Available online at
ScienceDirect
www.sciencedirect.com
Elsevier Masson France
EM|consulte
www.em-consulte.com/en
Diabetes & Metabolism 40 (2014) 76–81

Original article

Abdominal obesity and low-grade systemic inflammation as markers of subclinical organ damage in type 2 diabetes

E.M. Dahlén [a,*], A. Tengblad [a], T. Länne [a], B. Clinchy [b,c], J. Ernerudh [b,c], F.H. Nystrom [a,d], C.J. Östgren [a,d]

[a] *Department of Medical and Health Sciences, Division of Community Medicine, Linköping University, 581 83 Linköping, Sweden*
[b] *Department of Clinical and Experimental Medicine, Division of Clinical Immunology, Linköping University, Linköping, Sweden*
[c] *Department of Clinical Immunology and Transfusion medicine, Linköping University Hospital, Linköping, Sweden*
[d] *Diabetes Research Centre, Linköping University Hospital, Linköping, Sweden*

Received 22 January 2013; received in revised form 22 October 2013; accepted 29 October 2013

Abstract

Aim. – This study aimed to explore the associations between abdominal obesity, inflammatory markers and subclinical organ damage in 740 middle-aged patients with type 2 diabetes.

Methods. – Waist circumference (WC) and sagittal abdominal diameter (SAD) were measured, and blood samples were analyzed for C-reactive protein (CRP) and IL-6. Carotid intima–media thickness (IMT) was evaluated by ultrasonography, and aortic pulse wave velocity (PWV) measured with applanation tonometry.

Results. – Abdominal obesity as determined by SAD and WC was significantly correlated with IL-6 (WC: $r=0.27$, $P<0.001$; SAD: $r=031$, $P<0.001$), CRP (WC: $r=0.29$, $P<0.001$; SAD: $r=0.29$, $P<0.001$), IMT (WC: $r=0.09$, $P=0.013$; SAD: $r=0.11$, $P=0.003$) and PWV (WC: $r=0.18$, $P<0.001$; SAD: $r=0.21$, $P<0.001$). In multiple linear regressions with IMT and PWV as dependent variables, and age, gender, statin use, systolic blood pressure (SBP), body mass index (BMI), CRP and HbA_{1c} as independent variables, both SAD and WC remained associated with IMT and PWV. On stepwise linear regression and entering both SAD and WC, the association between SAD and PWV was stronger than the association between WC and PWV.

Conclusion. – Both SAD and WC are feasible measures of obesity, and both provide information on inflammation, atherosclerosis and arterial stiffness in type 2 diabetes, while SAD appears to be slightly more robustly associated with subclinical organ damage than WC.

Keywords: Type 2 diabetes; Obesity; Anthropometric measurements; Cardiovascular disease

1. Introduction

Cardiovascular disease (CVD) is a major cause of morbidity and mortality in patients with type 2 diabetes [1]. Traditional risk factors such as high low-density lipoprotein (LDL) cholesterol, low high-density lipoprotein (HDL) cholesterol, hypertension and smoking do not fully explain the increased cardiovascular risk in patients with type 2 diabetes [1]. Thus, it is of great importance to identify clinically feasible, inexpensive and non-invasive risk-factor assessment tools to predict CVD.

Low-grade inflammation is thought to be involved in the atherosclerotic process, as it has previously been shown that patients with type 2 diabetes present with higher levels of inflammatory markers compared with those without diabetes [2].

Continuous deposition of oxidized lipoproteins in the vascular wall leads to an inflammatory response from endothelial cells that transmit signals to monocytes to transform into macrophages. However, macrophages can scavenge lipoproteins and become foam cells that lead to fatty streaks in vessel walls. This then initiates the cascade of events that eventually results in atheroma formation in arterial walls [3]. Also, macrophages not only form fatty streaks, but also secrete proinflammatory cytokines [4]. Systemic low-grade inflammation can be measured through circulating levels of the acute-phase reactant C-reactive protein (CRP) and by levels of proinflammatory interleukin (IL)-6.

Development of type 2 diabetes is closely associated with obesity, and abdominal obesity is the best obesity-related

* Corresponding author. Tel.: +46 70 47 87 325; fax: +46 13 224 020.
E-mail address: elsa.dahlen@liu.se (E.M. Dahlén).

1262-3636/$ – see front matter © 2013 Elsevier Masson SAS. All rights reserved.
http://dx.doi.org/10.1016/j.diabet.2013.10.006

predictor of type 2 diabetes [5]. Anthropometric measures are useful in clinical practice as they are both non-invasive and inexpensive. Waist circumference (WC) is currently the most commonly used measurement for abdominal obesity and is highly associated with the risk of developing CVD. However, recent studies have suggested that sagittal abdominal diameter (SAD) may be a better measurement for assessing adverse metabolic profiles [6–8].

Intima–media thickness (IMT) of the carotid arteries measured by high-resolution B-mode ultrasound is a widely accepted non-invasive marker of subclinical atherosclerosis [9]. In addition, given its correlation with coronary atherosclerosis and its capacity to predict incident coronary events, carotid IMT has been proposed as a surrogate marker of coronary atherosclerosis [10]. Pulse wave velocity (PWV) measured by tonometry also provides a non-invasive estimate of arterial stiffness, and is an independent predictive risk factor for all-cause mortality and cardiovascular mortality [11–13].

The aim of the present study was to compare two different anthropometric measures of abdominal obesity, WC and SAD, in terms of low-grade systemic inflammation and subclinical organ damage as well as atherosclerosis and arterial stiffness in a middle-aged cohort of patients with type 2 diabetes. In addition, the study also explored the association between markers of low-grade systemic inflammation and subclinical organ damage in such a cohort.

2. Methods

Baseline data were analyzed from 740 patients who participated in the community-based cohort study Cardiovascular Risk Factors in Patients with Diabetes—A Prospective Study in Primary Care (CARDIPP). CARDIPP was launched in 2005 and completed in 2008 with the aim of identifying markers for CVD to facilitate earlier and individually adjusted interventions in middle-aged patients with type 2 diabetes. CARDIPP comprised data from extended annual follow-ups of patients aged 55–66 years with type 2 diabetes who were consecutively recruited from 25 different primary healthcare centres in the counties of Östergötland and Jönköping in Sweden. Details of the structure and results from CARDIPP have been described and reported elsewhere [14,15]. The centres were located in different demographic areas and varied in size. However, the model for the treatment and care of type 2 diabetes was similarly organized, and all primary-care centres adhered to the same national guidelines for diabetes care. A total of 761 patients participated in CARDIPP up to 1st November 2008, but due to missing data in 21 cases, the present cohort was ultimately 481 men and 259 women.

2.1. Anthropometric measurements

At the primary healthcare centres, nurses specializing in the treatment of diabetes measured blood pressure (BP) after 5 min of seated rest, and the mean of three consecutive readings was used for the study analyses. Height (to the nearest cm) and weight (to the nearest 0.1 kg) were also measured with the patients wearing light indoor clothing. Waist circumference (WC) was measured with the patient standing after normal expiration to the nearest cm at a level midway between the lowest rib and iliac crest. SAD was recorded with the patient lying supine with bent knees, using a standardized sliding-beam caliper at the highest point of the abdomen.

The clinical investigation also included a standardized medical history, with data on diabetes duration and ongoing medication.

2.2. Laboratory tests

Blood specimens were drawn in the morning after a 10-h overnight fast. Routine tests such as for HbA_{1c}, plasma glucose and serum lipids were analyzed according to the usual routine of the primary healthcare centres. HbA_{1c} was analyzed according to the Swedish Mono-S high-performance liquid chromatography (HPLC) standard, which is approximately 1% below the Diabetes Control and Complications Trial (DCCT) standard. Blood samples were frozen for later analysis by high-sensitivity CRP assay, apolipoprotein (apo)B/apoA-I ratio and cytokines by the Department of Laboratory Medicine at Linköping University Hospital. CRP values > 10 mg/mL were excluded from the analyses as per the current guidelines [16]. Plasma levels of IL-6 and IL-10 were measured with an ultrasensitive cytokine bead assay kit (Invitrogen Corporation, Carlsbad, CA, USA) according to the manufacturer's instructions, and analyzed on a Luminex® 100™ system (Luminex Corporation, Austin, TX, USA). The limits of detection were 0.84 and 0.68 $pg.mL^{-1}$ for IL-6 and IL-10, respectively. The intra-assay coefficient of variation (CV) was 5–12%, while the interassay CV was 17–20%.

2.3. Physiological vascular examinations

Carotid ultrasound investigations and PWV and SAD measurements were performed at the Department of Physiology at Linköping University Hospital and at the County Hospital Ryhov in Jönköping. The IMT of the carotid arteries was evaluated using B-mode ultrasonography. A digital ultrasound system (HDI 5000, ATL Ultrasound, Bothell, WA, USA) equipped with a broadband linear transducer (L12-5) was used for scanning the carotid artery in longitudinal section. Electrocardiography (ECG) leads were also in place. For lumen diameter (LD) and IMT determinations during diastole, three consecutive frozen images focused specifically on the lumen–intima echo and media–adventitia echo from the far arterial wall were saved for later analysis. The digital B-mode images were subsequently transferred to a personal computer (PC) with software for offline measurement of LD and IMT (Artery Measurement System II, Image and Data Analysis, Gothenburg, Sweden). Calibration and subsequent measurements were performed by manually tracing a cursor along the leading edge of the intima–lumen echo from the near wall, and the leading edge of the lumen–intima echo and media–adventitia echo from the far wall. A 10-mm section of the common carotid artery in the proximity of the carotid bulb was selected for obtaining the mean LD and far-wall IMT. During analysis, the measurement window was hidden