Simplified Measurement of Insulin Sensitivity with the Minimal Model Procedure in Type 2 Diabetic Patients without Measurement of Insulinemia

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Abstract

This study aimed to evaluate a simplified minimal model protocol for measuring insulin sensitivity in mild and severe type 2 diabetes, considering that changes in serum insulin during an insulin-modified intravenous glucose tolerance test almost only reflect the insulin injection. Two groups of diabetics treated with high doses of antidiabetic agents were recruited. Mean insulin responses were calculated in group 1 (n = 30). In group 2 (n = 38), we compared insulin sensitivity (SI) obtained with reference protocol with SI calculated by a minimal model procedure including the theoretical average insulin profile determined in group 1, and with Homeostasis Model Assessment (HOMA-R). Additionally, the cost of each procedure was calculated. SI measured by the reference method strongly correlated with SI determined by the simplified protocol ($r = 0.966$, $p < 0.0001$), while no correlation was found with HOMA-R ($r = -0.349$, NS). Reduction of cost for HOMA-R and simplified minimal model procedure were – 92 and – 81 %, respectively. This simplified and relative inexpensive protocol, using minimal model procedure without insulin measurement, accurately measures SI regardless of β-cell defect degree. This approach could be of interest when limits of validity of simple indexes are reached.

Key words
Insulin Resistance · Type 2 Diabetes · Minimal Model · Basal Indexes · HOMA

Introduction

Insulin resistance is a major pathogenic mechanism of type 2 diabetes [1,2], although emphasis is now given on associated insulin secretory defects that are needed for developing this disease [3,4]. Diabetic patients whose values of insulin sensitivity are within the normal range, that is, far above the range of insulin resistance, are a common finding and may represent at least 5 % of patients classified as suffering from typical type 2 diabetes [5,6].

However, insulin resistance is a major contributor to the development of a majority of cases of type 2 diabetes, as evidenced by numerous epidemiological studies, so normoglycemia can apparently be preserved in type 2 diabetes-prone individuals in whom insulin sensitivity is maintained [2]. Thus, it might be interesting to gain the possibility of measuring insulin sensitivity in type 2 diabetic patients. The different reference methods *I* – glucose clamp technique or minimal model analysis [7] – are time-consuming and rather expensive. There has been a recent report of a rather good accuracy of the homeostasis model assessment (HOMA) as a measurement of insulin resistance in mild type 2 diabetes treated by diet or low dose antidiabetic agents [8]. However, it is clear that this model does no longer work in type 2 diabetes when insulin secretion becomes strongly deficient, due to the fact that its accuracy depends of the compensatory rise in insulin that mirrors insulin resistance [9]. Thus, there is a need for simple and accurate methods that can give a measurement of insulin sensitivity in type 2 diabetes, even when insulin secretion markedly declines.

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The minimal model has shown to provide such a measurement in type 2 diabetes, when a bolus of intravenous insulin is added during the intravenous glucose-tolerance test (IVGTT) [10,11]. This technique remains somewhat expensive, due to the cost of 15 to 20 insulin blood sampling.

We made the hypothesis that the precise measurement of insulin in these patients is not necessary, since there is a blunted first-phase insulin response, so that insulin levels during the IVGTT almost only reflects the insulin injection at the 20th min. Therefore, including a theoretical average insulin profile in the calculation rather than the actual one, may enable a less expensive measurement of SI, based only on blood glucose levels, with only a minor loss of accuracy.

In this study, we aimed at comparing the "classical" insulin-modified minimal model procedure to a simplified procedure in which insulin levels were replaced by a theoretical average insulin profile. Additionally, this evaluation was compared with the results obtained from homeostasis model assessment (HOMA-R).

Materials and Methods

Subjects

We recruited two groups of type 2 diabetic patients who came to our unit for a metabolic check-up. Diabetes was diagnosed according to the criteria of the American Diabetes Association [12]. All the patients were treated with diet and antidiabetics drugs (sulfonylureas and/or metformine). None of the subjects were receiving insulin, although some patients were secondary failers for oral antidiabetic agents.

In a first group of 38 subjects, we calculated the mean insulin responses to intravenous glucose. In the second group of 30 subjects, we compared the calculation obtained with these mean responses to the classical calculation and with the HOMA-R. Clinical characteristics of the patients are given in Table **1**. All subjects gave their informed consent before the beginning of the study, and the protocol was approved by the local ethics committee.

Intravenous glucose tolerance test protocol

After a 12 h fast, a cannula was placed in the cephalic vein at the level of the cubital fossa at 9 a.m. for blood sampling at various times, while glucose injection was performed in the controlateral cephalic vein. Glucose (0.5 g/kg, solution at 30%) was slowly injected during 3 precisely measured minutes. Insulin (0.02 units/kg body weight – 1 or 2 units) was injected intravenously immediately after time 19. Blood samples were drawn twice before the glucose bolus and at 1, 3, 4, 6, 8, 10, 15, 19, 20, 22, 24, 30, 41, 70, 90 and 180 min following the onset of the glucose injection [13–15].

Table **1** Clinical characteristics of the two groups of patients

	First Group ("Mean insulin responses")	*Second Group ("Evaluation")*
N	38	30
Sex (M/F)	25/13	20/10
Age (years)	59.4 ± 2.1	58.1 ± 2.4
BMI (kg/m^2)	27.4 ± 1.1	26.7 ± 1.0
Fasting plasma glucose (mmol/l)	9.9 ± 1.2	10.2 ± 1.3
Fasting serum insulin (μU/ml)	12.3 ± 1.4	12.7 ± 1.4

(mean ± S.E.M.).

Laboratory measurements

Plasma insulin was measured by radioimmunoassay (Insulin Bi-IRMA kit from ERIA Diagnostic Pasteur, France), without cross-reactivity with pro-insulin, and plasma glucose with a dry chemistry analyzer (Ektachem from Johnson & Johnson INC, USA).

Measurement of insulin sensitivity and glucose effectiveness

Minimal model analysis of IVGTT was assessed according to Bergman [10,11] with "TISPAG" software from the Department of Physiology of the University of Montpellier 1, France [13–15] which uses a non-linear least-square estimation. This program gave the values of insulin sensitivity (SI) and glucose effectiveness (Sg) from the following equations:

$$dG(t)/dt = -[p1 + X(t)]\,G(t) + p1\,Gb$$
$$G(0) = Go$$
$$dX(t)/dt = -p2\,X(t) + p3\,[I(t) - Ib]$$
$$X(0) = 0$$

where G(t) and I(t) are plasma glucose and insulin concentrations, X(t) is the insulin in a compartment remote from plasma ("insulin action"), and p1-p3 are model parameters. G0 is the glucose concentration that one would obtain immediately after injection if there were instantaneous mixing in the extracellular fluid compartment. Gb and Ib are basal values of glucose and insulin. Parameter p1 represents Sg, – the fractional disappearance rate of glucose, independent of any insulin response – and p3 and p2 determine the kinetics of insulin transport, respectively, into and out of the remote insulin compartment where insulin action is expressed. Insulin sensitivity SI is an index of the influence of plasma insulin to change glucose's own effect on glucose concentration. Thus, IS is equal to – p3/p2. The validity of our procedure using a reduced number of samplings has been tested and previously published described elsewhere [14].

Simplified procedure without insulin measurement

For the simplified procedure we employed the same software "TISPAG" [13–15], but only values of blood glucose for each subject were used for the calculations, while a slight modification in the software was introduced to modify the input for insulin values and to replace it by a fixed set of values representing the mean values obtained in the first group of 38 subjects (see Fig. **1**), namely at times – 15, 0, 1, 3, 4, 6, 8, 10, 15, 19, 20, 22, 24, 30, 41, 70, 90, 180 min, respectively 11.9, 12.6, 14.1, 13.5, 13.8, 13.2, 19.2, 18.8, 34.0, 35.9, 101.7, 126.3, 129, 70.2, 33.8, 27.3, 18.2, and 16.4 μU/ml ("DNIDPAG" software).

HOMA-R calculation

HOMA-R was calculated as previously described: fasting insulin (μU/ml) × fasting glucose (mmol/l)/22.5 [16].

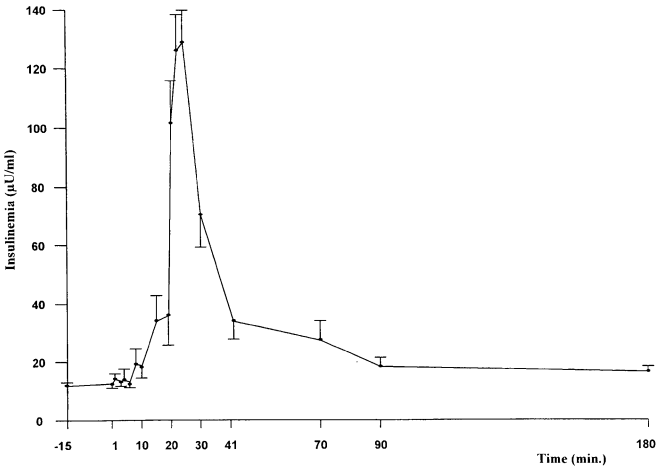

Fig. 1 Insulin response to IVGTT in the 38 type 2 diabetic patients of the group 1.

Economic aspects

We have calculated the cost of each protocol according to French regulations and prices.

Statistical analyses

Values are expressed as mean ± SEM. The normality was checked by the Kolmogorov-Smirnov procedure: if the distributions were not normal, corresponding values were Ln-transformed (HOMA-R). Accuracy was assessed by comparing the results of HOMA-R and of simplified protocol with the reference method. Statistical evaluation was performed using the software "method validator" [17]. We used the Deming regression analysis and the Bland and Altman procedure [18].

Results

We first calculated the mean insulin response to IVGTT in the 38 type 2 diabetic patients of group 1 (Fig. **1**).

The second group of 30 type 2 diabetics was used for the validation of the simplified procedure against the classical one. The prediction of insulin sensitivity SI whose values obtained by the classical method were comprised between 0.1 and 6 min – 1.10 – 4 (µU/ml) was satisfactory, as shown by the Deming regression procedure: r = 0.966, $p < 0.0001$ (Fig. **2**). The Bland and Altman difference plot showed a very satisfactory agreement between the sensor and the reference methods as presented in Fig. **3**.

Additionally, we evaluated the HOMA-R, in the second group, which was found to be non-significantly correlated to the Minimal Model procedure (r = – 0.349, NS, Spearman test).

Table **2** shows respective costs of each protocol, calculated according to the local regulations and prices.

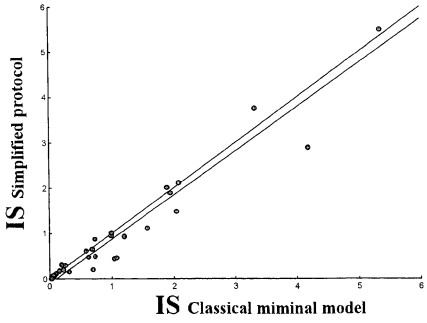

Fig. 2 Prediction of insulin sensitivity (IS) by simplified protocol (Deming regression procedure); r = 0.966, $p < 0.0001$.

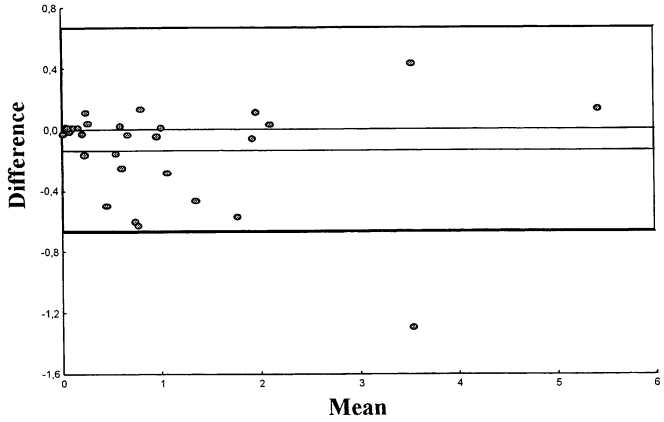

Fig. 3 Difference plot between simplified protocol and insulin sensitivity provided by the minimal model procedure (Bland and Altman).

Table 2 Economical evaluation of the three methods

	Classical minimal model	*Simplified protocol*	*HOMA-R*
Total cost in French Francs	1725	317	140
Total cost in Euros	263	48.3	21.3
Reduction of the cost	–	– 81 %	– 92 %

Discussion

This study shows that in type 2 diabetes, insulin sensitivity can be accurately calculated with a simplified and less expensive (reduction of 81 % of the cost of the measurements) minimal model procedure which introduces in the calculation an average insulin profile rather than the measurement of the subject's own insulin response to the test.

This is explained by the homogeneous pattern of this insulin response in those patients where first-phase insulin release is deficient so that insulin changes above baseline are almost only explained by the *iv* insulin added during the test. Since insulin addition is required for the validity of the minimal model procedure in type 2 diabetic subjects [10,11], the homogeneity of insulin profile after IVGTT in this population is likely to be a general situation, so that our simplified procedure using the average profile can probably be applied to all type 2 diabetic patients undergoing an insulin-modified IVGTT for measuring insulin sensitivity. It should be stressed, however, that this finding of a very uniform post-IVGTT insulin profile in NIDDM does not mean that

endogenous insulin plays only a minor role in such patients. The importance of β-cell dysfunction has been clearly demonstrated in recent studies [3–4,6]. Actually, since first-phase defect is an almost constant feature of type 2 diabetes and occurs very early, it is not surprising to observe that after an IVGTT in cases of overt diabetes, the insulin profile is remarkably uniform and is in fact mostly characterized by the artificial insulin peak resulting from the *iv* insulin bolus at time 19. Fig. **1** shows this uniform pattern. One could argue that the SEMs are not so low, but in fact they are explained by the differences in baseline levels of insulin, while the changes were essentially the same in all patients. This finding has given us the idea of this simplified procedure. It is likely that 10–15 controls would be enough for anybody wanting to define his own reference profile to apply this technique.

It should be stressed that, while we have shown here that without any measurement of insulinemia, the minimal model is still able to accurately calculate SI in type 2 diabetes, it is of course still possible to measure the first phase peak from the 1 min and 3 min samples, if the assessment of first-phase insulin release is also wanted. This will still be markedly less expensive than measuring the entire set of values.

Our new procedure, as a modification of the classical IVGTT-minimal model analysis, is validated against the minimal model itself and not against the euglycemic clamp, which is generally considered to still remain the "gold standard" [19]. While the minimal model has been employed in diabetics since a long time [10–11,20] there has been recently some discussion about its accuracy in this context [7]. The general agreement between clamp and minimal model when results are expressed with the same units is well-established [7,21], but extremely high or low values of SI detected with the IVGTT are sometimes less extreme with the clamp [7]. This has led to some discussion about the physiological meaning of so-called "SI zero" states that are frequently found with the minimal model in type 2 diabetes where clamp measurements are able to still detect some ability of insulin to induce glucose uptake by tissues. Whether those "SI zero" states are explained by "undermodeling" (the minimal model is "too minimal") or are really relevant is not fully clarified. In fact, for our purpose which is to develop a sensitive procedure for the differential diagnosis between insulin resistant and insulin sensitive type 2 diabetes, a technique that exacerbates to some extent the difference between normal and low insulin sensitivity, is especially interesting, these subtle methodological discussions notwithstanding. For this reason, our method was rather based on the minimal model with no comparison with clamp measurements.

We think that there is a lack of simple, accurate and inexpensive methods to measure insulin sensitivity in type 2 diabetes. Surrogate indexes based on baseline values of insulin and glucose, such as the homeostatic model assessment insulin resistance index (HOMA-R), have been reported to be accurate in cases of mild type 2 diabetic patients treated by diet or low doses of antidiabetic drugs [8]. While several reports support the validity of this procedure in type 2 diabetes [22,23], it should be noted that HOMA-R poorly reflected insulin sensitivity of our subjects in our study, in contrast with our simplified minimal-model approach. We already reported a poor accuracy of HOMA-R and other simple surrogated indexes of insulin resistance in type 2 diabetes [9]. The explanation for this appears obvious: such surrogate indexes are quite accurate when insulin secretion is able to mirror insulin sensitivity, due to the homeostatic loop described by Kahn [24], which implies that the product insulin sensitivity x insulin is constant. In situations where this homeostatic loop is disturbed, this approach gives erratic results. Thus, a good accuracy of the HOMA-R can be found in cases of mild diabetes [8,22,23], but at advanced stages of the disease when insulin release becomes frankly deficient, the observation that this method becomes inaccurate should not come as a surprise. Interestingly, another team found a coefficient of correlation between HOMA-R and insulin sensitivity ($r = -0.19$) even lower than ours ($r = -0.349$), clearly indicating that this method does not correctly assess insulin sensitivity in these samples of type 2 diabetic patients [25]. Obviously, all these studies do not mean that the HOMA-IR is of no value, but they stress the importance of keeping in mind the limits of validity – the situations where the basal assumptions that underline the accuracy of this attractive procedure are no longer correct.

Our sample includes a wide variety of type 2 diabetic patients that are likely to reflect the various situations that can be observed in clinical practice. Some patients were almost at the stage that they required insulin, and it is clear that this situation does not impair the accuracy of our simplified minimal model approach. The onset of insulin requirement may be a situation where the measurement of insulin sensitivity could be of interest. The assessment of this situation is not well standardized; it may be important to study the usefulness of a simple and accurate measurement of insulin sensitivity in order to discuss the therapeutic strategy. In these advanced stages of type 2 diabetes, HOMA-R is no longer accurate and a procedure such as our modified minimal model could be a simple alternative solution.

Conclusion

This study demonstrates that in type 2 diabetes, insulin sensitivity can be accurately measured with a relatively inexpensive procedure which uses the minimal model without insulin measurements. Since this method does not rely upon the integrity of insulin's compensatory responsiveness to declining insulin sensitivity, we think that it can be safely applied to all cases of type 2 diabetes, regardless their degree of β-cell defect, while this is probably not be the case for simpler surrogate indexes such as the HOMA-R.

References

[1] Reaven GM. Role of insulin resistance in human disease. Diabetes 1988; 37: 1595–1607

[2] Fujimoto WY. The importance of insulin resistance in the pathogenesis of type 2 diabetes mellitus. Am J Med 2000; 108 (Suppl 6a): 9S–14S

[3] Kahn SE. The importance of the beta-cell in the pathogenesis of type 2 diabetes mellitus. Am J Med 2000; 108 (Suppl 6a): 2S–8S

[4] Cavaghan MK, Ehrmann DA, Polonsky KS. Interactions between insulin resistance and insulin secretion in the development of glucose intolerance. J Clin Invest Aug 2000; 106 (3): 329–333

[5] Haffner SM, Howard G, Mayer E, Bergman RN, Savage PJ, Rewers M, Mykkänen L, Karter J, Hamman R, Saad MF. Insulin sensitivity and acute insulin response in African American, non Hispanic white, and

Hispanics with NIDDM. The insulin resistance atherosclerosis study. Diabetes 1997; 46: 63 – 69
[6] Gerich JE. Insulin resistance is not necessarily an essential component of type 2 diabetes. J Clin Endocrinol Metab 2000; 85 (6): 2113 – 2115
[7] Saad MF, Anderson RL, Watanabe RM, Kades WW, Chen YDI, Sands RE, Pei D, Savage PJ, Bergman RN. A comparison between the minimal model and the glucose clamp in the assessment of insulin sensitivity across the spectrum of glucose tolerance. Diabetes 1994; 43: 1114 – 1121
[8] Katsuki A, Sumida Y, Gabazza EC, Murashima S, Furuta M, Araki-Sasaki R, Hori Y, Yano Y, Adachi Y. Homeostasis model assessment is a reliable indicator of insulin resistance during follow-up of patients with type 2 diabetes. Diabetes Care 2001; 24: 362 – 365
[9] Brun JF, Raynaud E, Mercier J. Homeostasis model assessment and related simplified evaluations of insulin sensitivity from fasting insulin and glucose: no need for log transformation but beware of the limits of validity. Diabetes Care 2000; 23: 1037 – 1038
[10] Welch S, Gebhart SSP, Bergman RN, Phillips LS. Minimal model analysis of intravenous glucose tolerance test-derived insulin sensitivity in diabetic subjects. J Clin Endocrinol Metab 1990; 71: 1508 – 1518
[11] Yang YJ, Youn JA, Bergman RN. Modified protocols to improve insulin sensitivity estimation using the minimal model. Am J Physiol 1987; 253: 595 – 602
[12] The expert Committee on the Diagnosis and classification of Diabetes mellitus. Report of the Expert Committee on the Diagnosis and Classification of Diabetes mellitus. Diabetes Care 1997; 10: 1183 – 1197
[13] Brun JF, Guintrand-Hugret R, Boegner C, Bouix 0, Orsetti A. Influence of short submaximal exercise on parameters of glucose assimilation analyzed with the minimal model. Metabolism 1995; 44: 833 – 840
[14] Brun JF, Fédou C, Monnier JF, Jourdan NI, Orsetti A. Relationships between insulin resistance measured with the minimal model and microalbuminuria in type 2 (non-insulin dependent) diabetics. Endocrinology and Metabolism 1995; 2: 203 – 213
[15] Raynaud E, Pérez-Martin A, Brun JF, Fédou C, Mercier J. Insulin sensitivity measured with the minimal model is higher in moderately overweight women with predominantly lower body fat. Horm Metab Res 1999; 31: 415 – 417
[16] Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Turner RC. Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. Diabetologia 1985; 28: 412 – 419
[17] Marquis P. Comparaisons de méthodes analytiques. Ann Biol Clin 1999; 57: 737 – 738 (http://perso.easynet.fr/-philimar)
[18] Bland JM, Altman DG. Statistical methods for assessing agreement between two methods of clinical measurement. Lancet 1986; i: 307 – 310
[19] Foley JE, Chen YD, Lardinois CK, Hollenbeck CB, Liu GC, Reaven G. Estimates of *in vivo* insulin action in humans: comparison of the insulin clamp and the minimal model techniques. Horm Metab Res 1985; 17: 406 – 409
[20] Persson B, Edwall L, Hanson U, Nord E, Westgren M. Insulin sensitivity and insulin response in women with gestational diabetes mellitus. Horm Metab Res 1997; 29: 393 – 397
[21] Bergman RN, Prager R, Volund A, Olefsky JM. Equivalence of the insulin sensitivity index in man derived by the minimal model method and the euglycemic glucose clamp. J Clin Invest 1987; 79: 790 – 800
[22] Emoto M, Nishizawa Y, Maekawa K, Hiura Y, Kanda H, Kawagishi Shoji T, Okuno Y, Morii H. Homeostasis model assessment as a clinical index of insulin resistance in type 2 diabetic patients treated with sulfonylureas. Diabetes Care 1999; 22: 818 – 822
[23] Bonora E, Targher G, Alberiche M, Bonadonna RC, Saggiani F, Zen MB, Monauni T, Muggeo M. Homeostasis model assessment closely mirrors the glucose clamp technique in the assessment of insulin sensitivity: studies in subjects with various degrees of glucose tolerance and insulin sensitivity. Diabetes Care 2000; 23: 57 – 63
[24] Kahn SE, Prigeon RL, McCulloch DK, Boyko EJ, Bergman RN, Schwartz MW, Neifing JL, Ward WK, Beard JC, Palmer JP, Porte DR Jr. Quantification of the relationship between insulin sensitivity and b-cell function in human subjects: evidence for a hyperbolic function Diabetes 1993; 42: 1663 – 1672
[25] Mari A, Pacini G, Murphy E, Ludvik B, Nolan JJ. A model-based method for assessing insulin sensitivity from the oral glucose tolerance test. Diabetes Care 2001; 24: 539 – 548