

The association between insulin resistance, metabolic syndrome, and ischemic heart disease among Rumoi residents

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Abstract

Background: It has widely been proven that metabolic syndrome (MetS) increases the risk of ischemic heart disease (IHD). MetS is confirmed based upon insulin resistance (IR). Our aim of this study is to evaluate the role of MetS and IR in the prediction of IHD incidence.

Methods: A total of 404 non-diabetic participants who underwent 75 g oral glucose tolerance test (75 g OGTT) were enrolled from 2001 to 2009. Risk factors for IHD were measured as well. The homeostatic index of IR (HOMA-IR) and the homeostatic model assessment beta cell function (HOMA- β) were calculated according to the homeostasis model assessment. Cox proportional-hazard regression model was used to estimate hazard ratio (HR). All data were analyzed using SPSS 21 software (IBM, Armonk, NY, USA).

Results: In our study, the average follow-up period was 6.7 years. Eighteen subjects of IHD incidence were recorded. After adjusting for age and sex, subjects with IR or hyperinsulinemia had a high risk of IHD, the hazard ratio (95% confidence intervals) for IHD were 4.58 (1.59-13.15), 4.25 (1.64-11.91), respectively. The highest hazard ratio was 7.56 (2.27-25.18) which was found among the subjects with both IR and hyperinsulinemia. In addition, the hazard ratio (95% confidence intervals) of subjects with MetS was 2.80(1.10-7.09).

Conclusions: IR and hyperinsulinemia are related to the risk of IHD. IR combined with hyperinsulinemia may be superior to MetS for predicting the IHD incidence.

KEYWORDS

hyperinsulinemia, insulin resistance, ischemic heart disease, metabolic syndrome

1 | INTRODUCTION

Metabolic syndrome (MetS) is defined as a cluster of glucose intolerance, hypertension, dyslipidemia, and central obesity. Many epidemiological studies indicated that MetS is associated with ischemic heart disease (IHD).¹⁻³ MetS is used to predict the risk of IHD in the clinical field, but sometimes it is encountered in IHD patients who do not meet the diagnostic criteria of MetS, or although diagnosed with MetS, are under good control. And for patients who have been diagnosed with MetS, achieving success in lifestyle changes is difficult, and increased

atherosclerosis is almost irreparable. In addition, the diagnostic criteria of MetS are not consistent in Japan, Europe, or America. Furthermore, there are some debates about the cutoff values of Japanese MetS diagnosis criteria, especially about the waist circumference cutoff value for Japanese women.³ Previous studies indicated that the MetS based on Japanese criteria had weak association with risk of IHD, predicted IHD less effectively.⁴ Therefore, using MetS to predict the risk of IHD may be insufficient. Insulin resistance (IR) is described as a low response in adipose tissue, skeletal muscles, and liver to the insulin action. From the perspective of pathology, IR is known as the headstream of MetS.

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In the early stage of IR, only compensatory hyperinsulinemia appears, and as the pathological changes of IR progresses, IR can cause a series of pathological changes, such as dyslipidemia, a hypercoagulable state with increased plasminogen activator inhibitor (PAI)-1 and fibrinogen, hypertension and/or increased sympathetic nervous system tone, endothelial dysfunction, and hyperuricemia, as well as nonalcoholic steatohepatitis (NASH).⁵ Before the onset of MetS, if we can detect IR and conduct clinical intervention, it could help prevent IHD. The precise mechanism between IR and development of IHD is uncertain; however, recent studies have reported that IR is related to promote atherosclerosis.^{6,7} In Japan, IR has almost not been used as predictor of IHD in present clinical areas; in this study, we try to evaluate the role of IR and MetS in the prediction of IHD incidence.

2 | METHODS

2.1 | Subjects and data collection

The number of participants who underwent 75 g oral glucose tolerance test (75 g OGTT) from 2001 to 2009 in Rumoi Municipal Hospital was 485. We excluded 58 participants who had a history of IHD or who were undergoing anticoagulant and antiplatelet therapy; we also excluded 23 participants with missing data for height, weight, blood pressure, waist circumference, triglyceride (TG), and cholesterol. We enrolled rest of the 404 participants as our study subjects. Among these 404 participants, there were two initial purposes of 75 g OGTT test. One was a secondary health examination, because mild impaired fasting glucose was discovered in the primary health checks. The other one was regarding participants with obesity, hypertension, or hyperlipidemia who were recommended by their regular doctors. We recorded the following items: age, gender, height, weight, blood pressure, and waist circumference. In addition, TG, total cholesterol, low-density lipoprotein cholesterol (LDL-Cho), and high-density lipoprotein cholesterol (HDL-Cho) were measured.

2.2 | Definition of MetS

According to the *Metabolic syndrome-Definition and diagnostic criteria in Japan 2005*,⁸ the waist circumference cutoff values are 85 cm for men and 90 cm for women. In addition to central obesity, as determined by this definition, a diagnosis of MetS also requires any two of the following three factors: (i) increased TG levels: serum TG levels ≥ 150 mg/dL and/or reduced HDL-Cho levels; serum HDL-Cho levels of < 40 mg/dL; (ii) increased blood pressure: systolic blood pressure (SBP)/diastolic blood pressure (DBP) values of $\geq 130/85$ mm Hg; and (iii) increased fasting plasma glucose levels: fasting blood glucose levels of ≥ 110 mg/dL.

2.3 | Definition of IR and hyperinsulinemia

The homeostatic index of IR (HOMA-IR) and the homeostatic model assessment beta cell function (HOMA- β) were calculated according to the homeostasis model assessment as follows:

$HOMA-IR = \text{fasting insulin } (\mu\text{Units/mL}) \times \text{fasting glucose (mg/dL)} / 405$, $HOMA-IR \geq 1.7$ was defined as IR.

$HOMA-\beta = 360 \times \text{fasting insulin } (\mu\text{Units/mL}) / [\text{fasting glucose (mg/dL)} - 63]$, $HOMA-\beta \geq 60$ was defined as hyperinsulinemia.

2.4 | Incidence of IHD

The occurrence of IHD was confirmed by reviewing the medical records of Rumoi Municipal Hospital. For the first step, we accessed all the medical records which recorded diagnosis of IHD as I20-I25 (International Classification of Diseases 10). For the second step, we performed IHD event validation. In our study, IHD included acute myocardial infarction, angina pectoris and coronary revascularization. Acute myocardial infarction was diagnosed when the subject met at least three of the following criteria: (i) typical symptoms; (ii) cardiac enzyme levels of more than twice the upper limit of the normal range; (iii) evolving diagnostic electrocardiographic changes; and (iv) typical morphological changes on echocardiography. Regarding angina pectoris, we only adopted the cases of coronary artery stenosis which had been confirmed by coronary computed tomography angiography or coronary arteriography. We defined coronary revascularization as percutaneous coronary intervention or coronary artery bypass surgery. We considered the study subjects who moved away from Rumoi as study withdraws. However, we considered the study subjects who were diagnosed in other hospitals (if we could confirm the diagnosis by the patient referral document) as our study outcomes.

2.5 | Statistical analysis

Cox proportional hazard regression model was used to estimate hazard ratio (HR). We analyzed all data using SPSS 21 software.

2.6 | Ethical considerations

Our study was approved by the Ethics Committees of Rumoi Municipal Hospital.

3 | RESULTS

General baseline subject characteristics are listed in Table 1. The mean age was 63 years, the proportion of IR was 35.0%, and the proportion of MetS was 28.5% for both males and females.

In our study, the 5-year follow-up rate was 80.2% and the average follow-up period was 6.7 years. Eighteen subjects of IHD incidence were confirmed. After adjusting for age and gender, subjects with IR or hyperinsulinemia were positively related to the risk of IHD. The hazard ratios (95% confidence intervals) for IHD were 4.58 (1.59-13.15) and 4.25 (1.64-11.91), respectively. The highest hazard ratio was 7.56 (2.27-25.18) which was found among the subjects with both IR and hyperinsulinemia. We also evaluated the association between MetS and IHD, the hazard ratio (95% confidence intervals) of subjects with MetS was 2.80 (1.10-7.09) (Table 2).

TABLE 1 Subject baseline characteristics (n=404)

	Men (n=197)	Women (n=207)	Total (n=404)
	Mean±SD	Mean±SD	Mean±SD
Age(yrs)	62.2±13.0	64.2±13.0	63.2±13.0
Body mass index (kg/m ²)	25.0±3.5	24.8±4.9	24.9±4.3
Total cholesterol (mg/dL)	192.8±36.0	209.3±38.2	201.3±38.0
Triglycerides (mg/dL)	147.6±101.7	129.0±88.7	138.1±95.6
LDL-C (mg/dL)	112.2±31.4	122.8±33.4	117.7±32.9
HDL-C (mg/dL)	49.6±14.6	57.7±15.5	53.7±15.6
Fasting plasma glucose (mg/dL)	115.0±27.7	108.7±22.3	111.8±25.3
Insulin	6.0±4.1	6.6±5.0	6.3±4.6
HOMA-IR	1.7±1.5	1.8±1.6	1.7±1.5
Hypertension (Yes,%)	35.0	49.3	42.3
Insulin resistance (Yes,%)	33.0	36.9	35.0
Hyperinsulinemia (Yes,%)	21.3	29.5	25.5
Metabolic syndrome (Yes,%)	29.9	27.1	28.5

TABLE 2 Association between insulin resistance, hyperinsulinemia, metabolic syndrome, and ischemic heart disease (IHD)

		Risk of IHD HR ^a (95% confidence intervals)
Insulin resistance	No	1.0
	Yes	4.58 (1.59-13.15)
Hyperinsulinemia	No	1.0
	Yes	4.25 (1.64-11.91)
Insulin resistance and hyperinsulinemia	No	1.0 ^b
	Yes	7.56 (2.27-25.18)
Metabolic syndrome	No	1.0
	Yes	2.80 (1.10-7.09)

^aAdjusted for age and gender.

^bNeither insulin resistance nor hyperinsulinemia both insulin resistance and hyperinsulinemia.

We took the 100-HOMA-β (100 minus HOMA-β, in order to make the large numerical values of HOMA-β displayed in the center of the figure) as the vertical axis and the HOMA-IR as the transversal axis to make an ichnography—"Glucometabolic State—IHD Ichnography" (Figure 1). We tried to draw a region on this ichnography (circular dotted line; 4.1 > HOMA-IR ≥ 1.7, 155 > HOMA-β ≥ 60, and 126 mg/dL ≥ fasting plasma glucose > 80 mg/dL), in this region, the risk of IHD is

higher than other regions. The total number of the participants in the circular dotted line range is 74, and the outcome of follow-up is that 10 participants were diagnosed as IHD (incidence rate is 10/74); the total number of the participants out of the circular dotted line range is 330, and eight participants of them were diagnosed as IHD (incidence rate is 8/330); that is, the incidence rate of IHD in the circular dotted line range is 5.6-fold higher than other regions (10/74 divided by 8/330 is equal to 5.6).

4 | DISCUSSION

In our study, we found the strong associations between IR, hyperinsulinemia, and IHD. We also explored that the hazard ratios of the subjects with both IR and hyperinsulinemia for IHD was much bigger than the subjects with MetS. All these showed that IR combines with hyperinsulinemia can be used as a predictor of IHD, and is probably superior to MetS. We try to explain the reasons by expounding the mechanism of IR and MetS.

The result of IR is a relative lack of insulin reaction. In adipose tissue, the antilipolytic effect of insulin is reduced, which inhibits glucose uptake and increases free fatty acid (FFA) production. In skeletal muscles, FFA production and oxidation decrease glucose uptake and storage as glycogen. FFA also promotes gluconeogenesis in the liver. These changes result in hyperglycemia.⁹ In order to compensate for the relative shortage of insulin, pancreatic beta cell function increases and leads to hyperinsulinemia. Previous studies reported that IR and hyperinsulinemia were associated with increased incidence of IHD.¹⁰⁻¹³ Our study results are consistent with previous research results.

However, when the increasing requirements of insulin exceed the compensatory secretion ability of pancreatic beta cell, hyperglycemia will appear, and eventually evolve into type 2 diabetes mellitus.

On the other hand, when a person is in the early stage of IR, compensatory hyperinsulinemia can control blood glucose level within a normal range, and it is difficult to clinically screen out. However, if hyperinsulinemia is sustained, hyperinsulinemia-associated abnormalities may occur and lead to a variety of clinical syndromes.⁵

In 1988, Gerald Reaven first proposed the presence of the insulin resistance syndrome (IRS) and that the main features were dyslipidemia, hypertension, glucose intolerance, and hyperinsulinemia.¹⁴ The present definition of MetS is based on the IRS of Gerald Reaven.

IR should be highlighted as one of the origin pathology reasons. Why has IR not been widely used in clinical field? The main reason is that IR is difficult to measure accurately. The earliest of the measurement methods, and the generally acknowledged most accurate method, is the euglycemic hyperinsulinemic clamp.¹⁵ In this method, by injecting insulin continuously, insulin concentration is maintained at 100 μU/mL. To maintain a constant plasma glucose level, variable glucose is infused at the same time. Because plasma levels are negatively associated with insulin reactions, the glucose infusion rate is equal to the glucose intake by all the tissues in the body. Therefore, we can use this method to measure tissue sensitivity to exogenous insulin.

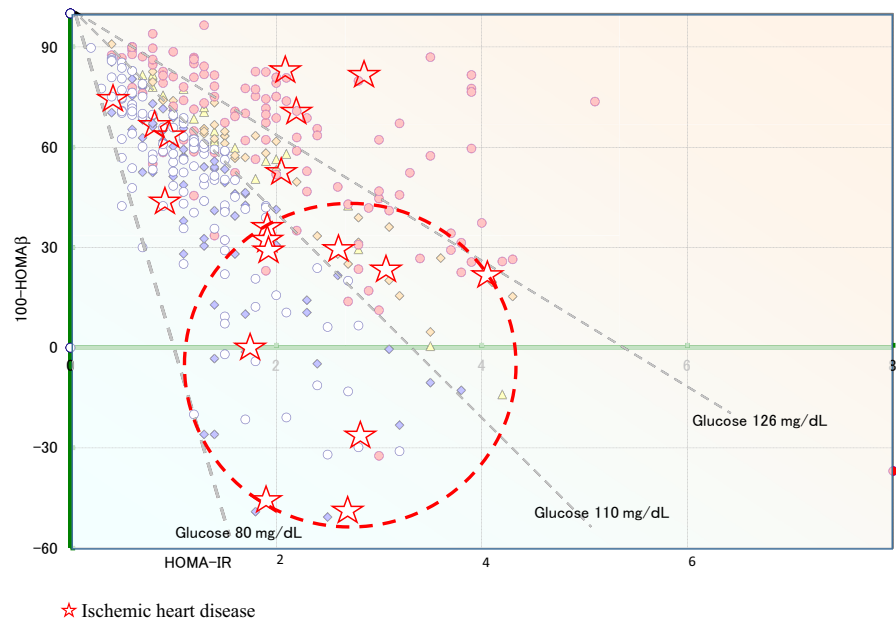


FIGURE 1 Glucometabolic State—IHD Ichnography

However, this method is so complicated that it cannot be widely used in clinical diagnosis and health diagnosis.

The homeostatic model assessment of insulin resistance (HOMA-IR) is a simple and practical method for evaluating IR, and it has been proved that there is a good correlation between HOMA-IR and the euglycemic hyperinsulinemic clamp technique.¹⁶ Therefore, in our study we used HOMA-IR to evaluate the IR.

Furthermore, in 2010, Sasagawa invented [the judgment method of diabetes and impaired glucose metabolism].¹⁷ According to this invention, we made Glucometabolic State—IHD Ichnography (Figure 1). We tried to draw a risk region on this ichnography. However, because the number of our study subjects was small, we used a simple circular curve to mark the risk region of IHD. According to our results, although in this region the fasting plasma glucose levels of the participants are within the range of 80 mg/dL–126 mg/dL (normal fasting plasma glucose or slightly increased but did not meet the diagnostic criteria of diabetes mellitus), the risk of IHD is 5.6-fold higher than other regions. This means that even if a participant has normal fasting plasma glucose levels, if the laboratory test results of HOMA-IR and 100-HOMA- β are in the circular dotted line range, we could anticipate the participant to have a high risk of IHD. Of course, in our study, the determining method of the risk region may be subjective; further studies are needed to demonstrate. However, we can reasonably infer if we can get an increased sample size, we could draw a more precise risk region, and the risk region may be an irregular region and perhaps contain more than one. Using this ichnography, we can judge the IHD risk of the participants intuitionistically.

The optimal cutoff point for HOMA-IR in nondiabetic Japanese is also controversial. We determined 1.7 (lower than 2.5; ie, the general standard) as the optimal cutoff point.¹⁸ The reason is that, including the Japanese, the pancreatic beta cell of East Asians is not robust because East Asians are very sensitive to insulin. However, if there is even a slight decrease in insulin sensitivity, IR will generate among the

East Asians who have no ability to increase insulin secretion further to compensate hyperglycemia.^{19,20}

Compared with normal fasting plasma glucose (<110 mg/dL) and normal hemoglobin A_{1c} (<6.1%) values, isolated postprandial hyperglycemia (2-hour postprandial glucose level >140 mg/dL) increases the risk of death from cardiovascular disease more than twofold.²¹ However, the present health examinations in Japan almost do not measure postprandial glucose. Therefore, individuals with isolated postprandial hyperglycemia are difficult to detect in present health examinations. HOMA-IR is easily calculated only by measure fasting plasma glucose and fasting plasma insulin. HOMA-IR must be given more importance in health examinations and for early prevention of IHD.

Rumoi City is located in the northwest area of Hokkaido. The population is only about 22 000, but people over 65 years old accounted for 33.2% (2015, Rumoi municipal office). Rumoi is well known because of the winter snowstorms. Winter in Rumoi is very long, and Rumoi residents have a high salt intake (more than 14 grams a day on average), fewer exercise chances, and higher prevalence of lifestyle-related disease. Winter is also a season for high incidence of IHD. We think that our study has clinical implications, especially in cold regions of Japan.

One the other hand, Rumoi municipal hospital is the only emergency hospital (it takes at least one hour to drive to the other emergency hospital if patients need to go there), almost all the emergency and severe patients of Rumoi, such as acute myocardial infarction and stroke were treated here. And in Rumoi, the migration population is small. All these were helpful for our study data collection and follow-up.

The potential limitations of our study should not be ignored. First, this is a prospective study, but the participant numbers are small. Second, because of the missing data, potential confounders, such as smoking habits and family history of IHD, were not adjusted for. Third, we did not adjust the influence of the multiple drug therapies in the participants. Many drugs, such as statins, are possible preventives for IHD.²²

5 | CONCLUSION

IR and hyperinsulinemia are related to the IHD. IR combines with hyperinsulinemia is probably superior to MetS for predicting the incidence of IHD.

CONFLICT OF INTEREST

The authors have stated explicitly that there are no conflicts of interest in connection with this article.

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