A Study to Evaluate Surrogate Markers of Insulin Resistance in Forty Euglycemic Healthy Subjects

AK Gupta*, SK Jain**

Abstract
Objective: Insulin resistance (IR) is increasingly being recognized as an important pathophysiological determinant of not only diabetes but also a number of other clinical states. Methods for directly estimating IR like euglycemic clamp technique and Insulin suppression test (IST) are experimentally demanding and impractical tool for large scale epidemiological studies. We evaluated several surrogate markers of IR in 40 healthy subjects.

Methods: Study included 40 euglycemic normal healthy north Indian subjects (33 males, 7 females) of mean ± SD age 38.9 ± 8.6 yrs, BMI 20.5 ± 3.6 kg/m² and WHR 0.87 ± 0.05. All subjects were tested for fasting and postprandial (2 hr post 75 gm glucose) glucose and insulin. Then all the subjects underwent IST by modified Harano’s method (simultaneous infusion of 20% dextrose @ 6mg/kg/min and plain human insulin @ 50 mU/kg/hr). Metabolic clearance rate for glucose (MCR = glucose infusion rate/steady state plasma glucose, ml/kg/min) was calculated for 120-150 min of infusion. Correlation of MCR with various surrogate markers which included fasting glucose (FG), fasting insulin (FI), fasting glucose/insulin ratio (FGIR), 120 min glucose (PPG), 120 min insulin (PPI), 120 min glucose/insulin ratio (PPGIR), homeostatic model assessment of insulin resistance (HOMA-IR), quantitative insulin sensitivity check index (QUICKI), fasting glucose insulin product (FIGP), insulin sensitivity index (ISI), fasting insulin resistance index (FIRI), insulin ratio (IRa) and insulinogenic index (II) were evaluated.

Results: MCR was found to be significantly (p <0.05) correlated with FI (r= -0.347), PPI (r= - 0.402), PPG (r= - 0.317), PPGIR (r= 0.356), HOMA-IR (r= - 0.348), FIGP (r= - 0.348), and FIRI (r= - 0.348).

Conclusions: Among the surrogate markers which were significantly correlated to MCR, there was no significant superiority of one marker over the other. We suggest that measuring insulin levels alone in a single fasting sample can serve as a simple, cheap and convenient indirect qualitative index of IR.
is also problematic because of necessity of frequent blood sampling and analysis. Thus there is a pressing need to evolve indirect or surrogate markers of insulin resistance which are more applicable for large population-based epidemiological investigations. Several such markers have been proposed.\textsuperscript{12-18} The utility and significance of these surrogate estimates of insulin resistance depend on the degree to which they correlate with the direct estimate of this variable. Due to extreme importance of this issue, we attempted to define the degree of correlation between a quantitative measure of insulin resistance i.e. metabolic clearance rate for glucose (MCR) determined by modified Harano’s method\textsuperscript{11} and various surrogate markers in 40 euglycemic subjects.

**MATERIALS AND METHODS**

Study was conducted in 40 normal and healthy north Indian subjects. There were 33 males and seven females subjects with mean ± SD age of 38.9 ± 8.6 years (range 22-57), BMI of 20.5 ± 3.0 kg/m\(^2\) (range 16.0-27.7) and WHR of 0.87 ± 0.05 (range 0.76-0.96). The study was conducted at the Department of Medicine, Lady Hardinge Medical College and Dr. RML Hospital and Radioimmunoassay Lab, INMAS, Delhi. All subjects had a normal medical history, and routine clinical laboratory tests. Written informed consent of each subject was taken before undertaking the procedure.

All subjects were tested for plasma glucose and serum insulin which were measured before (fasting) and 120 min after the ingestion of 75 g oral glucose challenge. On a separate admission, all subjects underwent IST. After an overnight fast insulin (regular, Human Actrapid, Novo Nordisk) @ 50 mU/kg/hr, and glucose as 20% dextrose @ 6 mg/kg/min were infused through an I/V catheter placed on one arm by a syringe infusion pump (Model Pilot A2, Fresenius, Germany) and a volumetric infusion pump (Cure Mate Model SM 2100, Jong Sang Techno Co. Ltd, Korea) respectively. Blood samples were collected at every five minutes interval between 120 to 150 min of infusion through another I/V catheter placed on the other arm. Insulin levels were measured by radioimmunoassay (Coat-A-Count Insulin kits of Diagnostic Products Corporation, US) and glucose by autoanalyser (glucose oxidase method). The mean concentration of glucose in the seven samples (120-150 min) was calculated representing steady state plasma glucose (SSPG). Metabolic clearance rate for glucose (MCR) was calculated representing steady state plasma glucose concentration of glucose in the seven samples (120-150 min) by different authors were calculated and then correlated with Metabolic clearance rate (MCR) determined by modified Harano’s method\textsuperscript{11} and various surrogate markers in 40 euglycemic subjects.

Various surrogate markers of insulin resistance as reported by different authors were calculated and then correlated with MCR (Table 1). All data are expressed as mean ± SEM or mean ± SD, and all analysis were performed using the SPSS 10.0 package for windows. Pearson’s correlation (r) between MCR and all surrogate measures of insulin resistance were calculated. P < 0.05 was considered to indicate statistical significance.

### Table 1: Various surrogate markers calculated

<table>
<thead>
<tr>
<th>Correlation</th>
<th>Pearson’s correlation (r value)</th>
<th>p value</th>
</tr>
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<tbody>
<tr>
<td>Fasting glucose (FG)</td>
<td>0.150</td>
<td>0.355</td>
</tr>
<tr>
<td>Fasting insulin (FI)</td>
<td>([+] 0.162 to 0.462)</td>
<td></td>
</tr>
<tr>
<td>Fasting glucose/insulin ratio (FGIR)</td>
<td>0.209</td>
<td>0.195</td>
</tr>
<tr>
<td>Fasting insulin resistance product (PPI)</td>
<td>0.209</td>
<td>0.028*</td>
</tr>
<tr>
<td>120 min glucose (PPG)</td>
<td>0.317</td>
<td>0.046*</td>
</tr>
<tr>
<td>120 min insulin (PPI)</td>
<td>0.402</td>
<td>0.010*</td>
</tr>
<tr>
<td>120 min glucose/insulin ratio (PPIR)</td>
<td>0.356</td>
<td>0.024*</td>
</tr>
<tr>
<td>Homeostatic model assessment of insulin resistance (HOMA-IR)</td>
<td>0.348</td>
<td>0.028*</td>
</tr>
<tr>
<td>Quantitative Insulin sensitivity check index (QUICKI)</td>
<td>0.149</td>
<td>0.360</td>
</tr>
<tr>
<td>Fasting insulin glucose product (FIGP)</td>
<td>0.348</td>
<td>0.028*</td>
</tr>
<tr>
<td>Insulin sensitivity index (ISI)</td>
<td>0.209</td>
<td>0.195</td>
</tr>
<tr>
<td>Fasting insulin resistance index (FIRI)</td>
<td>0.348</td>
<td>0.028*</td>
</tr>
<tr>
<td>Insulin ratio (IR)</td>
<td>0.251</td>
<td>0.010</td>
</tr>
<tr>
<td>Insulinogenic index (II)</td>
<td>0.550</td>
<td>0.048*</td>
</tr>
</tbody>
</table>

*p <0.05. Confidence interval given in parentheses.
Results

Values of MCR and various surrogate markers of insulin resistance for the 40 subjects are shown in Table 2. Pearson’s correlation (r) of MCR with these surrogate markers of insulin resistance calculated are shown in Table 3. These results demonstrated that simple Pearson’s correlation coefficients between MCR, and fasting insulin, 120 min insulin, 120 min glucose, 120 min glucose/insulin ratio, HOMA-IR, FIGP and FIRI were statistically significant (p <0.05) (Fig. 1). The 120 min insulin was found to be most closely related to MCR (p= 0.01). No significant correlations of MCR were achieved with fasting glucose, fasting glucose/insulin ratio, QUICKI, ISI, insulin ratio, and insulinogenic index. Out of the various surrogate measures which are variations of a formula that involves fasting insulin and fasting glucose i.e. HOMA-IR, FGIR, QUICKI, FIGP, FIRI and ISI, only HOMA-IR, FIGP and FIRI achieved statistically significant (p <0.05) correlations with MCR glucose. The r value was similar for all of these variables (r= -0.348). Also all of these measures, based on

![Fig. 1: Relationship of MCR glucose with (A) 120 min glucose, (B) fasting insulin, (C) 120 min insulin, (D) 120 min glucose/insulin ratio, and (E) HOMA-IR.](image-url)
fasting glucose and insulin were found to be highly significantly correlated with each other (p < 0.001).

Large majority of the healthy subjects had FI less than 10 µU/ml. However, five subjects had extremely high FI more than 20 µU/ml. Furthermore, these five subjects had higher levels of PPI (Fig. 1C) and HOME-IR (Fig. 1E), and lower values of both fasting and PP glucose/insulin ratio (Fig. 1D), when compared to rest of the group.

**DISCUSSION**

We studied correlations of presently available surrogate markers of IR with MCR and also compared these markers with each other. Metabolic clearance rate for glucose (MCR) was found to be statistically significantly correlated with fasting insulin, 120 min insulin, 120 min glucose, 120 min glucose/insulin ratio, HOME-IR, FIGP and FIRI (p < 0.05).

The highest degree of correlation of MCR was achieved with 120 min insulin (r = 0.402) closely followed by fasting insulin (r = 0.347). Thus both fasting and post-glucose load insulin were found to be significantly related to direct estimate of insulin resistance (MCR) with no significant difference in their correlations with MCR. Since it is very convenient to take a single fasting sample, fasting insulin as a surrogate marker of insulin resistance can serve as convenient, simple, cheap and reliable qualitative marker of insulin resistance that simply measuring fasting insulin levels may serve as a significant advantage.

Also in an interesting observation, five subjects had extremely high FI (> 20 µU/ml) associated with higher PPI, higher HOME-IR, and low levels of both fasting and PP glucose/insulin ratio as compared to rest of the subjects. These subjects are otherwise normal and healthy. They may belong to syndrome X. Other manifestations of the syndrome like hypertension, diabetes, coronary artery disease, dyslipidemia which although are not apparent at present may appear later in the life.

In summary, we evaluated almost all of the presently reported surrogate markers of insulin resistance in a single study and could demonstrate significant correlations of quite a few of them with direct measure of insulin resistance i.e., MCR derived from modified Harano’s method. We conclude that simply measuring fasting insulin levels may serve as a simple, cheap and reliable qualitative marker of insulin resistance, and measuring other variables do not offer any significant advantage.

**References**

2. DeFronzo RA, Bonadanna RC, Ferrannini F. Pathogenesis of


13. Legro RS, Fine Good D, Dunia F. A fasting glucose to insulin ratio is a useful measure of insulin sensitivity in women with polycystic ovary syndrome. *J Clin Endocrinol Metab* 1998;83:2694-98.


**Announcement**

**XXIV Annual Conference of Association of Physicians of India, Orissa Chapter - 2004** will be held on 13th and 14th November, 2004 at IMA House - Berhamper, Orissa.

For further details, please contact: **Dr. LM Meher**, Organising Secretary, Conference Secretariat of Medicine Dept. MKCG Medical College, Berhampur, Orissa 760 004.

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