The impact of diet and physical activity on musculoskeletal and cardiometabolic health during menopause: The role of myokines and gene expression.

Chatzivasileiou P [a], Paschou S [a], Armeni E [a] , Karagouni I [a], Kontou L [a], Augoulea A [a] , Kaparos G [b], Baka S [b], Antoniou A [a], Panoulis K [a], Lambrinoudaki I [a]

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Introduction

Menopause is a transitional period in women's life during which significant hormonal and metabolic changes occur, often associated with adverse effects, such as cardiovascular events, osteoporosis and dyslipidemia. Reduction in muscle mass and strength during aging lead to limited physical activity, enhancing the subcutaneous and visceral body fat accumulation. The combined presence of both muscle loss and increased total and abdominal adiposity are responsible for metabolic and cardiovascular disorders. Exercise improves physical performance through a beneficial effect on muscle mass and strength, delays osteoporosis and reduces fracture risk. Moreover, improvement in dietary behavours restrict the onset of diet- or age-related diseases.

Objectives

This study aims to investigate the impact of diet and physical activity on sarcopenia, skeletal health, cardiometabolic parameters and subclinical atherosclerosis in postmenopausal women. Moreover, we will examine the relation of specific myokines and genetic polymorphisms to changes in body composition with advancing age.

Materials & Methods

Study population

Three hundred postmenopausal women will be recruited from the Menopause Clinic of Aretaieio University Hospital, Athens, Greece. Exclusion criteria will be obesity (BMI > 40 kg/m^2), diabetes mellitus, inflammatory or cardiovascular disease, hepatic or renal insufficiency and tumor of any origin, women with history of recent surgery or under treatment with steroids, nitrates, hormone replacement therapy and selective oestrogen receptor modulators during the last 6 months or bisphosphonates and / or denosumab intake. Menopausal status will be characterised by the absence of menstruation for 12 consecutive months, serum follicle-stimulating hormone (FSH) levels > 25 mIU / mL and estradiol (E2) levels < 50 pg / mL. MetS will be defined according to the presence of three of more of the following: i) triglyceride levels >150 mg/dL (ii) HDL-cholesterol <50 mg/dL, (iii) systolic blood pressure (SBP) >130mmHg and/or diastolic blood pressure (DBP) > 85mmHg, (iv) fasting hyperglycaemia (FBG) between 100 and 125 mg/dL and (v) waist circumference > 80 cm (22).

All women will provide an informed consent and the research protocol of the present study will be approved by the Local Ethics Committee.

The short version of the International Physical Activity Questionnaire – IPAQ will be used for the assessment of physical activity Dietary intake will be evaluated by a 65-item semi-quantitative food frequency questionnaire developed and validated for the Greek population. Adherence to the Mediterranean dietary pattern will be assessed by the Mediterranean Dietary Score (MedDietScore) scaled from 0-55. (23). Body weight will be measured by a digital weight scale and height by a stadiometer in upright position. Body mass index (BMI) and waist-to-hip ratio (WHR) will be estimated using traditional equations. Fasting venous blood samples will be collected, centrifuged, when necessary and stored at − 80 °C until assessment.

All vascular tests will be performed in a fixed order by the same experienced operator, blinded to the medical history of the participant.

Body composition

Body composition will be estimated by dual-energy X-ray absorptiometry (DXA) (General Electric Lunar Corporation, Madison, WI, USA) and subjects will be positioned for regional and whole-body scans, according to the manufacturer's protocol.

Bone densitometry

Bone mineral density (BMD) will be measured at lumbar spine (LS) and femoral neck (FN), by dual energy X-ray absorptiometry (DXA) (Norland-Excell Plus-XR-36 Densitometer, Norland Medical Systems, Inc., Fort Atkinson, WI, USA) (within-subject coefficient of variation 1.1% at the LS and 1.85% at the FN). Osteopenia and osteoporosis will be determined according to the World Health Organisation operational BMD definition. Osteopenia will be defined as a BMD T-score between -1 and -2.5 while osteoporosis as a BMD T-score less than -2.5 at any site.

Hand grip strength

Muscle strength will be assessed by the hydraulic hand dynamometer (Jamar®) (Sammons Preston, Illinois) according to the manufacturer's instructions. The analysis will assess the mean of three consecutive measurements in each hand (intraclass correlation coefficient 0.94-0.98 depending on the tested side).

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Materials and methods (continued)

Vascular and haemodynamic measurements

IMT will be assessed by B-mode ultrasound imaging (14.0-MHz multifrequency linear array probe, Vivid 7 Pro, GE) and measured in three paired segments of both right and left common carotid artery (CCA), carotid bulb (CB), and internal carotid artery (ICA) from a fixed lateral transducer angle. Three measurements of the maximal IMT in the far wall will be averaged in each segment and the average IMT will be calculated for both carotid arteries. The right and the left carotid IMT average value will be defined as combined IMT. All scans will be digitally recorded for off-line analysis (mean carotid IMT coefficient variation-CV 10.6%). Femoral IMT (FA-IMT) will be assessed in the far wall of 1-cm-long arterial segment proximal to the femoral bifurcation. The presence of atherosclerotic plaque will be defined as a clearly identified area of focally increased IMT >1.5 mm.

PWV will be measured non-invasively by the validated Complior device (Artech Medical) between the common carotid artery and common femoral artery (intraoperator coefficient of variation (CV) = 2.4%) repeated twice. Central pressure waves will be produced by use of transfer functions and calibration from peripheral blood pressures by applanation tonometry on the radial artery (SphygmoCor System, AtCor Medical Pty Ltd).

Central systolic and diastolic blood pressure (BP) (CV = 5% for two repeated measurements for both systolic and diastolic BP) and augmentation index (Aix, CV=9% for two repeated measurements) will be defined as the augmentation of aortic systolic BP by the returning reflected waves, expressed as a percentage of aortic pulse pressure. For each subject peripheral blood pressure will be recorded twice after 1-minute interval time by oscillometry using the automated Omron 705IT device (Omron, UK) and the average value will be used for data analysis. FMD will be measured using high resolution ultrasound (14.0 MHz probe, Vivid 7 Pro, General Electric, WI, USA) by a single experienced investigator (intraclass correlation coefficient=0.706).

Biochemical and hormonal assays

Biochemical assays (Glu, tChol, HDL-C, LDL-c) will be performed on the Architect c 8000 system (Abbott Diagnostics). C-reactive protein levels will be measured by immunoturbidimetry ((Abbott) (CV ≤5%). Hormonal assays (insulin, TSH, FT4, PTH, 25-OH Vit D, FSH, LH, PRL, E2, SHBG, testosterone) will be performed on the Architect i1000SR analyser (Abbott Diagnostics) by chemiluminescent microparticle immunoassay (CMIA) (Abbott). Insulin-like growth factor 1 (IGF-1) will be measured by chemiluminescence (CLIA) on Liaison XL system (DiaSorin). Homeostasis model assessment of insulin resistance (HOMA-IR) will be calculated as follows: fasting insulin (μU/mL) × fasting glucose (mmol/L)/22.5. Free estrogen index (FEI) and free androgen index (FAI) will be calculated using total E2 and total testosterone, respectively, as well as SHBG values by the following equations: FEI=E2 (picograms per milliliter) · 0.367/SHBG (nanomoles per liter); FAI= testosterone (nanograms per milliliter) · 347 /SHBG (nanomoles per liter).

Quantitative measurement of human tumor necrosis factor-a (TNF-a) and interleukin-l (IL-6) will be performed by commercially available enzyme-linked immunosorbent assay (ELISA) whereas the UCP3 polymorphism rs11235972 will be detected by real-time polymerase chain reaction (RT-PCR) according to the manufacturer's instructions.

Statistical analysis

Qualitative data will be expressed as frequencies (percent values). The normality of distributions will be evaluated using both exploratory data analysis and the Kolmogorov–Smirnov test. Normally distributed quantitative data will be presented as mean value ± standard deviation (mean ± SD) and non-normally distributed quantitative data will be presented using median values (min, max) and interquartile range (IQR). Differences between continuous variables will be assessed using the independent samples t-test or one-way ANOVA as well as the Mann–Whitney U test or the Kruskal–Wallis test. Differences between dichotomous variables will be assessed using Chi-square analysis (x^2 test).

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Linear regression analysis will be used to evaluate the potential association of the combined presence of diet and physical activity on body composition and indices of cardiovascular risk. Statistical analysis will be performed by SPSS version 27.0. Statistical significance will be set at the level of $p < 0.05$ and results with $0.05 < p<0.10$ will be considered suggestive. The prevalence of Met Syndrome in non-diabetic female Greek population was estimated to be as high as 17.8% (24). The respective age-standardised prevalence rate of MetS in non-diabetic women is estimated as 14.2% in Europe (25), and up to 37.3% in non-diabetic postmenopausal Taiwanese women (26). Accordingly, we hypothesised that aiming to detect prevalence of MetS of at least 20% in our postmenopausal population, a sample size of 229 women would be sufficient to detect statistically significant differences with an error level of 0.05 and effect size of 0.01 (statistical power 95%, two-tailed). The prevalence of sarcopenia in the elderly population has been recently evaluated in a meta-analysis (27) according to which the rates differed depending on the method of assessment (i.e., sarcopenia prevalence, DXA use: 8% in women; bio-electrical impedance analysis use: 13% in women). Therefore, the sample size required to detect a prevalence of sarcopenia equal to 8%, estimated by DXA method, would be a total of 144 women (effect size 0.10, statistical power 0.95, two tailed).

Primary endpoints of this study will involve the potential association between the results of the MedDietScore and scores from IPAQ with the following outcomes i) the diagnosis of sarcopenia or sarcopenic obesity, ii) the development of atherosclerotic plaques and subclinical vascular disease, iii) the diagnosis of metabolic syndrome , iv) the diagnosis of osteoporosis.

Scientific and social impact

Changes in body composition and increased metabolic risk are major causes of morbidity and mortality in the aging population. With the increasing life expectancy and rapid growth of the aged population, sarcopenia is currently an emerging public health issue with adverse socioeconomic impact. The present study aims to investigate the association of novel biomarkers with sarcopenia as well as the beneficial impact of diet and physical expenditure interventions on musculoskeletal health and deceleration or prevention of cardiovascular events during menopause.

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