Hemoglobin A1c as A Potential Indicator for Intraplaque Hemorrhage of Carotid Artery Atherosclerosis in Asymptomatic Adults

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Abstract

Background

To investigate the association between hemoglobin A1c (HbA1c) and intraplaque hemorrhage (IPH) in carotid atherosclerotic plaque detected by high-resolution magnetic resonance imaging (HR-MRI) in a community-based population.

Methods

In this cross-sectional, community-based study, a total of 598 participants were recruited from May 2015 to September 2019. All participants underwent carotid artery HR-MRI. Data on demographics, medical history, and physical examinations were obtained through face-to-face interview, and fasting blood sample were collected. HbA1c was determined using high-performance liquid chromatographic analysis. Presence or absence of carotid plaque IPH was determined by HR-MRI. Multiple stepwise logistic regression analysis was performed to investigate the association between HbA1c levels and carotid plaque IPH.

Results

Of the 598 participants, 317 (53.0%) had atherosclerotic plaques, and 25 (4.2%) had IPH in carotid arteries. HbA1c was associated with the presence of IPH (OR, 1.94; 95% CI, 1.38-2.73) in the univariate analysis, and the association remained significant after adjustment for age, sex, traditional vascular factors, high-sensitivity C-reactive protein, and other potential confounders (OR, 1.70; 95% CI, 1.14-2.52).

Conclusions

This study showed that high HbA1c was associated with carotid plaque IPH detected by HR-MRI, which suggests that individuals with high HbA1c may have a higher risk of developing vulnerable carotid plaques.

Background

Carotid atherosclerotic disease, particularly vulnerable plaque, is one of the major causes of ischemic cerebrovascular events (1). Vulnerable plaque is susceptible to resulting in plaque disruption (2). Intraplaque hemorrhage (IPH) is one of the main characteristics of vulnerable plaques (3). Therefore, early identification of IPH in carotid plaque is of great significance in stroke prevention.

Hemoglobin A1c (HbA1c), a long-term measurement of glycemia, has already been reported to be related to atherosclerosis (4, 5). Previous studies also demonstrated the associations between HbA1c and ischemic stroke in people with and without diabetes (6, 7). Furthermore, a recent study conducted in hypertensive stroke patients found elevated HbA1c may have an adverse effect on carotid plaque vulnerability. The possible mechanism may due to glycosylation products trigger oxidative/inflammatory...
responses, promote the progression of atherosclerotic lesions and adverse cardiovascular events (8). However, the HIRISC study conducted in carotid stenosis patients did not found an association between IPH and HbA1c (9). The association between HbA1c and IPH in carotid plaque is still uncertain.

This study aimed to evaluate the association between HbA1c and IPH in carotid plaque detected by high-resolution magnetic imaging (HR-MRI) in a community-based population.

**Methods**

**Study population**

The study participants were recruited from Tsinghua community, which located in Haidian District, Beijing municipality and its residents were mainly staff or retirees of Tsinghua University. All residents of the Tsinghua community aged 18–85 years were eligible to participate in this study. The exclusion criteria were as follows: participants with (1) known malignant tumors; (2) severe clinical conditions; (3) stenting therapy; (4) contraindications to MR imaging; (5) claustrophobia; (6) pregnancy; or (7) contraindications to MRI examination.

**Data Collection**

All the demographic characteristics were collected by trained research coordinators using a structured questionnaire through face-to-face interviews. The following clinical information was collected: age, gender, history of smoking and alcohol consumption, medical history, and blood pressure. Body mass index (BMI) was calculated as weight in kilograms divided by height per square meter. The medical history of hypertension, diabetes mellitus, and dyslipidemia was recorded if the participants had been diagnosed according to the current clinical diagnostic criteria. The smoking and drinking status were self-reported. Smoking status was categorized as never smoker or ever smoker, and alcohol consumption was defined as having consumed alcohol in the past 12 months.

**Measurement of HbA1c and Other Biochemical Parameters**

Blood samples were collected after an overnight fast. Plasma specimens were delivered to the central laboratory in Beijing Tiantan Hospital for measurement blindly. HbA1c was measured by high-performance liquid chromatographic analysis (HLC-723G8, TOSH0, Japan). Fasting blood glucose was measured enzymatically with the Hexokinase/Glucose-6 phosphate dehydrogenase method. High-sensitivity C-reactive protein (Hs-CRP) was measured on a clinical chemistry analyzer (LABOSPECT008AS, Hitachi, Japan).

**Assessment of Carotid Plaque and IPH**

Carotid plaque imaging was performed on a 3.0T MR scanner (Achieva TX, Philips Healthcare, Best, The Netherlands) with a custom-designed 36-channel neurovascular coil. The carotid arteries were scanned using the following imaging protocol and parameters: 3D Motion Sensitized Driven Equilibrium prepared
Rapid Gradient Echo (3D-MERGE) sequence: fast field echo sequence; time of repetition (TR)/ time of echo (TE), 9.3/4.4 ms; flip angle, 11°; field of view (FOV), 16 cm × 16 cm × 4 cm; resolution: isotropic 0.8 mm × 0.8 mm × 0.8 mm; scan time: 4min02s; 3D simultaneous non-contrast angiography and intraplaque hemorrhage (SNAP) sequence: fast field echo sequence; TR/TE, 10/4.8 ms; flip angle, 11°; FOV, 16 cm × 16 cm × 4 cm; resolution: isotropic 0.8 mm × 0.8 mm × 0.8 mm; scan time: 2min17s.

Two radiologists who had more than five years of vascular imaging experience independently interpreted all carotid MR images, and the radiologists were blinded to clinical information and blood test results. If there were disagreements in image review between two radiologists, another senior radiologist with more experience in vascular imaging would conduct the peer review. The presence of atherosclerotic plaque was defined as an eccentric thickening of the local arterial wall (10). The presence of IPH was defined as hyperintense compared to adjacent muscle (signal intensity ratio ≥ 1.5:1) on SNAP images (11).

**Statistical Analysis**

Continuous variables with normal distribution were presented as mean ± standard deviations (SD); variables with non-normal distribution were reported as median (interquartile range). Categorical variables were presented as frequency and percentage. All participants were categorized into two groups according to the existence of carotid IPH: non-IPH group and IPH group. Continuous normally distributed variables were examined using independent samples Student’s t-test. Comparison of Categorical variables was analyzed using Chi-square or Fisher’s exact test. Multiple stepwise logistic regression analysis was performed to investigate the association between HbA1c and carotid IPH with adjusting for all potential confounding factors including age, sex, history of hypertension and dyslipidemia, smoking and alcohol consumption, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, triglycerides, total cholesterol, hs-CRP, and fasting glucose.

SAS version 9.4 software (SAS Institute Inc, Cary, North Carolina) was used to analyze all the data. A 2-sided P value of < 0.05 was considered statistically significant.

**Results**

**Demographic characteristics of the participants**

A total of 598 subjects were recruited from the Tsinghua community in this study between May 2015 to September 2019. The mean age was 59.7±13.8 years old, and 251 (40.1%) are males. Of all the 598 subjects, 317 (53.0%) had carotid plaques, and 25 (4.2%) had carotid IPH. Compared to non-IPH group, subjects in IPH group were more likely to be male (80.0% vs. 38.6%, P <0.001) and older (72.6±8.4 years old vs. 59.3±13.8 years old, P <0.001), and had a higher proportion of hypertension (64.0% vs. 32.3%, P =0.001) and diabetes mellitus (44.0% vs. 11.0%, P <0.001). No significant differences were found in the proportion of smoking, alcohol consumption, and dyslipidemia, and the levels for triglycerides, low-density lipoprotein cholesterol, total cholesterol, and hs-CRP between subjects in non-IPH group and IPH group (all P >0.05) (Table 1).
Association between HbA1c and carotid IPH

HbA1c level was significantly higher in IPH group than that in non-IPH group (6.42±1.07 vs. 5.78±0.70, P <0.001) (Table 1). In this study population, potential risk factors including age, sex (male), medical history of diabetes mellitus, hypertension, fasting glucose level, and HbA1c level were associated with increased risk of carotid IPH in the univariate analysis (Table 2). In the multivariate model, age- and sex-adjusted association was found between HbA1c level and carotid IPH (OR, 1.66; 95% CI, 1.11-2.48) (Model 1). Association in the multiple stepwise logistic regression was remained significant after further adjustment of the potential cofounders including history of hypertension and dyslipidemia, smoking and alcohol consumption, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, triglycerides, total cholesterol, hs-CRP, and fasting glucose. (OR, 1.70; 95% CI, 1.14-2.52) (Model 2).

Among subjects with carotid plaque (n = 317) (Table S1), 25 (7.89%) had carotid intraplaque hemorrhage. In the multivariate analysis, after adjusting age, sex, history of hypertension and dyslipidemia, smoking and alcohol consumption, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, triglycerides, total cholesterol, high-sensitivity C-reactive protein, and fasting glucose, HbA1c level was significantly associated with carotid IPH (OR, 1.76; 95% CI, 1.13-2.75) (Supplement Table S3).

Discussion

This community-based study investigated the association between HbA1c and carotid IPH detected by HR-MRI. We found that high HbA1c was significantly associated with carotid plaque IPH, which suggested that HbA1c may be an independent indicator for IPH in carotid plaques.

In this study, the prevalence of intraplaque hemorrhage was 4.2% (25/598), broadly in line with the prevalence of IPH in Atherosclerosis Risk in Communities (ARIC) study (5.4%)-an asymptomatic community-based cohort (12). In the population-based Rotterdam study, the prevalence of IPH detected by high-resolution MRI was almost 25% (13) (14), which was much higher than the prevalence in our study. However, a comparison of IPH prevalence between our study and the Rotterdam study was not reasonable because the difference of enrollment criteria. The Rotterdam study was conducted in participants with carotid wall thickening≥ 2.5 mm on ultrasound, and these selected subjects underwent MRI scanning. Furthermore, subjects from the Rotterdam study were elder compared with our study (70.3±10.2 vs.59.7±13.8), which could also contribute to the prevalence discrepancy. Generally, the prevalence of carotid IPH increases with age (15).

In this study, we found that the level of HbA1c was associated with carotid IPH, which was a primary characteristic of vulnerable plaques. Previous studies have identified the association between HbA1c and subclinical atherosclerosis, suggesting that HbA1c may be involved in the early stage of atherosclerosis (4, 5, 16, 17). As the development of atherosclerosis, the rupture of vulnerable carotid plaques could result in ischemic stroke (1). Association between glycation and ischemic stroke has also been observed (6, 18-22). Chronic exposure to raised glycemia could play an essential role in developing stroke (23, 24). This is consistent with the hypothesis that advanced glycation end products may be involved in every stage of
atherosclerosis. Recently, in the population-based Rotterdam study, Mujaj and colleagues found that serum insulin levels were associated with the presence of IPH (OR, 1.42; 95% CI, 1.12-1.7) (25). They speculated that insulin medicated abnormal neovascularization through an increased level of vascular endothelial growth factor. The association between HbA1c and IPH in carotid plaque may be explained by the inflammatory response in adventitia induced by hyperglycemia. IPH is primarily caused by leakage and rupture of immature neovessels, which were a result of invasion from the adventitia vasa vasorum towards the intima (26). About 80% of the vasa vasorum within the plaque had poor integrity and was vulnerable to leakage (27). Adventitial inflammation has been associated with vasa vasorum neovascularization, which plays a role in red blood cell extraction, macrophage activation, and lipid core expansion, further promoting the destabilization of atherosclerotic plaques (2, 26, 28-30). Besides, oxidative stress induced by hyperglycemia increased micro-vessels in plaques according to the extent of inflammatory cells, such as the increased activity of macrophage matrix metalloproteinase. Micro-vessel density in plaques is further increased in patients with diabetes, leading high risk of intraplaque hemorrhage (31).

Another plausible explanation would be that hyperglycemic injury may also be a major cause of microvascular damage. The production of reactive oxygen species (ROS), which contributed to the formation of advanced glycation end products (AGE), could lead to endothelial damages (32) and, finally, microvascular injuries. The cascades triggered by AGE played a dominant role in the onset and progression of microvascular complications of diabetes (33, 34). Moreover, tissue hypoxia, due to decreased oxygen-carrying capacity of hemoglobin in a hyperglycemic environment, could promote neovascularization, leading to leakage and hemorrhage.

In terms of clinical practice, our findings may have clinical implications given that the HbA1c level conveys information on IPH, which is regarded as the most vulnerable plaque component. As a trigger of plaque vulnerability (35), the presence of IPH may predict cerebrovascular events (36) (37). Early identification of IPH in carotid plaques is of great significance in stroke prevention (38). The association found in this study between IPH and HbA1c may explain to some extent the association between HbA1c and ischemic stroke. These findings provide further clues for the risk stratification of patients in clinical practice.

Limitations and Future Directions

This study has some limitations that should be acknowledged. First, this study was designed as a cross-sectional study, and follow-up information on stroke events was not collected. Consequently, only the association HbA1c and carotid plaque IPH was investigated, and the causal relationship could not be determined. Second, given that all the participants in this study were recruited from the Tsinghua community in Beijing, potential selection bias should be considered when considering the generalization of the findings. Third, the sample size was not large enough. Large-scale, more representative samples and prospective studies are needed to investigate the association between HbA1c and carotid plaque IPH in the future.
Conclusion

In conclusion, we found that HbA1c was associated with carotid plaque IPH detected by HR-MRI in a community population. Higher-level HbA1c was associated with a higher risk of carotid plaque IPH. These findings suggested that HbA1c might be used as an indicator for carotid plaque IPH and provide further clues for patients' risk stratification in clinical practice.

Abbreviations

HbA1c: Hemoglobin A1c; IPH: Intraplaque hemorrhage; HR-MRI: high-resolution magnetic resonance imaging; BMI: Body mass index; Hs-CRP: High-sensitivity C-reactive protein; 3D-MERGE: 3D Motion Sensitized Driven Equilibrium prepared Rapid Gradient Echo; TR: Time of repetition; TE: Time of echo; FOV: Field of view; SNAP: Simultaneous non-contrast angiography and intraplaque hemorrhage; SD: Standard deviations; ROS: Reactive oxygen species; AGE: Advanced glycation end products; OR: Odds ratio; CI: Confidence interval.

Declarations

Ethics approval and consent to participate

The Ethics Committee approved this study of the Beijing Tiantan Hospital. All participants included provided written informed consent.

Consent for publication

Not applicable.

Availability of data and materials

The datasets used in the current study will be available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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**Authors’ contributions**

YW contributed to the analysis and interpretation of data, drafting of the manuscript. RZ contributed to the acquisition, interpretation of data and critically revision of the drafting of the manuscript. YJ, MY, HQ, HH, RS, ZN contributed to the acquisition of data. GL and XZ contributed to study concept and design, study supervision or coordination, modification of the manuscript’s drafting and served as the document’s corresponding authors. All authors read and approved the final manuscript.

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Tables

Table 1 Comparison of baseline characteristics between non-intraplaque hemorrhage group and intraplaque hemorrhage group
| Characteristics                        | Total (n=598) | Non-intraplaque hemorrhage group (n=573) | Intraplaque hemorrhage group (n=25) | p   |
|---------------------------------------|---------------|-----------------------------------------|------------------------------------|-----|
| Age (years)                           | 59.7±13.8     | 59.3±13.8                               | 72.6±8.4                           | <0.001|
| Male, n (%)                           | 251(40.1)     | 221(38.6)                               | 20(80.0)                           | <0.001|
| Smoking, n (%)                        | 90(14.4)      | 82(14.3)                                | 5(20.0)                            | 0.430|
| Alcohol consumption, n (%)            | 282(45.1)     | 256(44.7)                               | 15(60.0)                           | 0.132|
| Medical history, n (%)                |               |                                         |                                    |     |
| Diabetes mellitus                     | 79(12.6)      | 63(11.0)                                | 11(44.0)                           | <0.001|
| Hypertension                          | 210(33.6)     | 185(32.3)                               | 16(64.0)                           | 0.001|
| Dyslipidemia                          | 293(46.8)     | 267(46.6)                               | 14(56.0)                           | 0.357|
| Laboratory examination                |               |                                         |                                    |     |
| Fasting glucose (mmol/L)              | 5.00±1.03     | 4.98±1.00                               | 5.67±1.36                          | <0.001|
| Total cholesterol (mmol/L)            | 4.80±0.89     | 4.81±0.89                               | 4.62±0.83                          | 0.226|
| High-density lipoprotein cholesterol (mmol/L) | 1.47±0.38 | 1.48±0.38                               | 1.33±0.39                          | 0.022|
| low-density lipoprotein cholesterol (mmol/L) | 2.93±0.83 | 2.92±0.84                               | 2.91±0.87                          | 0.723|
| Triglycerides (mmol/L)                | 1.39(1.02-1.95) | 1.40(1.00-1.98)                  | 1.38(1.19-1.82)                    | 0.689|
| high-sensitivity C-reactive protein (mg/ml) | 0.90(0.50-1.70) | 0.9(0.50-1.70)                        | 0.60(0.50-1.30)                    | 0.291|
| Hemoglobin A1c (%)                    | 5.80±0.72     | 5.78±0.70                               | 6.42±1.07                          | <0.001|

Table 2 Univariate analysis of the association between potential risk factors and carotid intraplaque hemorrhage
| Variable                      | OR (95% CI)       | P    |
|-------------------------------|-------------------|------|
| Age (year)                    | 1.10(1.05-1.15)   | <0.001|
| Male                          | 6.37(2.36-17.22)  | <0.001|
| Smoking                       | 1.50(0.55-4.10)   | 0.433 |
| Alcohol consumption           | 1.86(0.82-4.20)   | 0.137 |
| Medical history               |                   |      |
| Diabetes mellitus             | 6.36(2.77-14.62)  | <0.001|
| Hypertension                  | 3.73(1.62-8.60)   | 0.002 |
| Dyslipidemia                  | 1.50(0.65-3.27)   | 0.359 |
| Fasting glucose (mmol/L)      | 1.45(1.14-1.85)   | 0.003 |
| Triglycerides (mmol/L)        | 0.96(0.67-1.38)   | 0.824 |
| Total cholesterol (mmol/L)    | 0.78(0.49-1.25)   | 0.307 |
| High-density lipoprotein cholesterol (mmol/L) | 0.30(0.09-1.03)   | 0.055 |
| Low-density lipoprotein cholesterol (mmol/L) | 0.99(0.61-1.59)   | 0.954 |
| High-sensitivity C-reactive protein (mmol/L) | 0.99(0.82-1.21)   | 0.980 |
| Hemoglobin A1c (%)            | 1.94(1.38-2.73)   | <0.001|

Table 3 Multivariate analysis model of the association between HbA1c levels and carotid intraplaque hemorrhage

| Variable                      | OR (95% CI)       | P    |
|-------------------------------|-------------------|------|
| Model 1                       | 1.66(1.11-2.48)   | 0.013 |
| Model 2                       | 1.70(1.14-2.52)   | 0.008 |

OR: odds ratio, CI: confidence interval.

Model 1: adjusted for age, sex;

Model 2: adjusted for age, sex, history of hypertension and dyslipidemia, smoking and alcohol consumption, LDL cholesterol, HDL cholesterol, triglycerides, total cholesterol, high-sensitivity C-reactive protein, and fasting glucose (stepwise selection).