Insulin Resistance and Heart Disease

Subjects: Others
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Insulin resistance is defined as an impaired biological response to insulin actions in the insulin-responsive tissues and is considered key to metabolic syndrome. The prevalence of insulin resistance has increased globally, and it is known to be from 15.5 to 46.5% of adults. Previous studies have suggested that insulin resistance is significantly related to the development and progression of coronary atherosclerosis and adverse plaque characteristics and is a major risk factor for cardiovascular diseases via pathophysiological mechanisms. Insulin resistance is also the common pathophysiology of prehypertension and prediabetes.

Keywords: metabolic score for insulin resistance ; cardiometabolic risk ; longitudinal study ; ischemic heart disease

1. Overview

The metabolic score for insulin resistance (METS-IR) is a novel noninsulin-based marker for assessing the risk of insulin resistance and cardiometabolic risk. However, whether METS-IR is associated with incident ischemic heart disease (IHD) risk is unknown. Therefore, we aimed to investigate the longitudinal effect of METS-IR on incident IHD risk in a large cohort of Korean adults without diabetes. We assessed 17,943 participants without diabetes from the Health Risk Assessment Study (HERAS) and Korea Health Insurance Review and Assessment (HIRA) data. The participants were divided into four groups according to METS-IR index quartiles: (ln ((2 × fasting plasma glucose) + triglyceride) × body mass index)/(ln (HDL-cholesterol)). We prospectively assessed hazard ratios (HRs) with 95% confidence intervals (CIs) for IHD using multivariate Cox proportional hazard regression models over a 50-month period. During the follow-up period, 332 participants (1.9%) developed IHD. HRs of IHD for METS-IR quartiles 1–4 were 1.00, were 1.62 (95% CI 1.04–2.53), 1.87 (95% CI 1.20–2.91), and 2.11 (95% CI 1.35–3.30), respectively, after adjusting for potential confounding variables. A higher METS-IR precedes future IHD among Koreans without diabetes. Moreover, compared with metabolic syndrome, METS-IR had a better predictive value for IHD.

2. Insulin Resistance

Cardiovascular diseases (CVDs) are the leading cause of death worldwide in 2019, and the majority of deaths from CVD are caused by ischemic heart disease (IHD), with most deaths occurring between the ages of 30 and 70 [1][2]. IHD is a major cause of rising medical expenses. The early onset of IHD in the aging population is important because it lowers the quality of life and increases the burden of social, medical expenses [3].

Insulin resistance is defined as an impaired biological response to insulin actions in the insulin-responsive tissues and is considered key to the mechanism of metabolic syndrome [4]. The prevalence of insulin resistance has increased globally, and it is known to be from 15.5 to 46.5% of adults [5]. Previous studies have suggested that insulin resistance is significantly related to the development and progression of coronary atherosclerosis and adverse plaque characteristics and is a major risk factor for cardiovascular diseases via pathophysiological mechanisms [4]. Insulin resistance is also the common pathophysiology of prehypertension and prediabetes [6]. Moreover, some studies have found that nondiabetic individuals with IHD tend to exhibit a poorer prognosis than diabetic patients without IHD [7][8]. Thus, early detection of insulin resistance in the early stages of IHD is necessary in, for example, non-diabetes patients with metabolic risks and a high risk of IHD, preventing other diseases and reducing the socioeconomic burden for IHD.

Recently, the metabolic score for insulin resistance (METS-IR), a higher concordance with the hyperinsulinemic-euglycemic clamp, has been developed. It has been reported that METS-IR is strongly associated with hypertension and predictive abilities for type 2 diabetes [9][10]. However, to our knowledge, information is limited to the longitudinal association between METS-IR and incident IHD. Therefore, we prospectively investigated the association between METS-IR and IHD incidence in a large-scale, community-dwelling Korean population without diabetes using the Health Risk Assessment Study (HERAS) and Korea Health Insurance Review and Assessment Service (HIRA) database.

3. Conclusions

Among a community-based population of Korean adults without diabetes, we found that elevated METS-IR was positively and independently associated with IHD incidence in this longitudinal cohort study that included a 50-month follow-up. We also found that METS-IR outperformed the prediction for IHD compared to metabolic syndrome.

Insulin resistance is a low response to insulin action in adipose tissue, skeletal muscles, and the liver. Only compensatory hyperinsulinemia appears in the early stage of insulin resistance, and then, in the late stage, insulin resistance can cause the development of dyslipidemia, hypertension, CVDs, etc. [4]. According to pathophysiological mechanisms, insulin is known as the headstream of metabolic syndrome [4]. Insulin resistance is involved in atherosclerosis, and hyperglycemia plays an important role in the early stages of atherosclerosis, which is the main risk factor for developing IHD [11]. Previous studies also revealed that insulin resistance is associated with an increased risk of CVD in nondiabetic patients [12][13]. Thus, early detection of insulin resistance in adults at risk for future IHD is important for prevention and slowing the progression of IHD. HOMA-IR is the most widely used method to evaluate the degree of insulin resistance [14]. However, it is likely to cause bias depending on the use of insulin assay, including calibration setup in the kit and conversions between units [15][16]. Recently, METS-IR, a non-insulin-based insulin resistance, has been reported to have strong predictive abilities for CVD risk [9][10][17][18]. To date, there has been no research on the correlation between METS-IR and IHD.

Metabolic syndrome consists of a cluster of heart disease risk factors, including low HDL-C, high triglyceride, impaired carbohydrate metabolism, central obesity, and high blood pressure [19]. An important feature of metabolic syndrome is insulin resistance, characterized in nondiabetics by increased serum insulin levels, and it has been suggested that insulin itself is atherogenic [20]. Many epidemiological studies have indicated that metabolic syndrome is associated with IHD and used to predict the risk of IHD in the clinical field [21][22]. Our results are consistent with the findings of previous prospective studies showing that metabolic syndrome was associated with an increased incidence of IHD or CVDs [23][24]. However, the findings of our study showed that the METS-IR had higher predictive power than MetS as a dichotomous classification for IHD. Some possible explanations for this observed association deserve consideration. First, the diagnostic criteria for metabolic syndrome are inconsistent across countries. For example, some studies reported that metabolic syndrome based on Japanese criteria had a weak association with the risk of IHD and predicted IHD less effectively because of the difference in the cutoff values of waist circumference of Japanese metabolic syndrome diagnosis criteria [22]. Second, recent studies have shown that the prognostic role of metabolic syndrome does not increase more than the sum of its components [23][25]. Metabolic syndrome increases cardiovascular risk, and each of its components is associated with an increased risk of CVD [24][26][27][28]. Some studies found that an increased FPG level is a less competent indicator of cardiovascular outcomes [29]. Moreover, the role of BMI in CVDs remains debatable because different studies have presented conflicting results [30][31]. However, studies have demonstrated that triglyceride, HDL-C, glucose intolerance, and insulin levels expectedly correlate best with insulin resistance [32]. In Korea, obesity is strongly associated with insulin resistance. A combination of the triglyceride glucose (TyG) index and BMI was superior to other modified TyG indices for predicting insulin resistance in adults [33]. Previous studies have reported that the TyG index may be a useful predictive marker of CVD [34][35]. In addition, triglycerides and HDL-C have been more predictive of CVD than total cholesterol in the Asia Pacific region [36]. Thus, METS-IR may be regarded as a more favorable predictor of IHD than metabolic syndrome because the combination of triglyceride, BMI, FPG, and HDL-C may lead to a better explanation of the cardiometabolic risk for CVD outcome. Third, some studies have suggested that the risk of cardiovascular disease increases with an increase in the number of metabolic syndrome components [37][38]. Previous studies have suggested that the incidence of coronary heart disease and incident CVD risk shows a progressive increase from one to five metabolic syndrome components [39][40]. Some studies found that the risk of developing CVD increased significantly with an increasing number of metabolic syndrome components, and this trend persisted even after adjusting for sex, drinking status, and family history of hypertension, diabetes, and CVD; participants with ≥3 metabolic syndrome components were at three times higher risk of developing CVD than those without any components [37][38]. We also found that the number of components of metabolic syndrome was more highly predictive of IHD than metabolic syndrome as a dichotomous classification among individuals without diabetes. Thus, consideration of the number of risk components of metabolic syndrome may be more informative than metabolic syndrome as a dichotomous classification when determining the risk of IHD.

A significant strength of the work was that we conducted a cohort study using many Korean individuals linked to HIRA data from the universal coverage system in Korea. However, the HERAS-HIRA dataset assessed only newly developed IHD, not coronary angioplasty, myocardial resuscitation, or sudden death. Additionally, the study population may have

included some individuals with diabetes because hemoglobin A1c and 2-h postprandial glucose tests were not available at the baseline.

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