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Original article

Impaired endothelial function is not associated with arterial stiffness in adults with type 1 diabetes

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Abstract

Aim. – This study investigated the relationship between endothelial dysfunction (ED) and arterial stiffness (AS) in adults with type 1 diabetes and no clinical cardiovascular (CV) disease.

Methods. – A total of 68 patients with type 1 diabetes and 68 age- and gender-matched healthy (non-diabetic) subjects were evaluated. ED was assessed by reactive hyperaemia peripheral arterial tonometry (RH-PAT) and by serum concentrations of soluble intercellular adhesion molecule-1 (sICAM-1), soluble vascular cell adhesion molecule-1 (sVCAM-1) and E-selectin. AS was assessed by aortic pulse wave velocity (aPWV). All statistical analyses were stratified by gender.

Results. – Adults with type 1 diabetes had RH-PAT index scores similar to those of their matching controls [men: 1.55 (1.38–1.98)% versus 1.61 (1.40–2.17)%, $P = 0.556$; women: 2.07 (1.55–2.31)% versus 2.08 (1.79–2.49)%; $P = 0.215$]. However, after adjusting for potential confounders, type 1 diabetes emerged as the main determinant of the RH-PAT index in women. Also, differences between genders in both the controls and type 1 diabetes patients disappeared. Men with diabetes had higher serum concentrations of E-selectin, and women had higher serum concentrations of sICAM-1, sVCAM-1 and E-selectin than their respective controls. However, after adjusting for potential confounders, only the differences in sICAM-1 (women) and E-selectin (both genders) remained significant. No association was found between aPWV and the RH-PAT index and ED markers after adjusting for CV risk factors.

Conclusion. – ED was increased in adults with type 1 diabetes compared with age-matched non-diabetic subjects. Also, gender differences in ED were lost in type 1 diabetes. However, ED was not associated with AS after adjusting for potential confounders. These findings suggest that ED occurs earlier than AS in type 1 diabetes.

Keywords: Endothelial dysfunction; Arterial stiffness; Type 1 diabetes

Résumé

La dysfonction endothéliale n'est pas associée à la rigidité artérielle chez les adultes diabétiques de type 1.

Objectif. – Étudier la relation entre la dysfonction endothéliale (DE) et la rigidité artérielle (RA) chez les sujets diabétiques de type 1 sans maladie cardiovasculaire (CV) clinique.

Abbreviations: CV, Cardiovascular; ED, Endothelial dysfunction; RH-PAT, Reactive hyperaemia peripheral arterial tonometry; AS, Arterial stiffness; BMI, Body mass index; WHR, Waist-to-hip ratio; SBP, Systolic blood pressure; DBP, Diastolic blood pressure; MAP, Mean arterial pressure; sICAM-1, Soluble intercellular adhesion molecule-1; sVCAM-1, Soluble vascular cell adhesion molecule-1; aPWV, Aortic pulse wave velocity; CHD, Coronary heart disease; UAC ratio, Urinary albumin-to-creatinine ratio.

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Méthodes. – Soixante-huit diabétiques de type 1 et 68 volontaires sains (appariés selon l'âge et le sexe) ont été évalués. La DE a été évaluée par l'hyperémie réactive-périphérique tonométrie artérielle (RH-PAT) et par les concentrations sériques d'ICAM-1, VCAM-1 et E-Sélectine. La RA a été mesurée par la vélocité de l'onde de pouls aortique (aVOP). Toutes les analyses faites ont été stratifiées selon le sexe.

Résultats. – Les diabétiques avaient les mêmes valeurs de RH-PAT que leurs témoins (hommes : 1,55 % (1,38–1,98) versus 1,61 % (1,40–2,17) ; $P = 0{,}556$; femmes : 2,07 % (1,55–2,31) versus 2,08 % (1,79–2,49); $P = 0{,}215$). Toutefois, après l'ajustement pour les facteurs confondants, le diabète de type 1 a émergé comme le principal composant du RH-PAT (femmes). En outre, les différences entre les sexes dans la population générale, chez les diabétiques de type 1 ont disparu. Les hommes diabétiques avaient des concentrations sériques de E-Sélectine plus élevées comparativement aux sains. Les femmes diabétiques avaient des concentrations sériques de ICAM-1, VCAM-1 et E-Sélectine plus élevées comparativement à leurs témoins. Toutefois, après ajustement pour les facteurs confondants, seuls les différences d'ICAM-1 (femmes) et E-Sélectine (les deux sexes) sont restées significatives. Nous n'avons trouvé aucune association entre la aVOP et le RH-PAT ou des marqueurs de dysfonction endothéliale après ajustement pour les autres facteurs de risque CV.

Conclusion. – La DE est augmentée chez les patients diabétiques. En outre, les différences entre les sexes dans la DE ont disparu chez les patients diabétiques. Par contraste, la DE n'est pas associée à la RA après ajustement pour les facteurs confondants potentiels. Ces résultats suggèrent que la DE se produit plus tôt que la RA chez les sujets diabétiques de type 1.

Mots clés : Dysfonction endothéliale ; Rigidité artérielle ; Diabète de type 1

1. Introduction

The relative risk of cardiovascular (CV) disease in type 1 diabetes can be as much as ten times greater than in the non-diabetic population, especially in women [1], and is even greater than the risk in type 2 diabetes [2]. In fact, CV disease is the major cause of mortality in type 1 diabetes [2], representing around 40–47% of deaths in certain cohorts [3,4]. Diabetes results in an accelerated arteriosclerotic process that is not fully explained by classical CV risk factors. The pathophysiological mechanisms underlying CV events in type 1 diabetes are complex and still not fully understood, but are known to involve endothelial dysfunction (ED) as an important factor in the arteriosclerotic process.

ED is characterized by reduced bioavailability of certain vasodilators such as nitric oxide and increased production of certain vasoconstrictors [5]. Endothelial function can be estimated indirectly by measuring endothelium-dependent vasodilatation and by determining ED serum markers such as adhesion molecules [5]. Reactive hyperaemia peripheral arterial tonometry (RH-PAT) is a novel and promising non-invasive technique for assessing peripheral microvascular endothelial function. It measures changes in digital pulse volume during reactive hyperaemia [6]. In adults, it has shown excellent correlation with measures of coronary and peripheral ED [6,7]. Furthermore, RH-PAT has been associated with CV risk factors [8,9] and has recently been shown to be an independent predictor of late CV events [10]. In paediatric patients with type 1 diabetes, lower RH-PAT scores have been described compared with their respective controls, but no data are available in adults [11,12].

Arterial stiffness (AS) is an early sign of arteriosclerosis [13] and is therefore a highly promising method for detecting patients at risk of arteriosclerosis long before a CV event occurs. Indeed, AS has emerged as an independent determinant of CV events and mortality beyond the classical CV risk factors in several populations [14]. Previously, our group was able to demonstrate that AS is increased in patients with type 1 diabetes and no clinical CV disease [15].

Although the precise mechanisms responsible for the increase in AS are not yet fully understood, ED could be involved, leading to functional stiffening of the arterial wall [16]. In fact, ED has been associated with measures of AS in healthy subjects [17,18] and in patients with CV disease [19] or CV risk factors [20,21]. Also, type 1 diabetes has been associated with ED [22], thought to be an important factor in the pathogenesis of micro- and macrovascular complications [23–25]. However, the relationship between ED and AS in patients with type 1 diabetes remains unclear. For this reason, it was hypothesized that, in type 1 diabetes, ED (as assessed by RH-PAT and ED serum markers) would be increased and associated with AS. Thus, the present study was carried out in patients with type 1 diabetes without clinical CV disease and in age- and gender-matched healthy (non-diabetic) subjects.

2. Patients and methods

A total of 68 patients with type 1 diabetes (34 men and 34 women) aged 18–65 years and 68 age- and gender-matched healthy subjects were included. None of them had any condition associated with an inflammatory response (such as acute or chronic infectious diseases) or had received anti-inflammatory treatment within the previous 6 months, and none had experienced any previous clinical CV event. Patients with type 1 diabetes were consecutively recruited from our outpatients clinic and all had diabetes of at least 1 year's duration. The healthy control group was recruited from hospital staff members and their relatives and friends.

After an overnight fast, venous blood samples were taken and aliquots of plasma and serum stored at –80° C until processing. In women, all measurements were taken during the follicular phase of the menstrual cycle. The following information was recorded using a predefined standardized form: gender; age; diabetes duration; body mass index (BMI); waist-to-hip ratio (WHR); systolic and diastolic blood pressure (SBP and DBP); mean arterial pressure (MAP, defined as 1/3 SBP + 2/3 DBP); physical activity (by International Physical Activity Questionnaire [IPAQ]) [26]; cigarette-smoking; alcohol intake; insulin