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Independent association between glycated hemoglobin and arterial stiffness in healthy men

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ABSTRACT

Aims/Introduction: Many studies have reported that high levels of glycated hemoglobin (HbA1c) are strongly associated with an increased risk of cardiovascular disease. Many researchers have not studied the association of HbA1c with various subclinical atherosclerosis phenotypes. We evaluated the impact of HbA1c on arterial stiffness and atherosclerosis in healthy Korean healthy men.

Materials and Methods: The study population included healthy adult men who participated in health check-ups. All participants fasted for at least 8 h before taking the blood sample for fasting blood glucose, HbA1c, total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol and triglyceride. Arterial stiffness was measured using brachial-ankle pulse wave velocity. Hierarchical regression analysis allowed us to determine the relationship between brachial-ankle pulse wave velocity (baPWV) and potential risk factors for cardiovascular disease.

Results: Age and HbA1c were significantly related to baPWV, in model 1. In model 2, blood pressure was added to model 1. Systolic blood pressure was a more significant variable, which was more affected on baPWV than diastolic blood pressure. In the case of model 3, we included all variables regarding arterial stiffness. According to model 3, the most explainable variable was age, and then systolic blood pressure, body mass index and triglyceride, respectively.

Conclusions: We analyzed the associations between HbA1c, which is one of the risk factors, and arterial stiffness independently. An arterial stiffness measurement using baPWV can show the level of severity of the arteriosclerosis. When the level of stiffness has been increased, we could assume that the risk of arteriosclerosis would be increased. It can also be related to the increase of the risk of cardiovascular disease.

INTRODUCTION

Glycated hemoglobin (HbA1c) is a form of hemoglobin used primarily to identify the average plasma glucose concentration over prolonged periods of time. Glycation of hemoglobin has been associated with cardiovascular disease, nephropathy and retinopathy in diabetes mellitus. The 2010 American Diabetes Association Standards of Medical Care in Diabetes added HbA1c ≥6.5% as another criteria for the diagnosis of diabetes mellitus[1].

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Many studies have reported that high levels of HbA1c are strongly associated with an increased risk of cardiovascular disease (CVD) and microvascular complications[2–4], such as nephropathy and retinopathy. The study by Gerstein *et al.*[5] showed a strong dose–response relationship between HbA1c and the risk of acute myocardial infarction. Furthermore, elevated HbA1c levels, even within the prediabetic range, have been associated with increased risk of cardiovascular disease (CVD) in general populations[6]. However, the underlying mechanisms remain unknown[7]. It is not clear whether the unfavorable prognosis is attributable to CVD[8]. In one general population cohort study,

HbA1c was not associated with incident large-vessel disease[9]. Even after analyzing the results of the United Kingdom Prospective Diabetes Study (UKPDS) study, which is the largest and longest-running study of type 2 diabetes, it is unknown whether glucose control reduces a patient's risk of CVD[10]. However, recent studies have also suggested that HbA1c was significantly associated with large-vessel disease (coronary heart disease, stroke and peripheral artery disease) in persons with diabetes[11].

Pulse wave velocity (PWV), a classic evaluation of arterial dispensability[12], is a significant and independent predictor of cardiovascular mortality in patients with essential hypertension[13]. Abnormality in PWV could be a sign of arterial stiffness and a marker of atherosclerosis[14–18]. PWV has been identified as a strong independent predictor of cardiovascular risk[19,20]. A recent study has identified that PWV is independent of age and other conservative risk factors, and is identified as the most significant predictive factor in cardiovascular mortality[20].

Many studies have evaluated the association between these measures and HbA1c; however, most researchers have only studied the association of HbA1c with one or two variables[14,21]. Therefore, it has been difficult to assess the association between HbA1c and various subclinical atherosclerosis phenotypes. Furthermore, although HbA1c is a risk factor of atherosclerosis risk, studies lack representing risk factors of other cardiovascular disease, and atherosclerosis and its effect with PWV. Moreover, studies representing a healthy population in regard to HbA1c and PWV are not well represented. In the present study, we measured HbA1c, brachial-ankle PWV (baPWV) and ankle brachial pressure index (ABI), and evaluated the impact of HbA1c on the arterial stiffness and atherosclerosis in healthy Korean men.

METHODS

The study population included healthy adult men who participated in health check-ups from January 2007 to December 2007 at the Kangbuk Samsung Hospital, Seoul, Korea (n = 2,777). The clinical data including age, smoking, drinking, past diseases and drug use were collected by self-administered questionnaire. All participants fasted for at least for 8 h before taking the blood sample for fasting blood sugar, HbA1c, total cholesterol, high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C) and triglyceride (TG). FBS was assessed by the hexokinase method using ADVIA 1650 Autoanalyzer (Bayer Diagnostics, Leverkusen, Germany). HbA1c was assessed by using D-10 (Bio-Rad Laboratories, Hercules, CA, USA) high-performance lipid chromatography method. The enzymatic method was used to assess the total cholesterol, while HDL-C and LDL-C were assessed using the elimination-catalase method. Triglyceride was assessed by using the glycerol phosphate oxidase method. Arterial stiffness was measured using baPWV.

Those presenting with CVD, diabetes, hyperlipidemia and overall diseases in the results of the routine check-up were excluded from the study. Those who were taking antihypertensive treatment or hormone replacement therapy were also excluded from the study. Those who represented ABI <0.9 were excluded from the study. Overall, 2,777 healthy men were reviewed as participants of the study. The participants showed an average blood creatinine level of <1.3 mg/dL.

The baPWV, which provides qualitatively similar information to that derived from central arterial stiffness[22], was measured by the volume plethysmographic method. The baPWV was measured at rest using a vascular testing device (Form PWV/ABI; Colin Medical Technology, Komaki, Japan). Recordings were made in triplicate with participants in the supine position (automatic waveform analyzer: VP-2000; Colin Co, Komaki, Japan). Right baPWV and left baPWV were measured, and the mean value was considered as maximum baPWV.

The present cross-sectional study was approved by the institutional review board of Kangbuk Samsung Hospital. Data are presented as mean ± SD or actual numbers. The general characteristics of participants were average age, baPWV and other factors were assessed using Pearson's correlation. Multiple linear regression analysis was carried out using baPWV as a dependent variable and independent variables that showed significance assessing the affect of HbA1c on these factors. To analyze the interaction effect of baPWV, hierarchical regression analysis was carried out using model 1, 2 and 3. Hierarchical regression analysis of the relationship between baPWV and other associated variables showed that baPWV was associated with Age, BMI, HbA1c, blood pressure, lipoprotein and triglyceride. TG was log transformed to improve the normal distributions. A P-value <0.05 showed statistical significance. All analyses were carried out using a statistical software package (PASW SPSS 17.0 for Windows; SPSS, Chicago, IL, USA).

RESULTS

The clinical characteristics of the study participants are listed in Table 1. In linear regression analysis, baPWV was significantly positively associated with age, SBP, DBP, FBS, HbA1c, TG, total cholesterol, HDL-C and LDL-C (Table 2). BMI was negatively associated with baPWV.

Hierarchical regression analysis of the relationship between baPWV and other associated variables showed that baPWV was significantly positively associated with age, BMI, HbA1c, blood pressure, lipoprotein and triglyceride. Specifically, model 1 included age, BMI and HbA1c. Those variables were significantly related to baPWV under the 95% level. BMI affected baPWV negatively, but not significantly. In model 2, blood pressure was added to model 1. Systolic blood pressure was a more significant variable, baPWV was more affected by systolic blood pressure than diastolic blood pressure. BMI was a negatively significant variable. In the case of model 3, we included all variables regarding arterial stiffness. According to model 3, the most explainable variable was age, and then systolic blood pressure, BMI and triglyceride, respectively. Lipid profiles, such as HDL and LDL, were also significant in model 3 but the beta values were lower than other variables. The explanatory power of the model was increased more and more when the variables were added. Therefore, the R^2 values were becoming significantly higher (Table 3).

Table 1 | Characteristics of participants

Characteristics	Mean ± SD *n* (%)
Age (years)	47.1 ± 9.4
BMI (kg/m^2)	24.4 ± 2.8
SBP (mmHg)	118.4 ± 13.8
DBP (mmHg)	77.0 ± 8.7
FBS (mg/dL)	97.1 ± 14.2
HbA1c	5.5 ± 0.4
Total cholesterol (mg/dL)	196.8 ± 34.0
HDL-C (mg/dL)	47.7 ± 10.3
LDL-C (mg/dL)	118.7 ± 30.0
TG	161.3 ± 21.4
Smoking	
Smoker	1,260 (45.4%)
Ex-smoker	475 (17.1%)
Non-smoker	1,042 (37.5%)
baPWV	1,392.4 ± 171.1

n = 2,777. baPWV, brachial-ankle pulse wave velocity; BMI, body mass index; DBP, diastolic blood pressure; FBS, fasting blood sugar; HbA1c, glycated hemoglobin; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; SBP, systolic blood pressure; SD, standard deviation; TG, triglyceride.

Table 2 | Correlation of brachial-ankle pulse wave velocity and risk factors regarding arterial stiffness

Clinical variable	*r* (max) Mean	*P*-value
Age	0.359	<0.001
BMI	–0.056	0.003
SBP (mmHg)	0.325	<0.001
DBP (mmHg)	0.267	<0.001
FBS (mg/dL)	0.133	<0.001
HbA1c	0.144	<0.001
Total cholesterol	0.070	<0.001
HDL-C	0.045	0.018
LDL-C	0.042	0.026
TG	0.154	0.031
Smoking		
Smoker	1,387.48	0.316
Ex-smoker	1,392.60	
Non-smoker	1,398.36	

baPWV, brachial-ankle pulse wave velocity; BMI, body mass index; DBP, diastolic blood pressure; FBS, fasting blood sugar; HbA1c, glycated hemoglobin; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; SBP, systolic blood pressure; TG, triglyceride.

DISCUSSION

PWV, another measure of atherosclerosis, can reflect arterial stiffness, and is a marker of both the severity of vascular damage and the prognosis of atherosclerotic vascular disease in patients with hypertension and diabetes[23]. A recent report suggested that baPWV can be measured automatically by the oscillometric method within a few minutes, and might be useful as a marker of atherosclerotic vascular damage[24]. Hyperglycemia is also known to increase arterial stiffening[25]. Glucose, insulin and triglycerides contributed synergistically to the increase in arterial stiffness in type 2 diabetes[26].

In the present study, we independently analyzed the associations between HbA1c, one of the risk factors regarding cardiovascular diseases and arterial stiffness. We showed that healthy men have increased arterial stiffness with increased HbA1c level. An arterial stiffness measurement using baPWV could show the level of severity of arteriosclerosis. When the level of stiffness has increased, we could assume that the risk of cardiovascular disease would be increased. Arterial stiffness using baPWV reflects the level of arteriosclerosis. Increasing stiffness is an independent risk factor for cardiovascular diseases. PWV was strongly influenced by high blood pressure, age and HbA1C, in addition to the number of metabolic syndrome components[27]. Increased baPWV was also reported as an early marker of arteriosclerosis in mildly hyperglycemic patients[28].

Choi *et al.*[21] referred to the connection between baPWV, and age, sex, diabetes mellitus, hemodialysis, smoking, hyperlipidemia and blood pressure in univariate analysis. Regarding the multivariate analysis, in order of age, hemodialysis and systolic blood pressure had an influence on baPWV. Other studies reported that the powerful risk factors of baPWV were age, systolic blood pressure and sex. In particular, baPWV had a correlation with several cardiovascular risk factors and metabolic syndrome factors[14]. Meanwhile, Yun *et al.*[29] inspected the baPWV of diabetes mellitus patients for 1-year follow up, and reported that the most powerful factor was blood pressure. Also, in this study, the high systolic blood pressure influenced baPWV positively. Blood pressure elevation *per se* is a mechanical factor responsible for arterial stiffening[25].

Likewise, when several cardiovascular risk factors interact with each other, it is hard to seize the single effect. So, comprehensive management is important for controlling the artificial stiffness related to arteriosclerosis. Also, the effects of risk factors were different to each other individually. Therefore, it is important to verify the specific factors for efficient management.

In the present study, we analyzed the independent association between HbA1c and arterial stiffness in healthy men. The present results were consistent with some of the previous studies. The relationship between high HbA1c (5.7–6.4%) and increased arterial stiffness was reported in a Chinese adult population[30]. The increased arterial stiffness measured by baPWV was positively associated with HbA1c levels in patients with type 2 diabetes[31]. The present findings suggested that HbA1c as the marker of long-term glucose exposure might lead to increased arterial stiffness in healthy individuals. The explanatory mechanisms of how chronic glucose exposure could influence arterial stiffening are not fully understood[30]. BaPWV positively correlated with HbA1c and duration of diabetes in

Table 3 | Hierarchical regression analysis of the relationship between brachial-ankle pulse wave velocity and other associated variables

	Model 1			Model 2			Model 3		
	β	*t*-value	*P*-value	β	*t*-value	*P*-value	β	*t*-value	*P*-value
Age	0.333	18.605	<0.001	0.311	17.919	<0.001	0.319	18.461	<0.001
BMI	−0.033	−1.801	0.072	−0.102	−5.820	<0.001	−0.127	−6.833	<0.001
HbA1c	0.080	4.376	<0.001	0.073	4.233	<0.001	0.055	3.119	0.002
SBP				0.234	8.739	<0.001	0.236	8.894	<0.001
DBP				0.100	3.722	<0.001	0.084	3.139	0.002
HDL-C							0.034	1.896	0.058
LDL-C							0.048	2.806	0.005
TG							0.116	6.316	<0.001
R^2	0.135			0.230			0.242		
F	144.389			165.911			110.760		
P-value	<0.001			<0.001			0.001		

baPWV, brachial-ankle pulse wave velocity; BMI, body mass index; DBP, diastolic blood pressure; HbA1c, glycated hemoglobin; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; SBP, systolic blood pressure; TG, triglyceride.

patients with diabetes and hypertension[31]. Duration of type 2 diabetes and HbA1c were also independent predictors of arterial stiffness, although they explained just 1.3% and 0.9% of the variance, respectively[32]. Chronic hyperglycemia causes glycation of the proteins in the arterial wall, and these advanced glycation end-products have been associated with increased vascular stiffness, organ damage and atherosclerosis[33]. An increase in HbA1c of 2% resulted in a 1.9% higher PWV ($P = 0.0174$). It appears that changes in HbA1c were independently associated with change in PWV over follow up[34].

In contrast, HbA1c was not associated with measures of arterial stiffness[35]. Thus, as it is relatively short-lived, HbA1c might not serve well as a biomarker for early subclinical atherosclerotic changes in older adults without diabetes. An important consideration in the evaluation of HbA1c as an early biomarker for subclinical cardiovascular disease is its relatively rapid turnover of months rather than years because of the limited half-life of erythrocytes.

According to the present results, the significant variables regarding the correlation of baPWV were age, BMI, systolic and diastolic blood pressure, fasting blood sugar, HbA1c, total cholesterol, HDL and LDL cholesterol, and triglyceride. In particular, BMI is negatively related to baPWV. Harada *et al.*[36] also reported this result regarding the negatively relationship between baPWV and BMI. The most effective variables are BP and age, and then blood pressure is significantly related to baPWV. However, even they are not as critical as age or blood pressure, lipid profiles such as HDL, LDL and triglyceride are also important factors regarding baPWV. Choi *et al.*[21] reported that high baPWV is related to cardiovascular-related chronic disease risk; and Asmar *et al.*[37] reported that, excluding age, blood pressure is the most powerful variable among several risk factors. Meanwhile, another study reported that the higher the age and blood pressure, the lower the baPWV[14]. In addition, Yun *et al.*[29] reported that according to their 1-year follow-up study, the most severe risk factor regarding baPWV among type 2 diabetes patients is blood pressure. Likewise, the risk factors regarding cardiovascular diseases are very complicated in relation to each other. Therefore, it is impossible to discover the single effect power among a variety of interactions. If we consider arterial stiffness, we should control the several risk factors comprehensively. The level of risk factors' effectiveness is changed by personal characteristics. Therefore, we should check the customized risk factor for efficient management.

In summary, baPWV in healthy men, age and blood pressure were very significant factors that were affected by HbA1c, independently. According to Takechi[38], the value of baPWV and SBP showed a significant positive correlation. In addition, Kinouchi *et al.*[39] mentioned that HbA1c level was associated with an increased baPWV. Furthermore, many studies reported a positive correlation between HbA1c and artificial stiffness[40–42]. Therefore, we can use an invasive index, such as baPWV, as a cardiovascular risk factor.

Nevertheless, we had some limitations. First, the present study was a cross-sectional retrospective study, so we could not grasp the causal effect precisely. Second, we were not able to include the socioeconomic variables because of incomplete data. Third, even though baPWV could change as time went by, we did not use the time limitation. Despite these limitations, according to the present study, we evaluated the cardiovascular-related risk and the malfunctions of vessels using a simple index, baPWV, for healthy men, and we found the relationships of HbA1c.

DISCLOSURE

The authors declare no conflict of interest.

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