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Non-HDL cholesterol is an independent risk factor for aspirin resistance in obese patients with type 2 diabetes

Jong Dai Kim [a,1], Cheol-Young Park [a,1], Kue Jeong Ahn [b], Jae Hyoung Cho [c], Kyung Mook Choi [d], Jun Goo Kang [e], Jae Hyeon Kim [f], Ki Young Lee [g], Byung Wan Lee [h], Ji Oh Mok [i], Min Kyong Moon [j], Joong Yeol Park [k], Sung Woo Park [a,*]

[a] Division of Endocrinology and Metabolism, Department of Internal Medicine, Kangbuk Samsung Hospital, Sungkyunkwan University College of Medicine, #108 Pyung-Dong, Jongno-Gu, Seoul, Republic of Korea
[b] Division of Endocrinology and Metabolism, Department of Internal Medicine, Gangdong Kyunghee Hospital, Kyunghee University College of Medicine, #892 Dongnam-Ro, Gangdong-Gu, Seoul, Republic of Korea
[c] Division of Endocrinology and Metabolism, Department of Internal Medicine, Seoul Saint Mary's Hospital, The Catholic University of Korea College of Medicine, #222 Banpodae-Ro, Seocho-Gu, Seoul, Republic of Korea
[d] Division of Endocrinology and Metabolism, Department of Internal Medicine, Korea University Guro Hospital, Korea University College of Medicine, #148 Gurodong-Ro, Guro-Gu, Seoul, Republic of Korea
[e] Division of Endocrinology and Metabolism, Department of Internal Medicine, Pyungchon Sacred Heart Hospital, Hallym University College of Medicine, #896 Pyungchon-Dong, Dongan-Gu, Anyang, Gyunggi-Do, Republic of Korea
[f] Division of Endocrinology and Metabolism, Department of Internal Medicine, Samsung Seoul Hospital, University of Sungkyunkwan College of Medicine, #50 Ilwon-Dong, Gangnam-Gu, Seoul, Republic of Korea
[g] Division of Endocrinology and Metabolism, Department of Internal Medicine, Gil Hospital, Gacheon University College of Medicine, #774-2 Namdongdae-Ro, Namdong-Gu, Incheon, Republic of Korea
[h] Division of Endocrinology and Metabolism, Department of Internal Medicine, Severance Hospital, Yonsei University College of Medicine, #50 Yonsei-Ro, Seodaemun-Gu, Seoul, Republic of Korea
[i] Division of Endocrinology and Metabolism, Department of Internal Medicine, Bucheon Soonchunhyang Hospital, Soonchunhyang University School of Medicine, #170 Jomaru-Ro, Wonmi-Gu, Bucheon, Gyunggi-Do, Republic of Korea
[j] Division of Endocrinology and Metabolism, Department of Internal Medicine, Boramae Hospital, Seoul National University College of Medicine, #20 Boramae-Ro5, Dongjak-Gu, Seoul, Republic of Korea
[k] Division of Endocrinology and Metabolism, Department of Internal Medicine, Seoul Asan Hospital, Ulsan University, College of Medicine, #88 Olympic-Ro43, Songpa-Gu, Seoul, Republic of Korea

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ABSTRACT

Objective: We evaluated the prevalence of aspirin resistance and predictive factors for aspirin resistance in Korean type 2 diabetes patients.
Approach and results: A total of 1045 type 2 diabetes patients from 11 hospitals who were taking aspirin (100 mg/day for ≥2 weeks) and no other antiplatelet agents were studied to evaluate aspirin resistance. Aspirin resistance was measured in aspirin reaction units using VerifyNow®. Aspirin resistance was defined as ≥550 aspirin reaction units.
Aspirin resistance was detected in 102 of the 1045 subjects (prevalence 9.8%). Aspirin resistance was associated with total cholesterol ($P = 0.013$), LDL-cholesterol ($P = 0.028$), and non-HDL cholesterol ($P = 0.008$) concentrations in univariate analysis. In multivariate logistic regression analysis, only non-HDL cholesterol was associated with aspirin resistance in obese (BMI >25 kg/m^2) type 2 diabetes patients (adjusted odds ratio 3.55, 95% CI: 1.25–10.05, $P = 0.017$).
Conclusions: The prevalence of aspirin resistance in Korean type 2 diabetes patients is 9.8%. Non-HDL cholesterol is an independent risk factor for aspirin resistance, especially in obese type 2 diabetes patients.

1. Introduction

It is estimated that between 75 and 80% of diabetes-related deaths are attributable to cardiovascular complications [1].

* Corresponding author. Division of Endocrinology and Metabolism, Department of Internal Medicine, Kangbuk Samsung Hospital, Sungkyunkwan University College of Medicine, #108 Pyung-Dong, Jongno-Gu, Seoul 110-746, Republic of Korea. Tel.: +82 2 2001 2440; fax: +82 2 2001 2579.
E-mail address: sungwoo0913.park@samsung.com (S.W. Park).
[1] Jong Dai Kim and Cheol Young Park contributed equally to this study.

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Diabetes patients have a 2- to 4-fold increased risk of developing atherosclerotic cardiovascular disease [2]. Diabetes without previous myocardial infarction (MI) carries a risk for subsequent acute coronary events equivalent to non-diabetes patients with previous MI [3].

Current American Diabetes Association (ADA) guidelines recommend that aspirin be considered as a primary prevention strategy in subjects with type 1 or type 2 diabetes who are >50 years of age (men) or >60 years of age (women), and who have at least one additional major risk factor. Aspirin is recommended as a secondary prevention strategy in those with diabetes and a history of cardiovascular disease (CVD) [4].

In diabetes patients, aspirin is less effective than in non-diabetes patients for decreasing cardiovascular events [5]. Subjects with aspirin resistance have a 4-fold higher cardiovascular event rate than those without aspirin resistance [6]. And subjects with diabetes have higher aspirin resistance prevalence [4]. Once a subject begins to take aspirin, they should take it consistently. It may be helpful to identify aspirin resistance in subjects with type 2 diabetes as early as possible.

There is no consensus on when to check for aspirin resistance, and it may be useful to find clinical factors associated with aspirin resistance in type 2 diabetes patients. No large-scale, multicenter studies of aspirin resistance epidemiology in type 2 diabetes patients exist, so we investigated the prevalence of aspirin resistance and predicting factors for aspirin resistance in this multicenter study.

2. Research design and methods

2.1. Study participants

A total of 1056 type 2 diabetes patients over 20 years of age who were taking aspirin (100 mg/day for at least weeks) were recruited from 11 hospitals between March 2011 and May 2012 for our aspirin resistance research group. We excluded 11 subjects who had not had their aspirin reaction unit values checked.

Subjects were excluded if they had type 1 diabetes, gestational diabetes, were pregnant or lactating, had anemia (hemoglobin <80 g/L), thyrotoxicosis, hypothyroidism, active liver disease (aspartate aminotransferase (AST), alanine aminotransferase (ALT) ≥2 upper normal limit), liver cirrhosis or malignancy, were taking other anti-platelet agents (sarpogrelate, beraprost, indobufen, triflusal, clopidrogel, cilostazol or ticlipidine) or non-steroidal anti-inflammatory drugs (NSAIDS), were taking warfarin, coumarin or digoxin, were administered heparin within 24 h of enrollment, or had a history of bleeding disorders, a platelet count $<150 \times 10^9$/L or $>500 \times 10^9$/L, a history of myeloproliferative disorder, or a history of thrombocytopenic disorder.

The study protocol was approved by the institutional review board at each participating institution. This study was conducted in accordance with the Declaration of Helsinki. All participants provided signed, written informed consent.

2.2. Anthropemetric and laboratory measurements

Laboratory aspirin resistance was measured using a commercially available Ultegra Rapid Platelet Function Assay-ASA (VerifyNow® System; Accumetrics, SanDiego, CA, USA), which measures agonist (arachidonic acid)-induced platelet aggregation by detecting optical signal changes caused by aggregation and is expressed as aspirin reaction units (ARUs). Aspirin resistance was defined as ≥550 aspirin reaction units (ARUs) according to the manufacturer's manual.

Anthropometric measures (height, weight, abdominal circumference), systolic blood pressure (SBP), diastolic blood pressure (DBP), peak wave velocity (PWV), fasting serum glucose, fasting insulin, hemoglobin A1C (HbA1C), homeostasis model assessment-insulin resistance (HOMA-IR), blood pressure, lipid profile, complete blood count (CBC), blood urea nitrogen (BUN)/creatinine (Cr), AST/ALT, ophthalmological medical records, and 24 h urine or spot urine microalbumin values were checked. Several clinical parameters were used within six months from the time ARU was checked.

Questionnaires for diabetes duration, past medical history for angina, myocardial infarction, stroke, peripheral vascular disease, family history for angina, myocardial infarction, stroke, peripheral vascular disease, alcohol history, and smoking status were completed.

BMI (kg/m^2) was calculated as body weight in kilograms divided by height in meters squared. HbA1c levels were measured using high performance liquid chromatography (HPLC). Serum insulin levels were measured using an immunoradiometric assay. Insulin resistance was estimated using HOMA-IR, defined as [fasting plasma insulin (mU/L) × fasting plasma glucose (mmol/L)] ÷ 22.5. Chemistry values were determined using standard assays in each local laboratory. Glomerular filtration rate (GFR) was estimated by the Modification of Diet in Renal Disease (MDRD) Study Group formula [7]. A high HbA1C level is defined as above 6.5% [8]. Obesity is defined as a BMI ≥25 kg/m^2 by the WHO Asia-pacific region definition [9]. Remnant cholesterol was calculated as total cholesterol − high density lipoprotein (HDL) cholesterol − low density lipoprotein (LDL) cholesterol [10].

2.3. Statistical analysis

To compare clinical characteristics between the aspirin resistance group and aspirin sensitive group, the Chi-square test or Fisher's exact test was used for nominal variables, and a two-sample *t*-test or Mann–Whitney test was used for continuous variables. An analysis of the relationship between variables, with aspirin resistance as an independent risk factor, was performed through a backward stepwise regression method of logistic regression analysis. The odds ratios (ORs) and 95% confidence intervals (CIs) were calculated. Statistical significance was considered a two-tailed *P*-value<0.05. Statistical analysis was performed using PASW Statistics version 18 (SPSS Inc., Chicago, IL, U.S.A).

3. Results

We found that 102 of 1045 subjects had aspirin resistance; the prevalence of aspirin resistance was thus 9.8%. The clinical characteristics and parameters of the aspirin resistance group and aspirin non-resistance groups are described in Table 1. There was no difference in aspirin resistance by sex. A history of hypertension was more common in the aspirin non-resistant group; however, there was no difference in blood pressure values between the two groups by virtue of medication. Fasting serum glucose and HbA1C levels were higher in the aspirin resistant group, but were not significantly different between the two groups ($P = 0.158$ and 0.373, respectively). Among lipid parameters, non-HDL cholesterol ($P = 0.008$), total cholesterol ($P = 0.013$), and LDL cholesterol ($P = 0.028$) levels were associated with aspirin resistance. HDL, triglyceride (TG) levels and remnant cholesterol were not significantly associated with aspirin resistance ($P = 0.096$, 0.316 and 0.166 respectively), but TG/HDL ratio was significantly higher in the aspirin resistance group ($P = 0.036$).

We investigated the prevalence of aspirin resistance by non-HDL quartile and we defined high non-HDL cholesterol as the highest non-HDL cholesterol quartile (≥3.18 mmol/L). Prevalence of aspirin resistance was increased according to non-HDL quartile (Fig. 1). In multivariate logistic regression analysis, only high non-