Significance of Measuring Fasting Immunoreactive Insulin and Homeostasis Model Assessment of Insulin Resistance in Ningen Dock for the Prevention of Lifestyle Related Disease

Toshiki Fukui

Background It has been widely recognized that insulin resistance not only plays an important role in the pathophysiology of diabetes but in all lifestyle related disease that are closely associated with cardiovascular disease.

Methods Measurement of fasting immunoreactive insulin (F-IRI) was performed to examine its significance and usefulness as an index of insulin resistance in subjects in Ningen Dock.

Results The value of F-IRI increased as the number of risk factors for atherosclerosis increased, and we observed a stronger correlation between the value of F-IRI and BW than the degree of diabetes. We also found that there was a very strong correlation (correlation coefficient exceeding 0.9) between F-IRI and homeostasis model assessment of insulin resistance (HOMA-IR), which is the index of insulin resistance used most widely at present. Furthermore, we identified that the value of F-IRI changes in correlation with changes in the BW and that visceral fat accumulation is one of the independent factors affecting F-IRI. Finally, we examined the effect of lifestyle itself, namely exercise, drinking, and smoking, on the value of F-IRI, and found that exercise and drinking are independent factors associated with F-IRI.

Conclusions These results indicate the significance of measuring F-IRI as the most convenient index of insulin resistance, and also indicate its usefulness for the guidance of subjects in Ningen Dock from the viewpoint of the prevention of lifestyle related disease. (Ningen Dock 2007; 21: 57-62)

Key Words: insulin resistance, lifestyle related disease, fasting immunoreactive insulin (F-IRI), homeostasis model assessment of insulin resistance (HOMA-IR)

Insulin resistance has been widely recognized as playing an important role in the pathophysiology of type II diabetes besides a shortage of insulin secretion. However, a new concept of insulin resistance was proposed about two decades ago. At present, insulin resistance has been recognized as a basal cause of lifestyle related disease, such as hypertension, diabetes, obesity, and hyperlipidemia, and as being characteristic of a worsening of lifestyle. This concept has been proposed under several other names such as syndrome X, the deadly quartet, insulin-resistance syndrome, and visceral fat syndrome. Furthermore, since the Japanese criteria for the diagnosis of metabolic syndrome were defined, metabolic syndrome has been taken up by the mass media extensively and the importance of BW management for lifestyle related disease prevention has rapidly gained popularity. This new concept of metabolic syndrome emphasizes more the importance of visceral obesity located upstream of insulin resistance and other lifestyle related disease, but this concept also indicates the significance of insulin resistance in lifestyle related disease.

We have investigated the significance of measuring fasting immunoreactive insulin (F-IRI) in subjects in Ningen Dock, almost all of whom showed no symptoms of lifestyle related disease, from the viewpoint of the prevention of lifestyle related disease.

Methods To examine the significance of insulin resistance in lifestyle related disease in subjects of Ningen Dock in our institute, the relationship between the value of F-IRI and a number of atherosclerosis risk factors, including hypertension, diabetes, hyperlipidemia, and obesity, and the relationship between F-IRI and homeostasis model assessment of insulin resistance (HOMA-IR) were investigated. HOMA-IR was calculated according to the following formula: HOMA-IR=([F-IRI x fasting plasma glucose (FPG)]/4059. Measurements of F-IRI were performed on 3252 subjects (2789 males and 463 females). The average age of the subjects was 51±8 years. Subjects were divided into two groups according to the BMI: one with a BMI≥25 and the other with a BMI<25. Furthermore, each group was divided into three subgroups according to the stage of diabetes by the oral 75 g GTT: normal glucose tolerance group (NGT), impaired glucose tolerance group (IGT), and
Next, 386 subjects (315 males and 71 females, aged 48±9 years) underwent body fat distribution measurements by helical CT (Toshiba Medical Systems Corp., Tochigi, Japan) at the level of the vein, to research further independent predictors for F-IRI analyzed by multiple regression analysis. Furthermore, to examine the effect of BW changes on insulin resistance, changes in F-IRI and HOMA-IR were investigated in selected subjects who underwent Ningen Dock for two consecutive years and showed BW changes of more than 3 kg. Finally, a self-administered questionnaire about lifestyle, including exercise, drinking, and smoking habits were performed in the 1118 subjects (981 males and 137 females, aged 52±7 years) in Ningen Dock after obtaining informed consent to investigate the relationship between insulin resistance and lifestyle itself.

All of subjects were given written informed consent before participating in these studies. All procedures were approved by the Ethical Committee of NTT West Takamatsu Hospital.

**Statistical Analysis**

Comparisons among groups were analyzed using Student’s t-test for continuous data and a linear regression technique; multiple stepwise regression analysis was performed using StatView ver. 5.0 (SAS Institute, NC, USA).

The results are expressed as the mean±SD. Values of \( p<0.05 \) were considered to indicate significance.

**Results**

A positive correlation was found between F-IRI and the number of atherosclerosis risk factors. Number of atherosclerosis risk factors were classified as 0, 1, 2, 3, or 4. As the number of risk factors increased, the value of F-IRI also increased 5.0±2.6 μU/ml \((n=779)\), 6.1±3.2 μU/ml \((n=1059)\), 7.6±4.1 μU/ml \((n=852)\), 9.9±6.1 μU/ml \((n=442)\), 11.0±6.7 μU/ml \((n=120)\), respectively (Fig. 1). The correlation coefficient between F-IRI and HOMA-IR was very high \((r=0.977)\). However, a very weak correlation existed between FPG and HOMA-IR \((r=0.364)\) (Fig. 2). BMI was found to be the biggest independent predictor of a high F-IRI on multiple regression analysis. FPG was also selected as the second biggest positive predictor (Table 1). On the other hand, HbA1c was not selected although it is a prevalent predictor in diabetes.

The values of F-IRI and HOMA-IR were significantly higher in the high BMI group \((BMI \geq 25)\) compared with those of the normal BMI group \((BMI < 25)\) \((9.4±6.1 \text{ vs. } 5.6±3.5 \text{ μU/ml, } 2.5±1.8 \text{ vs. } 1.4±1.0, \text{ respectively})\). Furthermore, the difference in the value of F-IRI in terms of BMI was bigger than the difference

| Table 1. Multiple regression analysis for the value of fasting immunoreactive insulin (F-IRI) \((n=3252)\) |
|-----------------|-----------------|
| **BMI** | 0.392 |
| **FPG** | 0.145 |
| **HDL** | -0.126 |
| **TG** | 0.114 |
| **Heart Rate** | 0.094 |
| **Sex** | 0.062 |
| **Age** | -0.048 |

FPG: fasting plasma glucose.

**Fig. 1.** The relationship between the value of fasting immunoreactive insulin (F-IRI) and the number of atherosclerosis risk factors. Atherosclerosis risk factors: hypertension \((systolic \text{ BP} \geq 140 \text{ or diastolic BP} \geq 90)\), diabetes \((\text{FPG} \geq 110 \text{ or HbA1c} \geq 5.6)\), hyperlipidemia \((\text{T-cho} \geq 220 \text{ or HDL<40 or TG} \geq 150)\) and obesity \((\text{BMI} \geq 25)\). FPG: fasting plasma glucose, T-cho: total cholesterol.
of its presence in the stages of diabetes. These results are shown in Fig. 3. The values of F-IRI and HOMA-IR in the BMI<25 group were 5.3±2.9 μU/ml and 1.2±0.7 in NGT (n=1298), 5.9±3.1 μU/ml and 1.5±0.8 in IGT (n=489), and 6.0±3.1 μU/ml and 2.0±1.3 in DM (n=258), respectively. On the other hand, the value of F-IRI in the BMI≥25 group was 8.5±4.6 μU/ml and 2.1±1.2 in NGT (n=576), 9.7±5.5 μU/ml and 2.5±1.5 in IGT (n=403), and 10.5±6.3 μU/ml and 3.4±1.9 in DM (n=186), respectively.

To investigate a further predictor for the value of F-IRI, body fat distribution at the vein level by CT scan was performed. The single correlation coefficient between the value of F-IRI was the highest with BMI, and also a high correlation was found with waist circumference, total fat area, visceral fat area (VFA), and BW. BMI was the biggest independent predictor for a high value of F-IRI on multiple regression analysis. VFA was selected as the second biggest independent predictor for F-IRI (Table 2).

**Fig. 2.** The correlation between homeostasis model assessment of insulin resistance (HOMA-IR) and fasting immunoreactive insulin (F-IRI) or fasting plasma glucose (FPG)

**Fig. 3.** The differences of fasting immunoreactive insulin (F-IRI) and homeostasis model assessment of insulin resistance (HOMA-IR) by the difference of BMI and the stage of diabetes. *p<0.0005, **p<0.005 vs. NGT in BMI<25 ; +p<0.0001 vs. NGT in BMI<25 ; ++p<0.0001 vs. IGT in BMI<25 ; #p<0.0005, ##p<0.0001 vs. NGT in BMI≥25 ; bpb<0.0001 vs. IGT in BMI≥25. NGT : the normal glucose tolerance group, IGT : impaired glucose tolerance group, DM : diabetes mellitus group.
The results of the effect of changes in BW on insulin resistance are shown in Fig. 4. The number of subjects with a BW loss of more than 3 kg over two consecutive years was 75 (71.4±12.8 to 66.4±13.1 kg), and subjects with a weight gain of more than 3 kg numbered 45 (66.9±11.3 to 71.3±11.5 kg). The values of F-IRI and HOMA-IR in the weight loss group were both significantly decreased (9.1±6.3 to 6.9±5.2 μU/ml).

Table 2. The correlation coefficient between fasting immunoactive insulin (F-IRI) and various factors and multiple regression analysis for the value of F-IRI

<table>
<thead>
<tr>
<th>Correlation coefficient</th>
<th>p value</th>
<th>Standard regression coefficient</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>-0.077</td>
<td>.2896</td>
</tr>
<tr>
<td>Sex</td>
<td>-0.127</td>
<td>.0098</td>
</tr>
<tr>
<td>BW</td>
<td>0.425</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Waist circumference</td>
<td>0.470</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>BMI</td>
<td>0.496</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>% of body fat</td>
<td>0.387</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Visceral fat area</td>
<td>0.432</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Subcutaneous fat area</td>
<td>0.369</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Total fat area</td>
<td>0.460</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>FPG</td>
<td>0.253</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>PG 2h</td>
<td>0.172</td>
<td>.0049</td>
</tr>
<tr>
<td>HbA1c</td>
<td>0.150</td>
<td>.0022</td>
</tr>
</tbody>
</table>

BMI*: Correlation coefficient between BMI and waist circumference is very strong (r=0.859) and waist circumference is also the strongest independent predictive factor for F-IRI.

FPG: fasting plasma glucose, PG 2h: plasma glucose at 2h in 75 g oral glucose tolerance test, VFA: visceral fat area.

Weight loss group (n=75)

Weight gain group (n=45)

Fig. 4. The effect of BW change on the values of fasting immunoactive insulin (F-IRI) or homeostasis model assessment of insulin resistance (HOMA-IR) and the relationship between the F-IRI and HOMA-IR in the subjects who underwent ningen dock for two consecutive years.
2.5±2.0 to 1.8±1.5, respectively. On the other hand, the values of F-IRI and HOMA-IR in the weight gain group were both significantly increased (6.2±2.5 to 7.4 ±3.4 μU/ml, 1.5±0.6 to 1.9±0.9, respectively). The correlation coefficient between F-IRI and HOMA-IR was very high, exceeding 0.9 in both groups.

The effects of lifestyle on the values of F-IRI and HOMA-IR are shown in Fig. 5. Both the custom of exercise and drinking significantly decreased the values of F-IRI and HOMA-IR (exercise : 6.6±4.1 to 6.0±3.8 μU/ml and 1.7±1.4 to 1.5±1.1, drinking : 7.1±4.6 to 6.0±3.7 μU/ml and 1.9±1.5 to 1.5±1.2, respectively). Furthermore, there was a bigger difference in the values of F-IRI and HOMA-IR between subjects that have neither of customs of exercise and drinking compared to subjects that have both of them (7.6±4.4 to 5.8±3.4 μU/ml and 2.0±1.4 to 1.5±1.1, respectively). On the other hand, the custom of smoking did not significantly affect them (6.0±3.8 to 6.6±3.4 μU/ml and 1.5±1.2 to 1.7±1.4, respectively).

Discussion

We have investigated the significance of measuring F-IRI in subjects in Ningen Dock from several points of view, as follows:

1) Is insulin resistance really a marker not only for diabetes but also for lifestyle related disease?
2) Is the value of F-IRI or HOMA-IR really a useful evaluation marker in Ningen Dock?
3) Is there any true relationship between insulin resistance and visceral fat accumulation?
4) Does insulin resistance really alter with changes in BW?
5) Does lifestyle really affect insulin resistance?

We found that F-IRI increased as the number of risk factors for atherosclerosis increased, and also found a stronger correlation between F-IRI and BW than the degree of diabetes. BMI is selected as the biggest independent predictive factor for the value of F-IRI. Moreover, it was proved that a stronger correlation, with a correlation coefficient exceeding 0.9, was observed between the values of F-IRI and HOMA-IR in the subjects, the large majority of whom are healthy or do not have severe symptoms of lifestyle related disease. We have reported these results before. However, we have tried to investigate them again with an increased number of subjects, more than 3000, and the results were similar.

In this study, it was clearly proved that F-IRI is useful as an index of insulin resistance, and that the value of F-IRI depends on the BW more than the stage of type II diabetes. We investigated further and found that visceral fat accumulation is one of the independent predictive factors for the value of F-IRI, and also that F-IRI is one of the independent factors in visceral fat accumulation from multiple regression analysis. Thus, these two factors affect each other mu-

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**Fig. 5.** Effects of lifestyle, exercise, drinking, and smoking, and both exercise and drinking. NO : no custom of any of them, YES : at least one time or more in a week, HOMA-IR : homeostasis model assessment of insulin resistance, F-IRI : fasting immunoactive insulin.
tually, and these results show us the existence of a kind of vicious circle between visceral fat accumulation and insulin resistance. This is reasonable and easy to understand from the viewpoint that the physiological function of insulin induces the accumulation of fat tissue. Therefore, it is speculated that subjects who exhibit insulin resistance have more difficulty in reducing their BW than subjects with normal resistance.

Furthermore, we have proved that the values of F-IRI and HOMA-IR change in correlation with changes in BW in subjects who underwent Ningen Dock for two consecutive years. This indicates the significance of repeated measurements of F-IRI as a blood sampling item like FPG, HbA1c, HDL cholesterol, and TG in lifestyle related disease, because this demonstrates that the value of F-IRI is changeable according to changes in BW or the physical condition even in the same person. It was also shown that a very strong correlation exists between the values of F-IRI and HOMA-IR.

Finally, we examined the effect of lifestyle itself, exercise, drinking, and smoking, on the value of F-IRI and showed that both the custom of exercise and drinking decreased the values of F-IRI and HOMA-IR. It is reasonable to understand that a custom of exercise decreases insulin resistance. However, our results indicate that the group exercising twice a week showed the lowest F-IRI (data not shown). Therefore, it is still questionable how much exercise per week is suitable for an improvement of insulin resistance. The custom of drinking was also selected as an independent predictor for insulin resistance, but smoking was not selected in the multiple regression analysis. Many papers reporting that an appropriate amount of alcohol is helpful in preventing cardiovascular diseases have been published. However, further investigation is needed to assess whether drinking alcohol really improves insulin resistance, because the drinking of alcohol should be restricted in subjects who have liver dysfunction, high TG, or obesity. Several studies have shown the association between smoking and type II diabetes; however, it is still unclear whether smoking is directly associated with insulin resistance. It is a very important for us to guide subjects who undergo Ningen Dock appropriately. Therefore, we have to keep in mind that an excessive prescription of exercise and excessive restriction of alcohol intake in healthy subjects may not necessarily help patients to maintain a healthy life.

All results clearly indicate the significance of measuring F-IRI as the most convenient index of insulin resistance, and also indicate its usefulness for the guidance of subjects in Ningen Dock in order to prevent lifestyle related disease.

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References