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Glucosepane and oxidative markers in skin collagen correlate with intima media thickness and arterial stiffness in long-term type 1 diabetes

Kari Anne Sveen [a,g,*], Knut Dahl-Jørgensen [b,g], Knut Haakon Stensaeth [c], Kristin Angel [d], Ingebjørg Seljeflot [d,e,g], David R. Sell [f], Vincent M. Monnier [f], Kristian F. Hanssen [a,g]

[a] Department of Endocrinology, Morbid Obesity and Preventive Medicine, Oslo University Hospital, Oslo, Norway
[b] Department of Pediatrics, Oslo University Hospital, Ullevaal, Oslo, Norway
[c] Department of Radiology and Nuclear Medicine, Oslo University Hospital, Oslo, Norway
[d] Department of Cardiology, Oslo University Hospital, Oslo, Norway
[e] Center for Clinical Heart Research, Oslo University hospital, Ullevaal, Oslo, Norway
[f] Departments of Pathology and Biochemistry Case Western Reserve University, Cleveland, OH, USA
[g] Institute of Clinical Medicine, Faculty of Medicine University of Oslo, Oslo, Norway

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ABSTRACT

Aims: To study intima media thickness (cIMT) and arterial stiffness in type 1 diabetes of long duration, and their associations with the collagen cross-linker glucosepane and inflammatory and oxidative markers.
Methods: Twenty-seven individuals with type 1 diabetes mellitus of 40 years duration from the Oslo Study cohort and 24 age-matched controls were included. cIMT measurements of the carotid artery were performed longitudinally. Pulse wave velocity (PWV), augmentation index (AIx) and augmentation pressure (AP) were assessed cross-sectionally. Glucosepane and the oxidative product methionine sulfoxide (MetSO) were determined in skin collagen by liquid chromatography–mass spectrometry. Circulating inflammatory markers were determined by ELISAs.
Results: The diabetes patients had significantly increased cIMT and arterial stiffness compared to controls. Significant correlations were noted for skin glucosepane with cIMT ($r = 0.41$) and PWV ($r = 0.44$). Skin MetSO and monocyte chemoattractant protein-1 (MCP-1) correlated significantly with AIx and AP. After correcting for age and mean arterial pressure in multiple linear regression analysis, MetSO and MCP-1 were both independently associated with AIx and AP.
Conclusions: These results suggest more premature atherosclerosis and arterial pathology in individuals with diabetes compared to age-matched controls. They also suggest an association between the arterial pathology and markers of collagen crosslinking, oxidative damage and inflammation in type 1 diabetes patients of forty years disease duration.

1. Introduction

Diabetes is associated with an increased risk of macrovascular complications (Nathan et al., 2005). The mechanisms of arterial pathology in type 1 diabetes have not been fully elucidated, but hyperglycemia, glycation, and oxidation products are hypothesized to be involved in the development of endothelial dysfunction. A dysfunctional endothelium may in turn lead to vasoconstrictive, pro-inflammatory, and pro-thrombotic changes in the vessel wall (Basta, Schmidt, & De, 2004). Early stiffening of arteries in diabetes may be central to the pathogenesis. Arterial stiffness is accelerated by diabetes, indicating metabolic factors in its pathogenesis (Adji, O'Rourke, & Namasivayam, 2011). Carotid artery intima–media thickness (cIMT) is a reliable surrogate marker of generalized atherosclerosis and a predictor of cardiovascular disease (Greenland et al., 2000; Lorenz, von, Steinmetz, Markus, & Sitzer, 2006) and is recommended by the American Heart Association as a noninvasive imaging method for detecting atherosclerosis (Greenland et al., 2000). Carotid-femoral pulse wave velocity is recognized as a measure of aortic pulse wave velocity (aPWV) and is currently accepted as a "gold standard" measurement of arterial stiffness, and is a predictor of CVD (Laurent et al., 2006). Augmentation pressure (AP) is the contribution the pulse wave reflection makes to systolic arterial pressure. Augmentation index (AIx) is an indirect measure of wave reflection (Laurent et al., 2006).

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* Corresponding author at: Postbox 4959, Nydalen, 0424 Oslo, Norway. Tel.: +47 92069987.
E-mail address: k.a.sveen@medisin.uio.no (K.A. Sveen).

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Advanced glycation end products are associated with the development of vascular complications in diabetes. In the DCCT/EDIC study it was observed that the AGEs N- (carboxymethyl) lysine (CML) and pentosidine together with MetSO accumulate more rapidly in type 1 diabetes patients with complications than in controls (Yu et al., 2006). Rates of accumulation were also significantly higher with age in diabetes patients with complications than in those without (Yu et al., 2006). Glucosepane is one of the most prevalent AGE and protein cross-linkers of the extracellular matrix (Sell et al., 2005), making this AGE especially interesting in the pathogenesis of arterial stiffness and atherosclerosis development. Glucosepane has been found to be associated with outcomes of nephropathy, retinopathy and neuropathy in diabetes (Monnier et al., 2013). However, limited biological and clinical information is available on glucosepane and macrovascular complications in diabetes (Monnier et al., 2014).

An increasing body of evidence supports the involvement of inflammatory mechanisms in atherosclerosis and arterial stiffening (Libby, Ridker, & Hansson, 2009; Llaurado et al., 2012). Elevated circulating levels of MCP-1 might serve as a direct marker of inflammatory activity in individuals at risk of atherosclerotic vascular diseases (Braunersreuther, Mach, & Steffens, 2007). Oxidative stress also contributes in the atherosclerosis development (Lusis, 2000). Recent studies have focused on a pro-inflammatory subset of monocytes with high level of reactive O_2 species (ROS) and nitric oxide in atherosclerosis development (Libby et al., 2009). Methionine sulfoxide (MetSO) is a direct oxidation product of methionine independent of other chemical modifications (Onorato, Thorpe, & Baynes, 1998). It may therefore provide an independent assessment of oxidative damage to proteins and be used as indices of oxidative stress (Onorato et al., 1998).

No studies have reported on the association between macrovascular complications and the AGE cross-linker glucosepane (Monnier et al., 2014) in type 1 diabetes. Few studies have also investigated the relationship between the different vascular variables to AGEs, inflammatory and oxidative markers. Except the data from DCCT/EDIC (Polak et al., 2011), longitudinal cIMT measurements in long term type 1 diabetes are still sparse. Therefore our aims were to study cIMT longitudinally and arterial stiffness in a well characterized cohort of type 1 diabetes of long duration, and to define factors associated with these parameters, especially the AGE glucosepane together with inflammatory and oxidative markers.

2. Materials and methods

2.1. Study design

In the Oslo study starting in 1982, 45 patients with type I diabetes were randomized to either continuous subcutaneous insulin infusion with portable pumps, multiple (>5) daily insulin injections, or continued conventional treatment with 2 daily injections. After 4 years of intensified treatment, the progression of microvascular complications was retarded. Consequently, all patients were offered intensified treatment, and followed prospectively. Criteria for inclusion were as follows: age 18–45 years, diagnosis of type 1 diabetes at <30 years of age, disease duration more than 7 but less than 30 years, C-peptide <0.1 nmol/l, and no or minimal microvascular complications (Dahl-Jorgensen et al., 1986). After 27 years of follow-up, 33 participants were still being followed. Two had died of causes not related to diabetes, another six declined to participate in this last follow-up. During this last follow-up period one patient died of reasons possibly associated with diabetes and one had to withdraw from the examinations because of newly diagnosed cancer. Twenty seven participants included in the present study completed all the examinations and had also performed cIMT in 1999 as previously described (Larsen et al., 2005). These participants were included in the final analysis. The 27 who underwent examination did not differ significantly from the total group of participants regarding age, sex, and glycemic control or disease duration.

The reference population for the arterial stiffness measurements and cIMT was 24 age- and gender-matched healthy volunteers recruited from the Oslo University hospital staff. None of the included control participants used blood pressure-lowering or lipid-lowering medication.

Informed consent was obtained from each participant and the study protocol conforms to the ethical guidelines of the Declaration of Helsinki and was approved by the Regional Committee for Ethics in Medical and Health Research of South-Eastern Norway.

2.2. Measurements of arterial stiffness

Pulse wave velocity (PWV), augmentation pressure (AP) and augmentation index (AIx) were measured with the SphygmoCor devise version 7.1 (AtCor Medical) and a validated tonometer (SPC-301, Millar Instruments) as previously described (Angel et al., 2010) and in concordance with the standardizations recommended in the expert consensus document on arterial stiffness (Laurent et al., 2006).

PWV was assessed as the carotid-femoral pulse wave velocity. The wave travel distance was obtained by subtracting the distance from the carotid location to the sternal notch from the distance between the sternal notch and the femoral site of recording (Laurent et al., 2006). Peripheral pressure waveforms were recorded at the radial artery at the wrist with a validated tonometer. Corresponding central aortic waveforms were generated by integrated software, from which central hemodynamics, AP and aortic AIx were calculated (Pauca, O'Rourke, & Kon, 2001). The AIx values in this report are the heart rate adjusted AIx. Mean arterial pressure (MAP) was determined from the pressure waveforms calibrated with brachial blood pressures. All of the AP, AIx and PWV measurements were made in triplicate by the same examiner (K.A.), and the mean values were used in the analyses.

2.3. Common carotid artery ultrasonography

A standardized protocol and strict quality control procedures were implemented to achieve reliable ultrasonic measurements of cIMT in 1999 (Larsen et al., 2005) and again ten years later. An experienced sonographer, blinded to the participants' diabetes status and risk factor levels, did all the examinations.

The subjects were studied under standardized conditions (quiet room, comfortable temperature) with the participant in the fasting state. Blood pressure was measured under resting conditions. High-resolution ultrasonography was performed with a Siemens Acuson Sequoia 512 (Siemens Acuson; Mountain View, CA) ultrasound scanner equipped with a linear array 14-MHz transducer. The participants were examined in the supine position with the head turned slightly to the side. After identifying the bulb, longitudinal images of the common carotid artery (CCA) were obtained by combined B-mode and color Doppler. The scan was focused on the far wall, and the resolution box was used to magnify the far wall segment 10–20 mm proximal of the carotid bulb, where all measurements were done. Several images were acquired by using an anterior oblique (30° from midline) and/or lateral (100° from midline) angle (Touboul et al., 2004). The IMT of the far wall was measured during end diastole. Three scans from both carotids were selected, and nine measurements of maximum far wall IMT on both sides were averaged; thus, the conclusive mean IMT of each patient was calculated from a total of 18 measurements. All scans were digitally stored on the internal hard disk for subsequent offline analysis. One experienced reader (K.H.S.), blinded to the subjects' clinical details, performed all measurements.