Adaptation of Five Indirect Insulin Sensitivity Evaluation Methods to Three Populations: Metabolic Syndrome, Athletic and Normal Subjects

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***Abstract*— Insulin sensitivity is determined using direct or indirect methods. Indirect methods are less invasive than direct methods, but have lower accuracy. The accuracy is set through the Spearman's rank correlation coefficient between the indirect method and a direct method. Since the set of parameters of each indirect method has been set empirically, different values of insulin sensitivity have been reported when they are applied on different populations. In this paper, five indirect methods (Avignon, HOMA–IR, QUICKI, Raynaud, and Matsuda) used to determine insulin sensitivity were adapted to three different populations: athletics, metabolic syndrome and normal subjects. The parameters of each method were varied in a range of values until the optimal value that gives the best correlation coefficient with a gold standard was obtained. Results show that the adaptation procedure led to an improved correlation coefficient. Additionally, the method of Matsuda was the most accurate, followed by the method of Avignon. We have confirmed that each indirect method needs a different set of parameters when it is applied to a specific population in order to obtain an accurate value of insulin sensitivity.**

I. INTRODUCTION

Insulin sensitivity is a condition associated with pre-diabetes. It is defined as the reaction of cells to the presence of insulin. Low values of insulin sensitivity have been related to inflammation, obesity, and cardiovascular risk [1], [2], [3]. Moreover, diabetes mellitus type II and metabolic syndrome has been associated with low values of insulin sensitivity [4], [5]. The early diagnosis and treatment of low insulin sensitivity are crucial to prevent diabetes.

Insulin sensitivity can be determined using direct methods or indirect methods. Direct methods are highly invasive, risky and expensive but have higher accuracy, therefore they are mainly used in research studies. On the other hand, indirect methods are commonly used in clinical practice because they are simpler, cheaper and less invasive, but the protocol behind these methods is still painful and unconformable for patients. Indirect methods use the values of glucose and insulin at different time instants of the oral glucose tolerance test (OGTT). The OGTT is a distressing test (two hours long) performed in three steps: i) fasting blood draw for glucose and insulin measurement, ii) oral intake of 75 gr. of glucose, and iii) four or one blood draws to measure the insulin and glucose after the glucose oral intake.

The accuracy of the indirect methods can be evaluated by computing the Spearman's rank correlation coefficient (r) between a direct method and an indirect method [6], [7]. The indirect method is better as the Spearman's rank correlation coefficient (positive or negative) approaches to one. Differences in the accuracy of indirect methods have been reported in people from different ethnics and in people with different pathologies [8], [9], [10]. Some indirect methods are more accurate in subjects with metabolic syndrome or diabetes than in normal subjects, and particularly, the indirect method HOMA–IR is accurate in patients with low insulin sensitivity but not on diabetic patients with impaired function in beta cells [11].

Indirect methods are composed of a set of fixed parameters that have been chosen empirically. For that reason, differences in the accuracy are observed when they are applied in different populations. The aim of this work is thus to adapt the parameters of five indirect methods to three different populations: athletics, metabolic syndrome and normal subjects. To adapt the indirect methods, the set of parameters are modified from a large range of values. The combination of parameters that produce the best Spearman's rank correlation coefficient (close to ± 1) is selected as the best set of parameters. However, due to the difficulty of applying any direct method, the method of Caumo [12] has been retained as the gold standard. This is also an indirect method, but since it was derived from the minimal model method (a direct method) [13], it has a good correlation coefficient ($r = 0.89$) with this direct method on normal subjects. Five indirect methods are adapted in this work: Avignon [14], HOMA–IR [10], QUICKI [15], Raynaud [16], and Matsuda [17]. Despite the method of Caumo is highly accurate, it is not widespread among clinicians because of the mathematical complexity for insulin sensitivity estimation. The less accurate method HOMA–IR is instead the preferred method due to its simplicity.

II. METHODS

A. OGTT database

The values of glucose and insulin were obtained from the 5-point OGTT, i.e., the insulin and glucose are measured in five blood samples: one taken in fasting (minute 0) and four others after the glucose intake, at intervals of 30 minutes (minutes 30, 60, 90, and 120). The database is thus composed of the values of glucose and insulin at these time instants from 40 subjects from three different populations:

- Normal subjects (NS): composed of 10 healthy people (10 men, age $= 26.90 \pm 4.17$ years, height $= 176.60 \pm 8.78$ cm, weight $= 73.01 \pm 13.56$ kg, body

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mass index $= 23.28 \pm 3.47$ kg/m^2, waist circumference $= 83.51 \pm 10.75$ cm).

- Metabolic syndrome subjects (MSS): composed of 15 people (15 men, age $= 31.40 \pm 6.97$ years, height $= 174.41 \pm 6.58$ cm, weight $= 104.66 \pm 23.13$ kg, body mass index $= 34.02 \pm 7.44$ kg/m^2, waist circumference $= 114.23 \pm 22.11$ cm) diagnosed with metabolic syndrome according to [18].
- Athletic subjects (AS): composed of 15 people (13 men, age $= 33.00 \pm 8.21$ years, height $= 172.26 \pm 6.90$ cm, weight $= 62.10 \pm 6.75$ kg, body mass index $= 20.73 \pm 2.03$ kg/m^2, waist circumference $= 72.33 \pm 4.70$ cm). These people are professional marathon runners (200–240 kilometers per week for training).

B. Indirect methods to quantify insulin sensitivity

Indirect methods are composed by several parameters that have been set empirically at the moment of their definition. However, in this work we think that indirect methods can be adapted to any population by changing the values of the set of parameters, in order to obtain better values of insulin sensitivity. In this paper, five methods are adapted: Avignon (1), HOMA-IR (2), QUICKI (3), Raynaud (4), and Matsuda (5). In these equations (1–5): VD is the volume distribution of glucose (150 mL/kg of body weight), G_0 is the fasting plasma glucose level (mg/dL), I_0 is the fasting insulin level (μUI/mL), G_{120} is the plasma glucose at 2-h OGTT (mg/dL), and I_{120} is the plasma insulin at 2-h OGTT (μUI/mL), G_m is the mean glucose during OGTT, I_m is the mean insulin during OGTT, and α, β, γ and θ are the set of parameters to be optimized. The initial values (original value reported in the literature) of α, β, γ and θ are detailed in the result section. We have used variables α, β, γ and θ for simplicity, but they are not related among the indirect methods (1–5).

$$\text{Avignon} = \frac{1}{2}\left(\frac{10^8\alpha}{I_0 G_0 \text{VD}} + \frac{10^8\beta}{I_{120} G_{120} \text{VD}}\right) \quad (1)$$

$$\text{HOMA-IR} = \frac{(\alpha + G_0)(\beta + I_0)}{405} \quad (2)$$

$$\text{QUICKI} = \frac{1}{(\alpha \log G_0) + (\beta \log I_0)} \quad (3)$$

$$\text{Raynaud} = \frac{40}{\alpha + I_0} \quad (4)$$

$$\text{Matsuda} = \frac{10000}{\sqrt{(\alpha + G_0)(\beta + I_0)(\gamma + G_m)(\theta + I_m)}} \quad (5)$$

C. Gold standard for insulin sensitivity

As stated in the introduction, employing a direct method on large populations is a difficult task, for that reason the method of Caumo was retained as the gold standard for the values of insulin sensitivity. The method of Caumo is detailed in (6), where: f is the fraction of the ingested glucose dose that appears in the systemic circulation, D_{oral} is the ingested glucose dose per unit of body weight (mg/kg), AUC denotes the area under the curve, GE is the glucose effectiveness (milliliters per kg/min), $G(t)$ is the plasma glucose concentration, $\Delta G(t) = G(t) - G_b$ is the glucose excursion above basal (G_b), $I(t)$ is the plasma insulin concentration, $\Delta I(t) = I(t) - I_b$ is the insulin excursion above basal (I_b), 0 is the time corresponding to the beginning of the OGTT, t_0 is the time instant where $\Delta G(t)$ becomes negative, and T is the time corresponding to the end of the OGTT.

D. Parameter optimization

The values of parameters α, β, γ and θ were modified until the best Spearman's rank correlation coefficient (r close to ± 1) between the indirect method and the method of Caumo was obtained. For each indirect method, the original value of the set of parameters retrieved in the literature was used as an a priori. Then, the optimal value for the set of parameters is looked for around this supposition. The Spearman's rank correlation coefficient (r) between each indirect method and the method of Caumo was computed before and after the optimization process, for each population.

III. RESULTS

Tables I–V show the Spearman's rank correlation coefficient between indirect methods and the method of Caumo, as well as the values of the set of parameters (α, β, γ and θ) before (original value) and after (optimal value) the optimization process, for each population.

TABLE I
SET OF PARAMETERS AND r BEFORE AND AFTER THE ADAPTATION OF AVIGNON METHOD.

Population	Optimization	α	β	r
NS	Before	0.137	1	0.7576
	After	0.01	0.19	0.8909
MSS	Before	0.137	1	0.8036
	After	0.07	0.16	0.8857
AS	Before	0.137	1	0.4571
	After	-0.04	0.13	0.4643

TABLE II
SET OF PARAMETERS AND r BEFORE AND AFTER THE ADAPTATION OF HOMAI-IR METHOD.

Population	Optimization	α	β	r
NS	Before	0	0	0.5106
	After	-2	-5.95	0.8211
MSS	Before	0	0	-0.8821
	After	-2.05	0.35	-0.9000
AS	Before	0	0	-0.1357
	After	-2.1	-4.3	-0.3929

IV. DISCUSSION

The results obtained show that, for the three populations studied in this work, the method of Matsuda is the method that has the best correlation coefficient before and after

$$\text{Caumo} = \frac{f \cdot D_{oral} \frac{\text{AUC}[\Delta G(t)/G(t)]_0^{t_0} - \text{AUC}[\Delta G(t)/G(t)]_{t_0}^{T}}{\text{AUC}[\Delta G(t)]_0^{t_0} - \text{AUC}[\Delta G(t)]_{t_0}^{T}} - GE \cdot \text{AUC}[\Delta G(t)/G(t)]}{\text{AUC}[\Delta I(t)]} \quad (6)$$

TABLE III
SET OF PARAMETERS AND r BEFORE AND AFTER THE ADAPTATION OF QUICKI METHOD.

Population	Optimization	α	β	r
NS	Before	1	1	0.5106
	After	-0.04	0.01	0.766
MSS	Before	1	1	0.8821
	After	0.02	0.01	0.8857
AS	Before	1	1	0.1357
	After	-0.13	0.02	0.3607

TABLE IV
SET OF PARAMETERS AND r BEFORE AND AFTER THE ADAPTATION OF RAYNAUD METHOD.

Population	Optimization	α	r
NS	Before	0	0.5449
	After	-0.04	0.7396
MSS	Before	0	0.8639
	After	0	0.8639
AS	Before	0	0.2169
	After	-0.13	0.3444

TABLE V
SET OF PARAMETERS AND r BEFORE AND AFTER THE ADAPTATION OF MATSUDA METHOD.

Population	Optimization	α	β	γ	θ	r
NS	Before	0	0	0	0	0.8182
	After	21.5	17	0	0	0.9152
MSS	Before	0	0	0	0	0.9429
	After	0	14.5	0	0	0.9607
AS	Before	0	0	0	0	0.4750
	After	23	18	0	7	0.5857

the optimization process (see Table V): $r = 0.8182$ and $r = 0.9152$ for normal subjects, $r = 0.9429$ and $r = 0.9607$ for subjects with metabolic syndrome, and $r = 0.4750$ and $r = 0.5857$ for athletes. This may be due to the fact that the method of Matsuda includes all the glucose and insulin values of the OGTT for the computation of the insulin sensitivity (5), as the method of Caumo does (6). However, performing the five points of the OGTT to compute the insulin sensitivity using the method of Matsuda is painful and unconformable for patients.

Despite HOMA–IR is the preferred method by physicians, recent studies have shown that it is inaccurate [10], [11]. In this work we have confirmed this fact by observing that it is not HOMA–IR that presents the best correlation coefficient but the method of Matsuda. However, compared to the method of Matsuda, HOMA–IR method is simpler since it uses only the fasting glucose and insulin levels to estimate the insulin sensitivity.

Before optimization, the methods that have the lowest correlation coefficient are: HOMA–IR and QUICKI on normal subjects ($r = -0.5106$ and $r = 0.5106$) and athletes ($r = -0.1357$ and $r = 0.1357$), and Avignon ($r = -0.8036$) on subjects with metabolic syndrome. However, with the optimal parameters, the method of Raynaud presents the lowest correlation coefficient (see Table IV): $r = 0.7396$ on normal subjects, $r = 0.8638$ on subjects with metabolic syndrome, and r =0.3444 on athletes. This may be due to the fact that the equation of the Raynaud method (4) only uses the fasting insulin level to determine the insulin sensitivity.

With the optimal parameters, all indirect methods showed improvements in the correlation coefficient except the method of Raynaud when it is applied on subjects with metabolic syndrome: $r = 0.8639$ before and after optimization. We cannot find an optimal value of α that improves the correlation coefficient of this method.

The correlation coefficient obtained on subjects with metabolic syndrome is better than the obtained on other populations. Furthermore, a low correlation coefficient was obtained when indirect methods were applied on athletes. This may be because subjects with metabolic syndrome have low insulin sensitivity, while athletes have high insulin sensitivity [19], [20]. This result suggests that indirect methods would be inaccurate on people with high insulin sensitivity.

HOMA–IR method showed the greatest correlation coefficient increase after optimization (see Table II) on normal subjects (from $r = -0.5106$ to $r = 0.8211$) and athletes (from $r = -0.1357$ to $r = -0.3929$), whereas for subjects with metabolic syndrome, the method of Avignon (see Table I) showed the greatest increase of the correlation coefficient with the optimal parameters (from $r = 0.8036$ to $r = 0.8857$). On the other hand, the methods that showed the lowest correlation coefficient increasing after optimization were: Matsuda (from $r = 0.8182$ to $r = 0.9152$) on normal subjects (see Table V) Raynaud (r without increase) on subjects with metabolic syndrome (see Table IV) and Avignon (from $r = 0.4571$ to $r = 0.4643$) on athletes (see Table I).

From Tables I–V we can observe that the parameters α, β, γ and θ are adjusted until the best Spearman's rank correlation coefficient between the indirect method and the method of Caumo is obtained. This confirms our hypothesis that a correct value of insulin sensitivity will be obtained if indirect methods are previously adapted to the type of population to be applied.

Finally, the results of the correlation coefficient shown in this paper were obtained using the optimal parameters (α, β, γ and θ). However, we have noted that there are other optimal parameters that yield the same correlation coefficient values. In this paper we have decided to present the optimal

values closest to zero of α, β, γ and θ.

V. CONCLUSIONS AND FUTURE WORKS

We have adapted in this paper five indirect methods used to determine insulin sensitivity: Avignon, HOMA–IR, QUICKI, Raynaud, and Matsuda, to three different populations: normal, metabolic syndrome, and athletes. The approach was based on the modification of the set of parameters of each indirect method, from a range of possible values until the best Spearman's rank correlation coefficient between the indirect method and the method of Caumo was obtained.

Results obtained in this work show that it is possible to increase the accuracy of the indirect methods used to determine insulin sensitivity by modifying the parameters that compose these methods. Also, we have demonstrated that indirect methods must be previously adapted to the specific population, in order to obtain an accurate value of insulin sensitivity.

On the three populations studied in this work, the method of Matsuda was the most accurate to estimate insulin sensitivity since it presented the highest correlation coefficient with method of Caumo. Furthermore, the second most accurate indirect method was Avignon on normal subjects and athletes, and HOMA–IR on subjects with metabolic syndrome. However, the method of Matsuda uses the values of glucose and insulin during all the phases of the OGTT whereas the method of Avignon uses the values of glucose and insulin in fasting and at 2-h OGTT and the HOMA–IR method uses only the fasting glucose and insulin levels. This means that, applying the method of Matsuda is more painful and distressing than the HOMA–IR method.

Although HOMA–IR is a method widely used by physicians, results obtained in this study suggest that this method should not be applied on athletes because the obtained value of insulin sensitivity would not be the expected. Nevertheless, it was possible to obtain an important improvement on the accuracy of this method with the optimal parameters on normal subjects and on subjects with metabolic syndrome.

Future work will focus on the adaptation of other indirect methods using the methodology proposed in this paper. Also, we expect to adapt the indirect methods to other populations: Hispanic, African, Asian, Caucasian, ..., or using synthetic data of glucose and insulin [21]. Finally, we would like to adapt the indirect methods by computing the correlation coefficient between the indirect method and a direct method, rather than to the method of Caumo.

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