DIABETES RESEARCH AND CLINICAL PRACTICE 143 (2018) 322–331

Contents available at ScienceDirect

Diabetes Research and Clinical Practice

journal homepage: www.elsevier.com/locate/diabres

Echolucency-based phenotype in carotid atherosclerosis disease for risk stratification of diabetes patients

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ARTICLE INFO

Article history:
Received 25 June 2018
Accepted 23 July 2018
Available online 27 July 2018

Keywords:
Diabetes
Hemoglobin
Carotid atherosclerosis
Ultrasound
Plaque echolucency
Age-adjusted grayscale median

ABSTRACT

Aim: The study investigated the association of carotid ultrasound echolucent plaque-based biomarker with HbA1c, measured as age-adjusted grayscale median (AAGSM) as a function of chronological age, total plaque area, and conventional grayscale median (GSM_{conv}).
Methods: Two stages were developed: (a) automated measurement of carotid parameters such as total plaque area (TPA); (b) computing the AAGSM as a function of GSM_{conv}, age, and TPA. Intra-operator (novice and experienced) analysis was conducted.
Results: IRB approved, 204 patients' left/right CCA (408 images) ultrasound scans were collected: mean age: 69 ± 11 years; mean HbA1c: 6.12 ± 1.47%. A moderate inverse correlation was observed between AAGSM and HbA1c (CC of −0.13, P = 0.01), compared to GSM (CC of −0.06, P = 0.24). The RCCA and LCCA showed CC of −0.18, P < 0.01 and −0.08; P < 0.24. Female and males showed CC of −0.29, P < 0.01 and −0.10, P = 0.09. Using the threshold for AAGSM and HbA1c as: low-risk (AAGSM > 100; HbA1c < 5.7%), moderate-risk (40 < AAGSM < 100; 5.7% < HbA1c < 6.5%) and high-risk (AAGSM < 40; HbA1c > 6.5%), the

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https://doi.org/10.1016/j.diabres.2018.07.028
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area under the curve showed a better performance of AAGSM over GSM_{conv}. A paired *t*-test between operators and expert (P < 0.0001); inter-operator CC of 0.85 (P < 0.0001).

Conclusions: Echolucent plaque in patients with diabetes can be more accurately characterized for risk stratification using AAGSM compared to GSM_{conv}.

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1. Introduction

As per the statistics reported by World Health Organization (WHO), around 17 million people die due to cardiovascular diseases (CVD) mainly because of stroke and heart attack [1]. Moreover, males have been reported to show significantly higher events due to both of these disease as compared to females [2]. Vascular plaque build-up known as atherosclerosis is the main cause of these diseases [3,4]. Carotid arteries are the dominant pathways to supply the oxygen-rich blood to the brain and can also provide insight into the overall cardiovascular health of a person [5]. Blockage of carotid arteries can lead to an acute compromise of blood flow to the brain resulting in an ischemic stroke.

Carotid atherosclerotic disease has a strong association with chronological age of a person [6] and its prevalence increases with age [7]. Some studies have also indicated an increase in carotid plaque calcification and lipid core with an increase in age [8]. Furthermore, a high prevalence of softer plaque (so-called morphology) was reported in males compared to females which increase with the age of a person [9]. Besides the effect on carotid plaque morphology, chronological age of a person also contributes to the development of HbA1c levels that are generally used in the diagnosis and a therapeutic monitoring of diabetes [10]. Both, carotid plaque echolucency and higher levels of HbA1c are strongly associated with each other [11]. Furthermore, patients with diabetes have also been identified to possess hypoechoic nature of the carotid plaque [12]. Some studies have also been reported aiming to reduce the prevalence of echolucent plaque in the patients with diabetes [13,14]. It is therefore essential to investigate the simultaneous variations in both of the carotid plaque echolucency and HbA1c levels along with the chronological age of a patient for risk stratification and characterization of patients with diabetes.

Higher levels of HbA1c leads to elevation in carotid plaque burden which may further leads to stroke and cardiac events [15]. A large number of patients suffering from these diseases have facilitated the risk stratification system by providing additional information about the health status of a person. B-mode ultrasonography is a prevalent imaging technique which is commonly used to assess the morphology of carotid plaque. Compared to other non-invasive imaging modalities such as computed tomography/magnetic resonance imaging, carotid ultrasound (CUS) is a user-friendly and a cost-effective technique and therefore has been adopted in a wide range practice settings, including with a clinician's office. Plaque assessment using CUS image provides information about the morphological characteristics such as echogenicity and echolucency. The grayscale median (GSM) is a well-known biomarker that is used to measure the plaque echogenicity (hyperechoic or bright pixels intensity, calcified plaque) or echolucency (hypoechoic or dark pixel intensity, heterogeneous or mixed plaque) [16]. It is normally computed as a median value of all the grayscale intensities that represent the carotid plaque in an US scan. In general, carotid plaque can be of two types based on the intensity appearance in an ultrasound image.

Various studies showed the relationship between echolucent plaque and an increase in the risk of cardiovascular (CV) and stroke events [17–19]. The use of GSM_{conv} in diabetes patients has been reported by some studies to enhance the CVD or stroke risk assessment [12,20,21]. Two main findings can be drawn from these studies: (1) echolucent plaques (low GSM_{conv} value) are associated with elevated risk of stroke and CV events, and (2) patients with diabetes have a high prevalence of echolucent plaque. Although GSM_{conv} is considered as an important biomarker in carotid plaque assessment, it does not consider the chronological age of a person into its formulation and hence cannot explain the age-related variations in plaque morphology.

The main objective of the present study is to investigate the role of chronological age-adjustment in the conventional GSM_{conv} to risk-stratify diabetes patients using a novel age-adjusted GSM (AAGSM) biomarker. Further, we also present the association of AAGSM with HbA1c, which is a potential marker to demarcate the three risk classes such as low, moderate and high diabetes and finally discussions on therapeutic implications of AAGSM. In this paper we will interchangeably be using GSM or GSM_{conv} since they reflect the same meaning.

This study has the following layout: patients' demographics and methodology adopted for AAGSM formulation are discussed in "Subjects and Methods" section, correlation analysis between AAGSM and HbA1c, ROC analysis, and visual validation of three risk classes have been presented in "Results and Statistical Analysis" section. The strengths and limitations of this study along with benchmarking have been discussed in the "Discussion" section followed by "Conclusion".

2. Patient demographics and methodology

2.1. *Patients demographics*

A total of 204 volunteers (157 males and 47 females) with a mean age of 69 ± 11 years were recruited at Toho University Japan (IRB ethics approved and patient consent were taken). Among 204 subjects, 49 patients have diabetes and 155 were without diabetes. Out of 408B-mode ultrasound scans extracted from L/R CCA, one patient's left CCA artery image

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