods on the same subject. Evaluation of the importance of the differences is subjective *(29)*. This method requires a normal distribution of the differences.

References

1. Moller, D. E. and Flier, J. S. (1991). *N. Engl. J. Med.* **325,** 938–948.
2. De Fronzo, R. A., Tobin, J. D., and Andres, R. (1979). *Am. J. Physiol.* **237,** E214–E223.
3. Tritos, N. A. and Mantzoros, C. S. (1998). *J. Clin. Endocrinol. Metab.* **83,** 3025–3030.
4. Pacini, G. and Bergman, R. (1986). *Comp. Prog. Biomed.* **23,** 113–122.
5. Bergman, R. (1989). *Diabetes* **38,** 1512–1527.
6. Bergman, R. N., Prager, R., Volund, A., and Olefsky, J. (1987). *J. Clin. Invest.* **79,** 790–800.
7. Saad, M. F., et al. (1997). *Diabetes* **46,** 1167–1171.
8. Saad, M. F., et al. (1994). *Diabetes* **43,** 1114–1121.

9. Alpízar-Salazar, M. and Escalante-Pulido, J. M. (1998). *Rev. Endocr. Nutr.* **6,** 1–6.
10. Ta-chen, N., Ader, M., and Bergman R. N. (1997). *Diabetes* **46,** 1813–1821.
11. Kleinbaum, D. G. (ed.). (1998). *Applied regression analysis and other multivariable methods.* Duxbury Press: Pacific Grove, CA.
12. Richardson, D. K., Schwartz, J. S., Wienbaum, P. J., and Gabbe, S. G. (1985). *Am. J. Obstet. Gynecol.* **152,** 613–618.
13. Sackett, D. L., Haynes, R. B., Guyatt, G. H., and Tugwell, P. (1991). In: *Clinical epidemiology: a basic science for clinical medicine.* 2nd ed, Little, Brown and Company: Boston, MA.
14. Shrout, P. E. and Fleiss, J. L. (1979). *Psychol. Bull.* **86,** 420–428.
15. Escalante Pulido, J. M., Alpízar Salazar, M., and González Bárcena, D. (1994). *Rev. Endocr. Nutr.* **2,** 221.
16. Avogaro, A., Vicini P., Valerio, A., Caumo, A., and Cobelli, C. (1996). *Am. J. Physiol.* **270** (Endocrinol. Metab. 33), E532–E540.
17. Prigeon, R. L., Kahn, S. E., and Porter, D. Jr. (1994). *Am. J. Physiol.* **266** (Endocrinol. Metab 29), E279–E286.
18. Regittnig, W., Trajanoski, Z., Leis, H. J., Ellmerer M., et al. (1999). *Diabetes* **48,** 1070–1081.
19. Ta-chen, N., Ader, M., and Bergman, R. N. (1997). *Diabetes* **46,** 1813–1821.
20. Altman, D. G. (2000). In: *Statistics with confidence.* 2nd ed., British Medical Journal Books: Bristol, UK.
21. Mari, A. (1997). *Am. J. Physiol.* **272** (Endocrinol. Metab. 35), E925–E934.
22. Ihaka, R. and Gentleman, R. (1991). *J. Comput. Graph. Stat.* **5,** 299–314.
23. Fleiss, J. L. (1975). *Biometrics* **31,** 655–659.
24. Bartko, J. J. (1966). *Psychol. Rep.* **19,** 3–11.
25. Kramer, M. and Feinstein A. R. (1981). *Clin. Pharmacol. Ther.* **29,** 111–123.
26. Lin, L. I. (1989). *Biometrics* **45,** 255–268.
27. Nickerson, C. (1997). *Biometrics* **53,** 1503–1507.
28. Bland, J. M. and Altman, D. G. (1986). *Lancet* **1,** 307–310.
29. Bland, M. (ed.). (1995). An introduction to medical statistics. 2nd. ed. Oxford University Press: Oxford, UK.