Research Article

Prediction of insulin sensitivity grade from various demographic ,clinical, biochemical and hormonal variables among women with polycystic ovary syndrome

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Abstract

Aim of the study: Is to evaluate factors most correlated to homeostatic model analysis (HOMA-IR) and to construct a formula which can predict HOMA from the cheaper biochemical, biophysical and hormonal risk factors.
Study design; case control
Methods: A total of 34 patients with polycystic ovarian syndrome were recruited from infertility clinic in Al-Yarmuok teaching hospital. From the epidemiological characteristics the following were recorded: BMI, waist to hip ratio, menstrual cycle, hirsutism which was scored by modified Ferriman Gallwey system and the mean ovarian volume from measuring both ovaries while from the hormonal and biochemical variables, luteinizing hormone and follicle stimulating hormone, total testosterone and lipid profile were measured for each patient. For each group of variables stepwise regression followed by best subset regression were implemented to isolate the factors most correlated with HOMA. Coefficient of Mallows (Cp) was used to sort out the single most predictive variable.
Results: Coefficient of Mallows (Cp) was the smallest for BMI among the demographic and clinical characteristics hence the most correlated to HOMA-IR while from the hormonal and biochemical characteristics, high density lipoprotein was the factor most correlated to HOMA-IR as assessed by Coefficient of Mallows (Cp). Accordingly a formula which predicts HOMA-IR directly from BMI and HDL was designed through which HOMA can be estimated easily through the constructed table from the formula. In addition, its percentile can be accessed from an associated table to measure insulin resistance severity.
Conclusion: HOMA was shown in this study to be best correlated with BMI and HDL and from those factors predictive formula was constructed which can predict HOMA-IR and its percentile directly. However extreme caution is called when such formula is used in clinical practice as its validity is neither established nor such tables were constructed before, and not until their validity is established by further studies we advise extreme caution in interpreting results.

Key words: *insulin resistance, body mass index, polycystic ovary syndrome.*

INTRODUCTION

Despite insulin resistance is a common feature among women with polycystic ovary syndrome, [1] yet clinical practice indicates that this parameter is not constant in severity. Rather it has a wide range in such a way that women with full scale polycystic feature yet have no infertility, menstrual abnormalities or even mild hirsutism [2]. On the other hand a wide spectrum studies has been conducted to investigate those with polycystic features yet are resistant to the most accurate regime of various insulin sensitizers, clomifene citrate and other

antiandrogen drugs used for hirsultism [3]. This particular point has pushed lot of researchers to commit various studies trying to find the factors which are most associated as well as predictive of insulin sensitivity [4]. The factors which have been isolated range from simple epidemiological characteristics like body mass index passing through the hormonal factors like free serum testosterone up to the more complicated biochemical parameters like serum interleukins [5, 6]. So the aim of the study is to construct a simple model from two variables one epidemiological while the other hormonal-biochemical which if combined may produce more sensitive equation model for insulin sensitivity prediction. From this equation a table can be constructed which can calculate Homeo Static Model Analysis or HOMA-IR as well as its percentile among women with polycystic ovary syndrome.

PATIENTS AND METHODS

The study was conducted in AL Yarmook teaching Hospital in between December 2012 up to September 2013. The study protocol was approved by the Arab Board Committee for medical specialization. During this period a total of 34 polycystic women were recruited to participate in the study. All the patients were taken from the department of infertility mostly those with at least 3 years primary infertility. All the women in this study were nullipara. Verbal consent to participate in the study was taken for all women.

All women recruited in this study were collected from infertility clinic as they are already polycystic ovarian women who are nullipara as well as free for the last 6 months from any form of ovulation induction medications like clomifene citrate, tamoxifene. In addition free from any medical problem. For all the patients enrolled in the study the following parameters were measured as well as stored at the end of the study. From the demographis characteristics the followings were recorded, age, height, body mass index, waist hip ratio, hirsutism score by Ferimann Galloway scoring system, and the cycle period in days. As far as the hormonal and biochemical characteristics the following variables were taken, high and low density serum lipoprotein, serum triglycerides and serum cholesterol. In addition fasting serum plasma glucose as well as fasting insulin levels were taken to calculate HOMA as shown below. In addition serum luteinizing as well as follicle stimulating hormones and their ratio were taken. Free serum testosterone was taken also for all the patients. Unfortunately an important hormonal factor was missing namely sex hormone binding globulin due to the unavailability of the kit needed. For all the patients Homeo Static Model or HOMA, which is a sensitive index for insulin resistance, was calculated by the formula shown below;

$$HOMA-IR = \frac{\left[Fasting\ glucose\ (mM/l)\right] x \left[Fasting\ insulin\ (IU/ml)\right]}{22.5}$$

$$(Normal\ <3.0)$$

***m*M=mmol/l**

While body mass index was calculated by the routine formula as shown below

$$BMI\ (kg/m^2) = weight\ (kg)/\ [height\ (m)]^2$$

Fasting serum insulin level was measured by the kit which has the following code; [Diabetic Kit (Cat. No.R97420)].

Statistical analysis

Continuous data were expressed as mean and standard deviation. The factors which are most correlated with HOMA insulin resistance was measured by implementation of ***best subset regression*** with calculation of Cp or Coefficient of Mallows. The factors which are most correlated with HOMA-IR should have the lowest coefficient of Mallows From both demographic and hormonal/ biochemical factors which are most associated with HOMA-IR, a regression multiple linear formula was constructed with a table constructed. Through this table HOMA as well as its percentile was constructed to measure insulin resistance as easy as possible as shown in the result next section. In addition the distribution of HOMA variables was assessed by Shapiro- Francia test to ensure natural distribution so the formula can be applied to the whole society.

RESULT

In table 1 the overall characteristics of the demographic, hormonal and biochemical characteristics are shown. Clearly the overall patterns of the data are those of polycystic picture. BMI is mostly in the overweight range. The mean serum testosterone as well as fasting HOMA are elevated. There is increased level of low density lipoprotein while the high density lipoprotein is decreased.

In order to shed more light on the demographic, clinical, hormonal and biochemical characteristics a best subset regression mode was established for the above variables. The aim is to calculate the coefficient of Mallows or Cp which has the smallest values for variables most associated with the HOMA which represent the main dependent variable taken in this study. The results are shown in table 2.

Table 1. The demographic, clinical, hormonal and biochemical characteristics of the women enrolled in the study

characteristics	Mean±Sd	Median
Age(year)	28.118±6.333	28.00
BMI(kg/m^2)	29.048±6.864	26.385
Cycle	54.735±20.435	45.00
WHR	0.86000±0.05924	0.8500
Hirsutism	7.0294±5.1961	6.00
HOMA	3.4788±0.8646	3.2750
Fasting	13.927±2.853	13.297
FBG(mg/dl)	100.20±6.73	99
Total serum testosterone	0.65882±0.24010	0.600
LH/FSH	0.87812±47789	0.75000
Serum cholesterol	186.82±19.46	184.50
HDL(mg/dl)	46.529±6.491	47.00
LDL(mg/dl)	110.24±17.21	106.00
S.Triglyceride	150.24±45.46	142.50

In table 2 the overall variables taken in this study were categorized into two groups. The epidemiological which include body mass index, waist hip ratio, hirsutism score and cycle. While the hormonal- biochemical variables included seum testosterone, LH/FSH ratio, high and low density lipoprotein in addition to triglycerides and serum cholesterol levels.

Table 2. The coefficient of Mallows was calculated and arranged in ascending manner for both demographic and hormonal- biochemical variables

Demographic characteristics	
Characteristics	**Mallows- CP**
BMI	14.3
Waist hip ratio	33.9
Cycle	101.9
Hirsutism	122.7
Hormonal and biochemical characteristics	
Characteristics	**Mallows- CP**
HDL	2.7
LDL	18.6
Triglycerides	20.7
T Cholesterol	22.5
Testosterone	27.6
LH/ FSH ratio	31.6

In order to have more ideation about the results obtained in table 2, a 3D dimensional surface wireframe figure was constructed giving HOMA as a function of body mass index as well as high density lipoprotein as in figure 1. In addition the multiple linear regression formula was also constructed. While the distribution characteristics for HOMA-IR as well as basic test for distribution is shown in table 4. As the distribution of raw data for HOMA-IR is normal, the formula can be applied to the whole society with 95% confidence.

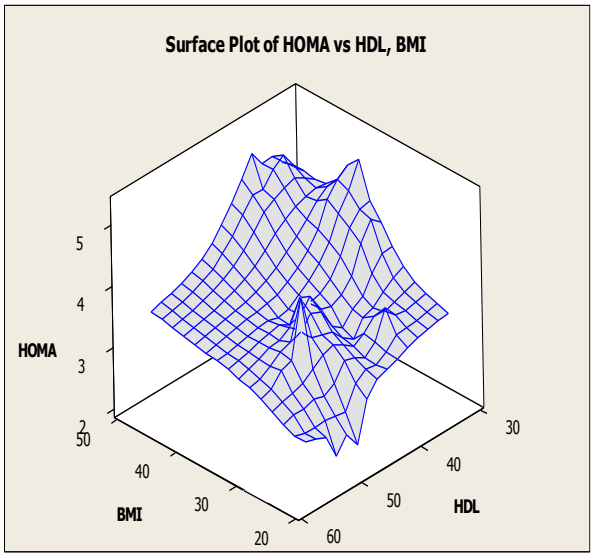

Figure 1. A 3 dimensional surface plot showing the positive correlation between increasing HOMA-IR versus increasing BMI and decreasing HDL

Regression Analysis: HOMA-IR versus BMI, HDL

HOMA-IR = 2.99 + 0.0813 BMI - 0.0403 HDL

The 3 dimensional surface plot shows the positive correlation between increasing body mass index and decreasing high density lipoprotein among women enrolled in this study.. In order to use the equation as a reference for insulin resistance a table was constructed from the formula with increasing body mass index and high density lipoprotein versus the corresponding HOMA-IR value as in table 3.

In table 3, two simple parameters are required to assess easily HOMA-IR value from body mass index and serum high density lipoprotein. For example a women with body mass index 30 and HDL 40 the intersecting columns shows HOMA-IR as roughly as ***3.816268*** which if compared with table 4 showing the percentile range we can see that this value is above than the 75th percentile indicating highly resistant state of insulin resistance

Table 3. The corresponding HOMA-IR value for corresponding body mass index and serum high density lipoprotein given in the left column and top row

BMI	HDL=30	HDL=35	HDL=40	HDL=45	HDL=50	HDL=55	HDL=60
20	3.406076	3.204707	3.003338	2.801969	2.6006	2.399231	2.197862
21	3.487369	3.286	3.084631	2.883262	2.681893	2.480524	2.279155
22	3.568662	3.367293	3.165924	2.964555	2.763186	2.561817	2.360448
23	3.649955	3.448586	3.247217	3.045848	2.844479	2.64311	2.441741
24	3.731248	3.529879	3.32851	3.127141	2.925772	2.724403	2.523034
25	3.812541	3.611172	3.409803	3.208434	3.007065	2.805696	2.604327
26	3.893834	3.692465	3.491096	3.289727	3.088358	2.886989	2.68562
27	3.975127	3.773758	3.572389	3.37102	3.169651	2.968282	2.766913
28	4.05642	3.855051	3.653682	3.452313	3.250944	3.049575	2.848206
29	4.137713	3.936344	3.734975	3.533606	3.332237	3.130868	2.929499
30	4.219006	4.017637	3.816268	3.614899	3.41353	3.212161	3.010792
31	4.300299	4.09893	3.897561	3.696192	3.494823	3.293454	3.092085
32	4.381592	4.180223	3.978854	3.777485	3.576116	3.374747	3.173378
33	4.462885	4.261516	4.060147	3.858778	3.657409	3.45604	3.254671
34	4.544178	4.342809	4.14144	3.940071	3.738702	3.537333	3.335964
35	4.625471	4.424102	4.222733	4.021364	3.819995	3.618626	3.417257
36	4.706764	4.505395	4.304026	4.102657	3.901288	3.699919	3.49855
37	4.788057	4.586688	4.385319	4.18395	3.982581	3.781212	3.579843
38	4.86935	4.667981	4.466612	4.265243	4.063874	3.862505	3.661136
39	4.950643	4.749274	4.547905	4.346536	4.145167	3.943798	3.742429
40	5.031936	4.830567	4.629198	4.427829	4.22646	4.025091	3.823722
41	5.113229	4.91186	4.710491	4.509122	4.307753	4.106384	3.905015
42	5.194522	4.993153	4.791784	4.590415	4.389046	4.187677	3.986308
43	5.275815	5.074446	4.873077	4.671708	4.470339	4.26897	4.067601
44	5.357108	5.155739	4.95437	4.753001	4.551632	4.350263	4.148894
45	5.438401	5.237032	5.035663	4.834294	4.632925	4.431556	4.230187

Table 4. Basic statistical characteristics of HOMA-IR sample in this study with various cut off value foe corresponding centiles

Variable	HOMA	
Sample size	34	
Lowest value	2.0600	
Highest value	5.2900	
Arithmetic mean	3.4788	
95% CI for the mean	3.1771 to 3.7805	
Median	3.2750	
95% CI for the median	3.0383 to 3.6917	
Variance	0.7476	
Standard deviation	0.8646	
Relative standard deviation	0.2485 (24.85%)	
Standard error of the mean	0.1483	
Coefficient of Skewness	0.6432 (P=0.1073)	
Coefficient of Kurtosis	-0.4614 (P=0.6059)	
Shapiro-Francia test for Normal distribution	W'=0.9377 accept Normality (P=0.0521)	
Percentiles	Value of HOMA-IR	95% Confidence Interval
2.5	2.1370	
5	2.3000	
10	2.5420	
25	3.0100	2.5841 to 3.0656
75	3.8500	3.4472 to 4.8238
90	4.9230	
95	5.1040	
97.5	5.2305	

DISCUSSION

Main finding in this study, BMI and HDL from the biometric, biochemical and hormonal variables are the factors most correlated with HOMA-IR. Fortunately, the literature is full of similar articles with close conclusion.

Kajaia et al. [7] in their study which used HOMA-IR as a measure for insulin resistance found that BMI and HDL are factors which most correlated with HOMA, a finding that coincide with the current study.

On the other hand, Gennarelli et al. [6] have found BMI correlate well with IR among biochemical/hormonal variables. In his study, sex hormone binding globulin SHBG is the factor most correlated with HOMA-IR. Unfortunately his finding cannot be compared with the result of our study as SHBG was not taken in this study.

While in the same context, Kalra et al. [8] in their study that involving 65 women with PCOS, reached a conclusion that lipid abnormalities in general and BMI are factors which correlates most with IR, however; he didn't calculate the lipid subtype which most correlate with IR, while in the current study we have isolated HDL as the protein most predictive of IR. Accordingly his conclusion agrees to a large extent with the result obtained by current study. Cibula et al [9] has reached a

conclusion through evaluating 41 non-obese women with PCOS and still they found that triglyceride and BMI are the factors most correlate with insulin sensitivity.

Wongwananuruk et al. [10] has conducted a study involved Thai women with PCOS and found that waist circumference, Acanthosis Nigricans (AN) and oral GTT, in addition to dyslipidemia in general are most predictive of IR in women with PCOS and this study raises an important question: do the racial factors affects the trend or the predictive variable of PCOS? for the time being we didn't' find such article in the web; however, this point deserves further investigations whether women with different racial origin has different values and this may explain the conflict shown above in this study so this points should be investigated in the future by further studies.

Mor et al. [11] has used primarily fasting insulin and glucose to measure HOMA. He found that AN, hirsutism and resistance to clomiphene citrate has a direct correlation to HOMA. He also found that simply HOMA remains the only reliable indicator of IR. It is upon this fact that our study been designed as HOMA cost about 100$ for 1 patient and that is why it has pushed as to make another alternative to evaluate HOMA from its predictor.

It has been shown in the current study that HDL, BMI are the factors most associated with HOMA and these are much cheaper and easier than HOMA cost and this is the rationale behind our study.

Ducluzeau et al. [12] has found an interesting finding that adiponectin which is secreted from the fatty tissue has a direct effect on low SHBG among women with PCOS and that explained why BMI is the factor most correlated with the resistance index, a finding which correlates well with the result of the current study.

Lastly Golbahar et al. [13] found that free androgen index (FAI) and SHBG are significantly associated with IR; however, he didn't include in his study the epidemiological variables and this explains the differences between the result of his study and the result of our. The epidemiological factors involved in this study are definitely associated with insulin resistance severity.

Finally, in addition to the finding that HDL and BMI were correlated directly with IR, a formula and table with easy use reference has been constructed. The cost of rough HOMA estimation by this method 90% lower than the measurement of HOMA by serum insulin level; however, these tables has not been tested in real world practice and extreme caution should be practiced in using these tables until their validity is confirmed or denied. Up to this moment we urge our colleagues to compare HOMA values measured by the routine ways (fasting insulin & FBG) with the HOMA estimated by this table until validity is established.

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