How much insulin resistance in polycystic ovary syndrome? Comparison of HOMA-IR and insulin resistance (Belfiore) index models

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Abstract

Introduction: Polycystic ovarian syndrome (PCOS), the commonest endocrinopathy of women in reproductive age, is often accompanied by insulin resistance (IR), hirsutism and/or fertility problems. The aim of the study was to assess the prevalence of IR in women diagnosed with PCOS.

Material and methods: The study involved 137 women diagnosed with PCOS, according to the Rotterdam consensus criteria (2003). Insulin resistance was assessed according to the HOMA-IR method and insulin resistance (Belfiore) index (IRI) derived from glucose and insulin during the oral glucose tolerance test.

Results: There was a significant (p < 0.0001) but relatively moderate correlation between IRI and HOMA-IR (r = 0.5 and r = 0.57 for a linear and non-linear model, respectively). Insulin resistance was more prevalent according to IRI (49.6%) than according to HOMA-IR (22.6% and 15.8% for 3.46 and 3.8 cut-off points, respectively, p < 0.01). The majority of patients with high HOMA-IR also had high IRI (e.g. 86%, for HOMA > 3.8), but the majority of patients with raised IRI would not be diagnosed as insulin resistant according to HOMA (61.7% and 73.5%, for HOMA-IR > 3.46 and HOMA-IR > 3.80, respectively).

Conclusions: The insulin resistance (Belfiore) index indicates more cases of insulin resistance than HOMA-IR in women with PCOS. Therefore, detection of insulin resistance among women with PCOS is highly method-dependent with more severe cases being detected with HOMA-IR than with IRI.

Key words: insulin resistance, polycystic ovary syndrome, HOMA, Belfiore index.

Introduction

The term polycystic ovarian syndrome (PCOS) represents a heterogeneous and multifaceted entity characterised by hyperandrogenism and/or ovulatory dysfunction. It is also the most common endocrinopathy of women of reproductive age [1], and is associated with an increased cardiovascular risk [2, 3]. According to the Rotterdam criteria (2003) [4] a diagnosis of PCOS can be established when at least two out of three criteria are present (oligo-/anovulation, clinical hyperandrogenism or biochemical hyperandrogenaemia and polycystic ovaries) on condition that other causes of oligo-/anovulation or hyperandrogenism/hyper-
Material and methods

The study involved 137 patients hospitalised in the Department of Endocrinology and Metabolic Diseases of the Medical University of Lodz (Polish Mother’s Memorial Hospital – Research Institute in 2013), i.e. all patients in whom a diagnosis of PCOS was unequivocally established during this year, according to the Rotterdam criteria (2003) [4]. The average age of the patients was (mean ± SD) 25 ±7 years, BMI 27.61 ±7.43 kg/m². Demographic as well as baseline metabolic characteristics of investigated patients are presented in Table I.

Insulin resistance index was calculated from changes of glycaemia and insulinemia during a 75 g oral glucose tolerance test (OGTT) according to the method described by Belfiore et al. [17]. The IRI was calculated through the formula: \( \text{ISI}_{(gly)} = \frac{1}{\text{INSp} \times \text{GLYp}} \) + 1, where INSp and GLYp are the measured insulin and glycaemic areas. In normal subjects \( \text{ISI}_{(gly)} \) is always around 1, with maximal variations between 0 and 2. This method is based on changes of glycaemia and insulinaemia during OGTT, and correlates well with the euglycaemic hyperinsulinaemic glucose clamp technique [18]. According to some authors the assessment of free fatty acids (FFA) during OGTT is equally effective for the purpose of calculation of the IRI [17]. The cut-off point for this method is quoted as > 1.27 [19].

HOMA-IR index was calculated according to the formula: \( \text{HOMA-IR} = \frac{\text{glucose} \times \text{insulin}}{22.5} \) [15].

As there is no universal agreement as to the best cut-off for the HOMA-IR model, we adopted the most commonly used cut-off of 3.8 [20]. There are, however, data based on the analysis of the same, i.e. Spanish population, suggestive that a lower cut-off point (3.46) might be more appropriate for the 90th percentile [21]. Hence, the testing was performed for both the abovementioned cut-off points for HOMA-IR model. The data were subsequently analysed by standard descriptive statistics and by both univariate (Spearman rank correlation) and multivariate models.

Statistical analysis

The Statistika 9.1 program was used for relevant calculations. Statistical significance was assumed for \( p < 0.05 \).

Results

Mean HOMA-IR value was 2.72 ±2.24 (median: 2.14, range: 0.33–16.78). The prevalence of insulin resistance in the researched group was 49.6% (68/137) according to IRI, 22.6% (31/137) and 15.8% (21/137) according to HOMA-IR (for the cut-off points of 3.46 and 3.8, respectively). In cases of insulin resistance according to IRI, there was concordance with HOMA-IR in 83.9% of cases (26/31), while in the case of HOMA-IR, concor-
dance was noted in 85.7% of cases (18/21). On the other hand, the majority of patients found to be insulin-resistant according to IRI (> 1.27) were not insulin resistant according to HOMA-IR (42/68 = 61.7% and 50/68 = 73.5%, for HOMA-IR3.46 and HOMA-IR3.80, respectively). There were only five and three cases of IR according to HOMA-IR with IRI < 1.27 (HOMA-IR 3.46 and HOMA-IR 3.80, respectively). Results of this analysis are presented in Tables II and III.

Interestingly, however, among the patients found to be insulin-resistant according to the IRI, those with a concomitant high HOMA-IR index were also found to have higher insulin resistance (Belfiore) indices (1.55 ±0.18 vs. 1.44 ±0.14, \( p = 0.014 \), and 1.60 ±0.18 vs. 1.44 ±0.13, \( p = 0.0008 \), for HOMA-IR3.46 and HOMA-IR3.80, respectively). Hence, patients with high HOMA-IR (both HOMA-IR3.46 and HOMA-IR3.80) generally tended to be more insulin resistant, with both methods applied.

In the next step we assessed the correlation between IRI and HOMA-IR models. The correlation between IRI and HOMA-IR was assessed both in the linear (Figure 1 A) and non-linear models (Figure 1 B). There was a highly significant (\( p < 0.0001 \)) but only moderate correlation between both models (\( r = 0.5 \) and \( r = 0.57 \) for a linear and non-linear model, respectively). Furthermore, in this model only 25% of the total variation in HOMA-IR can be explained by the relationship between HOMA-IR and IRI (\( R^2 = 0.25, p = 0.0001 \)).

### Discussion

The issue of insulin resistance in PCOS, though seemingly obvious, is indeed highly problematic, when supposed to be transformed from a theoretical concept into a clinical application. In a seminal paper by Dunäf et al. [22] insulin resistance in PCOS was assessed by means of euglycaemic glucose-clamp technique in obese (n = 19) and non-obese women with PCOS (n = 10) versus obese (n = 11) and non-obese controls (n = 8).

The authors concluded that insulin resistance was apparent not in terms of exceeding a predefined cut-off point, but as decreased insulin sensitivity in comparison to BMI-matched non-PCOS peers (expressed as per kilogram total weight or per kilogram fat-free mass or when divided by the steady-state plasma insulin during a euglycaemic clamp). Hence application of any surrogate insulin resistance indices must be viewed with extreme caution.

Furthermore, it must be noted that there is no universal agreement as to the best cut-off point for various insulin-resistance indices. First of all, any cut-off points should be related to particular studied population, as significant ethnic differences have been reported [12]. Secondly, some

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**Table I. Descriptive statistics for demographic and clinical data of examined group of 137 patients**

| Parameter                      | Mean       | 95% CI   | Median | Min. | Max. | St. dev. |
|-------------------------------|------------|----------|--------|------|------|----------|
| Age                           | 25         | 23–26    | 23     | 14   | 44   | 7        |
| BMI [kg/m²]                   | 27.61      | 26.39–28.83 | 26.00 | 16.50 | 49.60 | 7.43     |
| OGGT [mg/dl at 120’]          | 102        | 98–106   | 100    | 42   | 182  | 26       |
| IRI (Belfiore)                | 1.19       | 1.13–1.25 | 1.24   | 0.28 | 1.86 | 0.36     |
| Fasting glucose [mg/dl]       | 81         | 80–82    | 80     | 59   | 102  | 7        |
| Fasting insulin [mIU/ml]      | 13.35      | 11.62–15.09 | 10.49 | 2.25 | 87.14 | 10.60    |
| HOMA-IR                       | 2.72       | 2.36–3.09 | 2.14   | 0.33 | 16.78 | 2.24     |
| TSH [mIU/l]                   | 2.05       | 1.89–2.21 | 1.98   | 0.02 | 5.57 | 1.00     |
| Free T4 [ng/dl]               | 1.25       | 1.19–1.30 | 1.20   | 0.80 | 4.21 | 0.35     |
| HDL cholesterol [mg/dl]       | 53         | 50–56    | 51     | 29   | 206  | 18       |
| LDL cholesterol [mg/dl]       | 102        | 97–107   | 102    | 30   | 265  | 55       |
| Triglycerides [mg/dl]         | 109        | 100–119  | 102    | 30   | 265  | 55       |
| Total cholesterol [mg/dl]      | 165        | 160–171  | 165    | 71   | 273  | 34       |
| Oestradiol [pg/ml]            | 77.4       | 62.3–92.4 | 47.9   | 10.5 | 601.8 | 89.6     |
| Total testosterone [ng/ml]    | 0.52       | 0.49–0.56 | 0.50   | 0.14 | 1.2  | 0.20     |
| DHEA-S [µg/dl]                | 310.40     | 288.37–332.43 | 284.10 | 54.80 | 936.9 | 133.28   |
| Androstenedione [ng/ml]       | 4.44       | 4.05–4.84 | 3.92   | 1.19 | 12.4 | 2.35     |
The principal finding of our study is, however, a relatively weak association between the HOMA index derived from fasting glucose and insulin values and a Belfiore index, i.e. one of the methods based on assessment of glucose and insulin concentrations during OGTT. As this method, as well as its variations as described by Matsuda and DeFronzo [18], is principally based on assessment of the area under the curve for glucose and insulin excursions, such a relatively weak correlation \( r = 0.5 \) would also apply to the insulin sensitivity index (ISI)/Matsuda index. As a result of this assessment of insulin resistance by the HOMA-IR index and IRI yields significantly different results according to the method applied. For instance, for a HOMA-IR cut-off point of 3.46, for 68 subjects with raised IRI, only 26 (38.2\%) had raised HOMA-IR. This difference was even more striking for a HOMA-IR cut-off of 3.8. The opposite situation, i.e. high HOMA-IR and “normal” IRI, was very uncommon and applied to only 5 (7.25\%) and 3 (4.3\%) subjects, for HOMA-IR cut-offs of 3.46 and 3.8, respectively. As a result, many more women with PCOS would be diagnosed as insulin resistant with IRI than with HOMA-IR, though those with high HOMA-IR generally tend to have higher IRI indices. This implies that the HOMA-IR index (for a 90th percentile cut-off) also identifies the most insulin-resistant population according to the IRI method.

The discrepancy between HOMA-IR and IRI methods and their relatively weak correlation is

Table II. Comparison of HOMA-IR and insulin resistance (Belfiore) indices for assessment of insulin resistance in women with polycystic ovary syndrome (cut-off for HOMA-IR > 3.46)

| IRI \( \leq 1.27 \) | HOMA-IR \( \leq 3.46 \) | HOMA-IR > 3.46 | Total |
|---------------------|-----------------|-----------------|-------|
| \( \leq 1.27 \) | 64 \( \times 100\%/69 = 92.75\% \) HOMA/IRI concordance for subjects with IRI within the reference range | 5 \( \times 100\%/69 = 7.25\% \) HOMA/IRI discordance for subjects with IRI within the reference range | 69 (50.4\%) |
| \( > 1.27 \) | 42 \( \times 100\%/68 = 61.8\% \) HOMA/IRI discordance for subjects with raised IRI | 26 \( \times 100\%/68 = 38.2\% \) HOMA/IRI concordance for subjects with raised IRI | 68 (49.6\%) |
| Total | 106 \( \times 100\%/137 = 77.4\% \) subjects with HOMA-IR \( \leq 3.46 \) | 31 \( \times 100\%/137 = 22.6\% \) subjects with HOMA-IR > 3.46 | 137 |

\( P < 0.0001 \) (McNemar’s test).

Table III. Comparison of HOMA-IR and insulin resistance (Belfiore) indices for assessment of insulin resistance in women with polycystic ovary syndrome (cut-off for HOMA-IR > 3.80)

| IRI \( \leq 1.27 \) | HOMA-IR \( \leq 3.80 \) | HOMA-IR > 3.80 | Total |
|---------------------|-----------------|-----------------|-------|
| \( \leq 1.27 \) | 66 \( \times 100\%/69 = 95.7\% \) HOMA/IRI concordance for subjects with IRI within the reference range | 3 \( \times 100\%/69 = 4.3\% \) HOMA/IRI discordance for subjects with IRI within the reference range | 69 (50.4\%) |
| \( > 1.27 \) | 50 \( \times 100\%/68 = 73.5\% \) HOMA/IRI discordance for subjects with raised IRI | 18 \( \times 100\%/68 = 26.5\% \) HOMA/IRI concordance for subjects with raised IRI | 68 (49.6\%) |
| Total | 116 \( \times 100\%/137 = 84.7\% \) subjects with HOMA-IR \( \leq 3.80 \) | 21 \( \times 100\%/137 = 15.3\% \) subjects with HOMA-IR > 3.80 | 137 |

\( P < 0.0001 \) (McNemar’s test).
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not surprising, given that insulin resistance indices derived from fasting glucose and insulin predominantly reflect hepatic rather than peripheral insulin sensitivity [26]. Furthermore, some studies have cast some doubt on the previously assumed excellent correlation of data obtained from these indices and data obtained from a euglycaemic clamp technique, both for fasting glucose and insulin models [27] and for methods based on glucose and insulin during OGTT [28]. In the latter case, some authors raise the issue that indices derived from OGTT could be subjected to many confounders [29]. For instance, significant reductions in β-cell function (where changes in corresponding glucose levels are initially mild) might significantly overestimate insulin sensitivity, while variation in gastric emptying might account for approximately 35% of the variance in peak blood glucose concentrations after ingestion of oral glucose [30], and so this may also seriously alter results obtained from OGTT-based methods.

In conclusion, our study clearly demonstrated that assessment of insulin resistance in women with PCOS is highly method-dependent, and that in a significant percentage of the studied population women might be classified either as “insulin resistant” or “insulin sensitive”, according to the chosen method. Also there is no agreement as to what cut-off points should be used for surrogate measures of insulin resistance. Despite this, some clinicians use surrogate measures of insulin resistance, for instance in order to determine indications for metformin treatment. As the issue of the current place of metformin treatment in PCOS remains debatable, application of surrogate indices of insulin resistance as the sole determinant for the use of insulin-sensitising agents in women with PCOS must be viewed with extreme caution.

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Conflict of interest

The authors declare no conflict of interest.

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Figure 1. A – Correlation between IRI and HOMA-IR indices linear model (r = 0.50, p < 0.001, n = 137). B – Correlation between IRI and HOMA-IR non-linear model (r = 0.57, p < 0.001, n = 137).
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