

6.5% 미만의 당화혈색소와 경동맥 내막중격 두께의 관계

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The Correlation between Hemoglobin A1c and Common Carotid Artery Intima Medial Thickness of Both Genders with Less Than 6.5% HbA1c Based on Ultrasound Measurement

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Background: The glycemic control in diabetes is well known to arouse a medical risk of macrovascular regions. This study aimed for exploring the relationship between carotid artery intima media thickness (IMT) and the risk triggers of macrovascular diseases in the group of glycated hemoglobin value less than 6.5%.

Methods: The subjects were made of 336 health-check examinees in a university hospital and tested by glycated hemoglobin (HbA1c) including ultrasound application on carotid artery IMT to be measured. The relationship between values of HbA1c and carotid artery IMT was reviewed by use of Pearson's correlation, and then influential causes on the carotid artery IMT were analyzed with multiple linear regression models.

Results: Elements like age and fasting plasma glucose were associated with the carotid artery IMT in both men and women. HbA1c, C-reactive protein (CRP) in men and waist to hip ratio (WHR), high-density lipoprotein (HDL)-cholesterol in women showed statistically significant association with the carotid artery IMT. Age and HbA1c were recognized as variables affecting on the carotid artery IMT in men, in contrast, age was only a significant affecting factor in women with regarding various considerations such as fasting plasma glucose, CRP, HDL, WHR and smoking.

Conclusions: Our clinical investigation revealed that HbA1c was associated with the carotid artery IMT in normal and pre-diabetes with HbA1c less than 6.5%. The outcome might suggest preliminary glucose control be monitored and managed in order to detect and regulate the impairment of macrovascular diseases prior to the occurrence of diabetes.

Korean J Health Promot 2015;15(2):47-53

Keywords: Hemoglobin A1c, Carotid arteries, Carotid intima-media thickness, Diabetes mellitus

INTRODUCTION

It is very important to detect diabetes mellitus in its early stage in order to prevent vascular complications which

influence possibly on various arterial complications attributed by diabetes to increase the percentage of mortality. This metastasis is quite common cases to be found with chronic advanced inflammatory vessels when the patient is diagnosed as a diabetes mellitus.¹⁾

Moreover, as depending on the maintenance of the blood glucose level, the risk of cardiovascular malfunction could be also enhanced in spite of the blood glucose level in diabetes patients as well as primitive diabetes with normal range of blood glucose.^{2,3)}

■ Received : November 9, 2014 ■ Accepted : April 22, 2015

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Therefore, the usual condition of the blood glucose could elicit adverse effects on macrovascular sicknesses despite of non-diabetes, especially, impaired glucose tolerance (IGT) and impaired fasting glucose (IFG) which are prior state of progression into the diabetes are recognized as obvious risk factors of cardiovascular disease.^{4,5)}

In the observation upon carotid artery intima media thickness (IMT) and IGT, IGT was present at a significant risk element of cardiovascular disorders,⁶⁾ in contrast, IFG could not increase the thickness of intima media of blood vessel,⁷⁾ but IFG combined with IGT could cause arteriosclerotic changes of carotid artery.⁸⁾

As the blood test of HbA1c is becoming an accurate and standardized method, International Expert Committee such as American Diabetes Association (ADA), European Association for the Study of Diabetes and International Diabetes Federation suggested that HbA1c over 6.5% could be an absolute indication for the diagnosis of diabetes.⁹⁻¹¹⁾ Both ADA and Korean Diabetes Association are choosing the indication of HbA1c to confirm diabetes and pre-diabetes which is an initiative stage ongoing of genuine diabetes.¹²⁾

In addition, HbA1c is a useful measurement for estimating prognosis and predicting advancement of macrovascular complications in asymptomatic and symptomatic diabetes patients.¹³⁾ It is also one of important indicator to estimate the usual blood glucose status.

The thickness of intima media of carotid artery investigated by the ultrasound is corresponding to the actual thickness of the layer,^{14,15)} which is closely proven to be related with cardiovascular and cerebrovascular maladies in terms of various kinds of studies.¹⁶⁻¹⁸⁾ Recent research on the macrovascular complication of diabetes is being accomplished by device uses like ultrasound equipment.

The early discovery of this progressing change on arterial wall-thickening among non-patients by categorizing various considerations affecting on the modification of wall thickness such as age, hypertension, obesity, cholesterol, and cigarette smoking, which should be further surveyed prior to the medical decision about diabetes in male and female.

In this study, the following hypothesis was clinically attempted to test among individual subjects below 6.5% HbA1c: HbA1c related carotid artery wall changes involve both intima medial thickness on each of male and female ones.

METHODS

1. Subjects

Our clinical research began to accumulate the medical records of health examinees in a health promotion center of the University hospital. It consists of women and men (age 30-70 yr) who had no medical history of diabetes mellitus, cardiovascular and cerebrovascular diseases at baseline. The examination was completed from Jan 2010 to Jun 2012 with a total of 336 subjects (men, n=225; women, n=111) met by this criteria including the written informed consent, and they got involved to have IMT components (echogenic and echolucent layer) measures during health check-up.

2. Measurement

Smoking status, history of diabetes, hypertension, cardiovascular disease and dyslipidemia were sought by the interview and self-report through the questionnaire including the history of medication in all participants. Fasting plasma glucose, HbA1c, C-reactive protein and lipid profile such as total cholesterol, high-density lipoprotein (HDL)-cholesterol, low-density lipoprotein (LDL)-cholesterol and triglyceride (TG) were counted by the blood test while doing health examination. In addition, body mass index (BMI: kg/m²) and Waist to Hip Ratio (WHR) were assessed according to the World Health Organisation's data gathering protocol,¹⁹⁾ which was figured by the waist circumference to be measured at the midpoint between the lower margin of the last palpable rib and the top of the iliac crest, using a stretch-resistant tape that provides a constant 100 g tension and hip circumference for being measured around the widest portion of the buttocks, with the tape parallel to the floor.

The maximum intima medial thickness of common carotid artery and blood pressure were done by the ultrasound and automatic blood pressure monitor sphygmomanometer P-203RV II^R (Colin cooperation).

The criterion of hypertension was applied to the systolic pressure over 140 mmHg or diastolic pressure over 90 mmHg and previously reported hypertension containing the medication of anti-hypertensive drug. Diabetes confirmation was made of the result of HbA1c over 6.5%, fasting plasma glucose (FPG) over 126 mg/dL, and current anti-diabetic medication or insulin injection as well as pre-

vious diagnosis of diabetes. The history of percutaneous coronary angioplasty, and use of anti-platelet and anti-coagulant belonged to vascular disease criteria. Smoking status was classified by past, current, and non-smokers.

Arterial images were acquired with a high defined B-mode ultrasound scanner (sonoline G40^R, Siemens, Erlangen, Germany) with 13.5 MHz linear-array transducer). IMT measured subjects at the far wall of the artery in the 1 cm section of the common carotid 0.25 cm proximal to the bulb. The subjects were scanned along with two sides (right and left). The IMT maximum was determined by one of them which was thicker.¹⁴⁾ A single sonographer and ultrasound image analyst were used throughout the study to avoid inter-observer variation.

Prediabetes called a high risk group of diabetes is considered when it comes to 5.7 to 6.4% HbA1c.¹²⁾ As the study of Salonen and Salonen,²⁰⁾ common carotid artery IMT was verified as being abnormal with IMT measurement over 1.00 mm. Lipid profile was adopted to the criteria of Adult Treatment Panel III.

3. Statistic analysis

The data were analyzed with SPSS version 20.0 program (SPSS Inc., Chicago, IL, USA) and described with mean± standard deviation. Variables among groups which were sorted by male and female combining HbA1c level (<5.7% vs. >5.7%) were in comparison with each other by *t*-test.

The relationship of IMT and influential factors was proven by Pearson's correlation and multiple linear regressions showing the most affective factor on IMT in comparison with others ($P<0.05$).

RESULTS

1. Clinical features

Total subjects are composed of 336 (male n=225, female n=111), with having normal groups as HbA1c<5.7% was 225 subjects (144 male, 81 female), highly predisposed diabetes groups as HbA1c≥5.7% was 111 subjects (81 male, 30 female).

Having compared normal HbA1c group, the high risk one resulted in significant differences of FPG, carotid IMT, WHR, BMI, TG, LDL-cholesterol in men ($P<0.05$). There were no appreciable differences of systolic and diastolic blood pressure, total cholesterol, HDL cholesterol and C-reactive protein (CRP) between them.

In the high risk group of females, FPG, carotid IMT, BMI, HDL-cholesterol showed a meaningful discrepancies compared to normal female group ($P<0.05$). In contrast to the result of males, the high risk female group did not account for differences in WHR, TG, and LDL.

In both male and female, FPG, IMT, BMI, and HbA1c were common distinctive factors between high risk and normal group of HbA1c (Table 1).

Table 1. Clinical characteristics of participants with HbA1c of less than 6.5%^a

	Male			Female		
	HbA1c<5.7% (n=144)	HbA1c≥5.7% (n=81)	<i>P</i>	HbA1c<5.7% (n=81)	HbA1c≥5.7% (n=30)	<i>P</i>
Age, y	48.35±8.85	50.79±8.95	0.050	50.25±9.03	53.84±8.49	0.055
HbA1c, %	5.326±0.21	5.896±0.22	<0.001	5.300±0.24	5.922±0.21	<0.001
FPG, mg/dL	86.00±9.10	92.60±10.89	<0.001	82.67±8.56	97.13±9.80	<0.001
IMT, mm	0.653±0.229	0.743±0.303	0.021	0.575±0.176	0.656±0.231	0.047
SBP, mmHg	122.56±11.37	124.05±12.18	0.357	116.75±15.01	121.41±17.40	0.159
DBP, mmHg	76.83±7.82	78.12±8.76	0.257	73.22±9.16	72.59±10.45	0.753
WHR	0.89±0.05	0.91±0.06	0.006	0.822±0.07	0.848±0.05	0.055
BMI, kg/m ²	24.62±2.98	26.16±3.70	0.002	22.37±2.96	24.53±4.42	0.015
TC, mg/dL	203.06±31.87	211.72±32.08	0.052	206.53±33.18	212.13±43.77	0.464
TG, mg/dL	133.49±88.07	169.40±105.22	0.007	88.94±63.71	108.28±56.55	0.119
HDL, mg/dL	53.08±12.57	49.99±11.82	0.071	62.51±16.81	54.47±13.72	0.018
LDL, mg/dL	122.19±27.09	129.86±27.49	0.044	120.44±29.90	130.69±41.78	0.213
CRP, mg/dL	0.191±0.346	0.148±0.215	0.309	0.100±0.210	0.179±0.364	0.149

Abbreviations: FPG, fasting plasma glucose; IMT, intima media thickness of carotid artery; SBP, systolic blood pressure; DBP, diastolic blood pressure; WHR, waist-hip ratio; BMI, body mass index; TC, total cholesterol; TG, triglyceride; HDL, high-density lipoprotein; LDL, low-density lipoprotein; CRP, C-reactive protein.

^aValues are presented as mean±SD. Statistical significance was determined using Student *t*-test.

2. Comparison of carotid artery intima media thickness according to sex and smoking status

IMT in male was shown to be thicker than in female ($P<0.05$). No differences were notified among status of smoking (never smoker, quit \geq 1 yr, quit<1 yr, current smoker) as well as thickness of common carotid artery between non-smokers and previous smokers in both male and female (Table 2). Therefore, we analyzed various causes triggering the thickness of intima media in common carotid artery in each male and female.

3. The comparison on relationship and influence between each variables and carotid artery IMT

In male, age, HbA1c, FPG, and CRP presented the co-link to carotid IMT, in contrast, female subjects found that age, FPG, WHR, and HDL were influential elements on carotid IMT. Age and FPG were taken into account the common feature with artery thickness in both. HbA1c and CRP were to be related variables with artery thickness in men, while WHR and HDL were the prime components to stimulate the arterial thickness in women (Table 3).

4. The major affecting factors on intima media thickness of carotid artery

Age was seen to be the most powerful source to increase the thickness in comparison with others like HbA1c, FPG, CRP, WHR and smoking in non-diabetic male subjects. In

Table 2. Carotid artery intima media thickness according to gender and smoking status

	Variables (n)	Max CCA ^a	P
	Male (225)	0.694 \pm 0.275	
	Female (111)	0.614 \pm 0.233	0.007 ^b
Male	Never smoker (74)	0.708 \pm 0.269	
	Quit \geq 1 yr (52)	0.735 \pm 0.337	
	Quit<1 yr (12)	0.700 \pm 0.332	
	Current smoker (87)	0.657 \pm 0.223	0.394 ^c
Male	Never smoker (74)	0.708 \pm 0.269	
	Smoker with ex smoker (151)	0.688 \pm 0.278	0.603 ^b
Female	Never smoker (105)	0.622 \pm 0.234	
	Smoker with ex smoker (6)	0.450 \pm 0.104	0.077 ^b
	Total (336)		

Abbreviation: Max CCA, maximum common carotid artery.

^aValues are presented as mean \pm SD.

^bCalculated by *t*-test.

^cCalculated by ANOVA.

addition, HbA1c was accounted for another affective source. Reversely, age was solely related to contribute to intima media thickness in women, as being considered with HbA1c, HDL, WHR, FPG, smoking and CRP in normal and pre-diabetes. HbA1c was the only appreciable key-point to modify the wall thickness before diabetes occur (Table 4).

Table 3. Associations between affecting factors and carotid artery intima media thickness for individuals with HbA1c of less than 6.5%^a

	Male (225)		Female (111)	
	Correlation	P	Correlation	P
Age	0.465	<0.001	0.460	<0.001
HbA1c	0.271	<0.001	0.075	0.421
FPG	0.131	0.047	0.316	<0.001
SBP	0.093	0.164	0.051	0.591
DBP	0.049	0.468	0.039	0.682
WHR	0.086	0.191	0.197	0.032
BMI	0.019	0.775	0.148	0.111
TC	0.050	0.455	-0.056	0.557
TG	-0.044	0.509	0.065	0.484
HDL	-0.021	0.755	-0.242	0.008
LDL	0.045	0.500	0.081	0.386
CRP	0.168	0.011	0.010	0.917

Abbreviations: FPG, fasting plasma glucose; SBP, systolic blood pressure; DBP, diastolic blood pressure; WHR, waist-hip ratio; BMI, body mass index; TC, total cholesterol; TG, triglyceride; HDL, high-density lipoprotein; LDL, low-density lipoprotein; CRP, C-reactive protein.

^aCorrelation coefficient and *P*-value from bivariate correlation analysis.

Table 4. Multiple linear regression for affecting factors on carotid artery intima media thickness for individuals with HbA1c of less than 6.5%^a

		$\beta \pm SE$	Standardized β	P	R ²
Male	Age	0.012 \pm 0.002	0.424	<0.001	0.271 ^b
	HbA1c	0.145 \pm 0.051	0.182	0.004	
	HDL	0.000 \pm 0.001	0.021	0.730	
	FPG	0.002 \pm 0.002	0.070	0.287	
	WHR	-0.263 \pm 0.325	-0.052	0.419	
	Smoking	-0.013 \pm 0.034	-0.022	0.702	
Female	CRP	0.062 \pm 0.052	0.072	0.242	0.296 ^b
	Age	0.009 \pm 0.002	0.402	<0.001	
	HbA1c	-0.105 \pm 0.057	-0.175	0.068	
	HDL	-0.002 \pm 0.001	-0.165	0.061	
	FPG	0.004 \pm 0.002	0.189	0.070	
	WHR	0.097 \pm 0.310	0.027	0.755	
	Smoking	-0.122 \pm 0.088	-0.116	0.167	
	CRP	-0.022 \pm 0.077	-0.025	0.773	

Abbreviations: SE, standard errors; HDL, high-density lipoprotein; FPG, fasting plasma glucose; WHR, waist-hip ratio; CRP, C-reactive protein.

^aThe model is adjusted for age, HbA1c, fasting plasma glucose, c-reactive protein, high-density lipoprotein cholesterol, waist to hip ratio and smoking.

^b $P<0.05$.

DISCUSSION

Diabetes mellitus exacerbates atherosclerosis and becomes the major hazardous source of cerebro-vascular, peripheral vascular, and macrovascular disorders. It is estimated that one third of patients with diabetes may not be diagnosed as vascular complications even though they have them. A single FPG test is not a diagnostic tool, because most of Korean diabetic patients are non-obese compared to western patients with excessive insulin secretion.²¹⁾

HbA1c is a diagnostic index of diabetes and estimator of blood glucose status. In U.K. Prospective Diabetes Study²²⁾ and Finnish studies,²³⁾ type 2 diabetes mellitus was shown to be closely linked to cardiovascular inflammatory growth. The lower HbA1c was likely to be related to a slower development of atherosclerosis and less microangiopathy on carotid artery IMT in type 1 diabetes mellitus in the study of Jensen-Urstad et al.²⁴⁾

However, the clinical statement of Hanefeld et al.⁸⁾ and Kim et al.⁷⁾ presented that HbA1c was not associated with every multiple vascular diseases. In the study of Cho et al.²⁵⁾ correlation between carotid artery IMT and atherosclerotic risks exists significant in even non-diabetes subjects. As can be seen above research, it has been controversial to assume the risk of vascular disease prior to thickening of blood vessels in non-diabetic individuals.

Carotid artery IMT by ultrasonography is useful in diagnosing atherosclerosis and predicting of progression of cerebro-cardiovascular complications. Ultrasonography, as a screening test without harmful radiation, is the safest one and maintains non-invasive procedures to detect sub-millimeter changes of arteries.^{26,27)} It is preferable to clarify increased arterial wall thickness or non-occlusive atherosclerotic plaque rather than internal luminal narrowing of blood vessel in order to tackle vascular accidents.²⁸⁾

The latest study found that type 2 diabetes mellitus (T2DM) men had higher carotid intima medial thickness (CIMT) than T2DM women, especially in those with age ≥ 69 years. Age was the main risk factors of CIMT in both genders. However, the impact of ageing on CIMT progression only existed in male patients.²⁹⁾ Gender difference in CIMT was confirmed in T2DM patients. Moreover, impact of ageing on CIMT progression only existed in men, which might be the reason that gender difference in CIMT

increased with age.

In our study, we reviewed the data analysis that there was the relationship between HbA1c and carotid artery IMT, and determined forcible facts such as age, FPG, HDL-cholesterol, WHR, CRP and smoking on carotid IMT. In both male and female, age was the only affective factor on carotid artery IMT, after adjustment for age, subjects showed that HbA1c, FPG, CRP, HDL-cholesterol and WHR. HbA1c was important affecting trigger on carotid artery IMT in male. Age and HbA1c were considerable influencing elements to estimate blood vessel thickness. Particularly, HbA1c could be clinically important indicator to assume thickness of blood vessel without carotid artery ultrasound.

While Doruk et al.³⁰⁾ reported that HbA1c and age are not associated with carotid artery IMT in the healthy old (mean age 71.5 years). Our clinical configuration resulted in some different outcomes seen by healthy adults. Research of Cho et al.²⁵⁾ which focused on investigating the relation between carotid artery IMT and occurrences of atherosclerosis in Korean had similar conclusion with our result that age, blood pressure, BMI, WHR, LDL-cholesterol were related with IMT, except for cigarette smoking, glucose, TG and LDL-cholesterol that did not have correlation to carotid artery IMT. The mean value of carotid IMT is well known to have high reproducibility and thickening of carotid artery reflects harms of cardiovascular disease. Atherosclerotic change happens mainly at the bifurcation of internal carotid artery. We estimated not the mean value of carotid artery IMT but the maximal value of it, because it is commonly calculated to survey carotid artery thickness in practitioner's clinical office and hospital.

As the screening test tends to become emphasis on the early detection of diabetes, blood glucose test and initial assessment of vascular disease are becoming more general in health examination. This study was designed to confirm if there are predictable risk factors for the development of vascular complication prior to develop diabetes in normal individuals as well as prediabetes. HbA1c could be a useful test to assume the development of macrovascular disease. Meanwhile, prospective cohort study is needed to make a clinical criterion of HbA1c to estimate risk of vascular malfunction systematically.

요 약

연구배경: 본 연구에서는 당화헤모글로빈 6.5% 미만인 당뇨병 이전 단계에서 혈관질환의 위험성을 알아보기 위해 당화헤모글로빈과 경동맥 내막중격 두께의 관계를 알아보고자 하였다.

방법: 당화헤모글로빈 검사와 경동맥초음파 검사를 시행한 336명을 대상으로 당화헤모글로빈을 기준으로 정상과 고위험군으로 나누어 남녀에 따른 당화헤모글로빈과 경동맥 내막중격 두께의 상관관계를 Pearson's correlation으로, 경동맥 내막중격 두께에 더 큰 영향을 주는 요소를 알아보기 위해서 multiple linear regression model로 분석하였다.

결과: 나이와 공복 시 혈당은 남녀 모두에서 경동맥 내막중격 두께와 상관관계가 있었고, 남자에서는 당화헤모글로빈과 CRP, 여자에서는 고밀도지단백(HDL)과 허리엉덩이 둘레비가 경동맥 내막중격 두께와 의미 있는 상관관계를 보였다. 그중 남자에서는 나이와 당화헤모글로빈이, 여자에서는 나이만이 경동맥 내막중격 두께에 큰 영향을 주었다.

결론: 당뇨병으로 진단되지 않은 사람이라도 당화헤모글로빈과 경동맥 내막중격 두께가 상관관계가 있었고 이러한 결과는 당뇨병 환자뿐만 아니라 당뇨병 이전 상태에서도 혈당 상태를 확인하여 혈관 질환의 위험성을 예측할 수 있다.

중심 단어: 당화헤모글로빈, 경동맥, 경동맥 내막중격두께, 당뇨병

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