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Impact of serum 1,5-anhydro-*d*-glucitol level on prediction of major adverse cardiac and cerebrovascular events in non-diabetic patients without coronary artery disease

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ABSTRACT

Background and aims: Increasing evidence has demonstrated that postprandial hyperglycemia and fluctuation of glucose level affect cardiovascular events. The serum 1,5-anhydro-*d*-glucitol (1,5-AG) level rapidly decreases concomitantly with urinary glucose excretion in hyperglycemia and is a useful clinical marker of short-term glycemic status. However, there is few established evidence regarding the predictive value of 1,5-AG for cardiovascular events in individuals without diabetes mellitus (DM). The aim of this study is 1) to prove predictive value of 1,5-AG for cardiovascular events in high risk population, and 2) the predictive value is true of even in non-diabetic population.

Methods: Serum 1,5-AG values and coronary angiograms of 889 patients were evaluated. The study patients were divided into two groups (1,5-AG<10.0 μg/ml-group and 1,5-AG≥10.0 μg/ml-group) by their measured 1,5-AG values. They were followed-up and information regarding major adverse cardiac and cerebrovascular events (MACCE) was collected. MACCE consists of all causes of death, stroke, non-fatal myocardial infarction and cardiovascular hospitalization.

Results: During the follow-up period (757 ± 357days), 216 patients presented with MACCE. In all patients, the 1,5-AG <10.0 μg/ml -group demonstrated significantly higher risk of MACCE (adjusted hazard ratio 1.63). Even in non-DM patients without coronary artery disease, the 1,5-AG <10.0 μg/m-group showed significantly higher risk of MACCE (adjusted hazard ratio 2.34). Similar results were found even if the events were limited to: all cause death, non-fatal myocardial infarction and stroke (adjusted hazard ratio 4.07) or all cause death (adjusted hazard ratio 3.54).

Conclusions: Serum 1,5-AG value predicts MACCE even in non-DM patients without coronary artery disease.

1. Introduction

Type 2 diabetes mellitus (DM) severely impairs the prognosis of patients with cardiovascular disease (CVD) [1]. Because of the established relationship between hemoglobin A1c (HbA1c) and micro-vascular disease, the American Diabetes Association recommends the evaluation of HbA1c as a criterion for diagnosing DM [2]. However, in patients with advanced DM, intensive glucose control guided by HbA1c values does not always reduce macro-vascular complications, but in some cases increases the risk of death [3–5]. To reduce macro-vascular complications, early diagnosis and early intervention for glycemic abnormalities are important [6]. Increasing evidence has demonstrated that postprandial hyperglycemia and glucose level fluctuation affect mortality and CVD progression [7–13]. 1,5-anhydro-*d*-glucitol (1,5-AG) is a monosaccharide originating primarily from dietary sources that is found in constant concentrations in the blood in normal glycemic status. The serum 1,5-AG level rapidly decreases concomitantly with urinary glucose excretion in hyperglycemia (especially when the serum glucose level exceeds the threshold of urine glucose excretion of 160–180 mg/dl) and is an important and feasible clinical marker of short-term glycemic status [14,15]. Some previous reports have shown that 1,5-AG is superior to HbA1c in detecting the presence of coronary artery disease (CAD).[16 17] In

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addition, 1,5-AG values can predict the risk of cardiovascular events [18,19]. However, there is currently no established evidence regarding the predictive values of 1,5-AG for cardiovascular events, particularly in the non-DM population. The aim of this study is 1) to prove predictive value of 1,5-AG for cardiovascular events in high risk population, and 2) the predictive value is true of even in non-diabetic population.

2. Patients and methods

2.1. Study patients

A total of 926 consecutive patients who were admitted to the National Center for Global Health and Medicine between July 2011 and October 2014 and had undergone their first elective coronary angiography were offered the opportunity to be included in the study. Eight hundred and eighty-nine patients consented to the study, and their serum 1,5-AG values were evaluated. They were followed up and their cardiovascular events were collected. Coronary angiographies were performed to assess ischemic heart disease, heart failure, valvular disease, arhythmia and to preoperatively investigate for ischemic heart disease and other cardiac dysfunction (Supplementary Table 1). This study complied with the Declaration of Helsinki and was approved by the local ethics committee of National Center for Global Health and Medicine (NCGM-G-001896-00).

2.2. Measurement of 1,5-AG

The 1,5-AG levels were measured by colorimetric analysis using a Lana 1,5-AG auto liquid automatic analyzer (JCA-BM8060, JEOL Ltd.). The coefficient of variation was less than 5%. The blood samples were obtained within 7 days prior to the day of the corresponding coronary angiographies.

2.3. Definitions

Study patients were divided into two groups (1,5-AG<10.0 μg/ml-group and 1,5-AG≥10.0 μg/ml -group) by measured 1,5-AG values. This cut-off value was decided by a previous report and best cut-off point by receiver operating characteristic (ROC) curve in our study (Supplementary Fig. 1). Yamanouchi et al. showed that even in patients with good glycemic control by HbA1c value, a lower concentration of 1,5AG (<10.0 μg/ml) suggested a higher mean daily plasma glucose concentration [20]. Best cut-off point for prediction of MACCE by ROC curve in our study was 10.2 μg/ml. We adopted 10.0 μg/ml as the cut-off value (not 10.2 μg/ml) because of the broad utility.

Diabetes mellitus was defined as fasting plasma glucose ≥126 mg/dl and HbA1c ≥ 6.5% National Glycohemoglobin Standardization Program (NGSP), or the use of oral hypoglycemic agents or insulin. Major adverse cardiac and cerebrovascular events (MACCE) consist of all causes of death, stroke, non-fatal myocardial infarction (MI) and cardiovascular hospitalization. The scheduled hospitalization for intervention to coronary lesions which were detected by the first coronary angiography were excluded from MACCE. All cardiovascular outcomes were collected by review of clinical records by experienced cardiologists.

2.4. Angiographic analysis

Coronary angiographies were performed by experienced cardiologists using standard techniques in all study patients. All of the coronary arteries were injected and at least two views of the right coronary arteries and four views of the left coronary arteries were evaluated. The prevalence of CAD was analyzed by two or three experienced interventional cardiologists who were blinded to the patients' clinical data. The CAD prevalence was defined as the presence of significant stenosis (more than 75% stenosis by visual estimation) in the main epicardial coronary arteries. In the event of a disagreement, the opinion of a third observer was required, and the final decision was made by consensus of all three observers.

2.5. Statistical analysis

The Kolmogorov–Smirnov test was used to evaluate normal distribution. The continuous variables are described as medians and interquartile ranges (median [25th, 75th percentiles]) or mean values ± SDs. The categorical variables are presented as counts or proportions (percentages). The Mann-Whitney *U* test was used to compare the continuous variables. The occurrence of cardiovascular outcomes (1. MACCE, 2. All cause death, Non-fatal MI and Stroke, 3. All cause death) in both groups was evaluated using Kaplan-Meier methodology and compared using the log-rank test. To evaluate the associations of 1,5-AG with incident cardiovascular outcomes, Cox proportional hazards models were used to estimate hazard ratios and their corresponding 95% confidence intervals. In multivariate analysis, sex, age, hypertension, dyslipidemia, statin user, smoking status, estimated glomerular filtration rate and 1,5-AG groups were adjusted. These variables were considered traditional coronary risk factors and the main concerns in this study. Prevalence of DM and, HbA1c and serum glucose values had strong interaction with 1,5-AG value. Therefore, these valuables were not included in multivariate models. Prevalence of CAD also had significant interaction with 1,5-AG value. In addition, presence of CAD is directly associated with cardiovascular events in general. Therefore, analysis was performed in “All patients”, “Patients without CAD” and “Non-DM patients without CAD”. A *p*-value <0.05 was considered to be significant. SPSS ver. 23 (IBM Japan, Tokyo) was used for the analyses.

3. Results

3.1. Patient characteristics

Among the 926 consecutive candidates of this study, 889 patients consented to a blood sample and review of their clinical records. The median patient age was 71 years; 582 (65%) patients were male, and 434 patients (49%) had CAD. The patients were divided into two groups according to their 1,5-AG values (1,5-AG<10.0 μg/ml-group, N = 267 *vs.* 1,5-AG≥10.0 μg/ml-group, N = 622). The median values and interquartile ranges of the 1,5-AG in all study patients, in the 1,5-AG<10.0 μg/ml-group and the 1,5-AG≥10.0 μg/ml-group were 15.3 [8.3, 22.0] μg/ml, 5.6 [2.5, 7.7] μg/ml and 19.1 [14.4, 24.5] μg/ml, respectively. The 1,5-AG<10.0 μg/ml-group had a significantly higher prevalence of DM, hypertension, dyslipidemia and CAD (Table 1). There were 455 (51%) patients without CAD and 369 (42%) non-DM patients without CAD. During the follow up period (757 ± 357 days), 216 patients presented with MACCE.

3.2. Predictive values of 1,5-AG measurement for cardiovascular outcomes

In all patients (n = 889), Kaplan- Meier curves showed that the 1,5-AG<10.0 μg/ml-group demonstrated significantly higher risk of MACCE. The 1,5-AG<10.0 μg/ml-group also presented significantly higher risk of all cause death, non-fatal MI and stroke, and all cause death (Fig. 1). The adjusted hazard ratios of the 1,5-AG<10.0 μg/ml-group (Reference; 1,5-AG≥10.0 μg/ml-group) for each outcome