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Original Research

Serum Dehydroepiandrosterone Sulfate and Risk for Type 2 Diabetes in Older Men and Women: The Pro.V.A Study

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ABSTRACT

Objective: A large body of clinical data suggests the importance of endogenous sex hormones in the pathogenesis of diabetes, but very little is known about the possible relationship between dehydroepiandrosterone sulfate (DHEAS) and diabetes, particularly in the elderly. We aimed, therefore, to examine whether high serum levels of DHEAS have any protective effects on the incidence of type 2 diabetes and to elucidate the possible role of gender in a cohort of older subjects.
Methods: We followed 1258 community-dwelling subjects aged ≥65 years without type 2 diabetes who belonged to the Progetto Veneto Anziani (Pro.V.A.) for 4.4±1.2 years. DHEAS were measured at baseline and categorized into gender-specific tertiles. The incidence of type 2 diabetes was diagnosed in cases of fasting plasma glucose above 7.0 nmol/L, glycated hemoglobin ≥6.5%, use of glucose-lowering drugs or a 2-hour postload blood sugar level ≥11.1 nmol/L during the follow-up period.
Results: Although no significant differences in potential risk factors for diabetes were apparent across DHEAS tertiles at the baseline in either gender, when those with lower DHEAS were taken for reference, Cox regression analysis showed that males in the highest DHEAS tertile had lower risks for being diagnosed with diabetes during the follow up (HR=0.23; 95% CI: 0.11–0.51; p<0.0001), whereas no significant differences emerged across DHEAS tertiles for females or for the sample as a whole.
Conclusions: Higher serum DHEAS levels revealed a significant protective effect against the onset of type 2 diabetes in older men but not in older women, confirming different sensitivities of type 2 diabetes to DHEAS between genders.

Mots clés :
adultes qui résident dans la communauté
SDHEA
personnes âgées
diabète de type 2

RÉSUMÉ

Objectif : Un grand nombre de données cliniques montrent l'importance des hormones sexuelles endogènes dans la pathogenèse du diabète, mais on en connaît peu sur la relation possible entre le sulfate de déhydroépiandrostérone (SDHEA) et le diabète, particulièrement chez les personnes âgées. Par conséquent, nous avions pour objectif d'examiner si des taux sériques élevés de SDHEA ont des effets protecteurs sur l'incidence du diabète de type 2 et d'élucider le rôle possible du sexe dans une cohorte de sujets âgés.
Méthodes : Nous avons suivi 1258 sujets de ≥65 ans résidant dans la communauté et ne souffrant pas de diabète de type 2 qui faisaient partie de l'étude Progetto Veneto Anziani (Pro.V.A.) depuis 4,4±1,2 ans. Nous avons mesuré le SDHEA au début et l'avons classifié en tertiles selon le sexe. Nous avons observé l'incidence du diabète de type 2 dans les cas de glycémie veineuse à jeun au-dessus de 7,0 nmol/l, d'hémoglobine glyquée ≥6,5%, d'utilisation de médicaments hypoglycémiants ou de taux de glycémie 2 heures après ingestion de glucose ≥11,1 nmol/l durant la période de suivi.

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Résultats : Bien qu'aucune différence significative dans les facteurs de risque potentiels de diabète n'était apparente dans tous les tertiles de SDHEA au début dans les deux sexes, lorsque ceux ayant un SDHEA plus faible servaient de référence, l'analyse selon le modèle de régression de Cox montrait que les hommes qui étaient dans le tertile le plus élevé de SDHEA avaient de plus faibles risques de recevoir un diagnostic de diabète durant le suivi (RR=0,23; IC à 95% : 0,11–0,51; p<0,0001), tandis qu'aucune différence significative n'apparaissait dans tous les tertiles de SDHEA des femmes ou de l'échantillon dans son ensemble. *Conclusions :* Des taux sériques plus élevés de SDHEA révélaient un effet protecteur significatif contre l'apparition du diabète de type 2 chez les hommes plus âgés, mais non chez les femmes plus âgées, ce qui confirme les sensibilités différentes du diabète de type 2 aux SDHEA entre les sexes.

Introduction

Type 2 diabetes is one of the most common conditions occurring in older people, and its incidence is increasing exponentially. In the United States, between 1980 and 2011, the percentage of people over 65 years of age with diagnoses of type 2 diabetes rose from about 9% to 20% (1). It is, therefore, hardly surprising that more than 40% of the diagnosed cases of type 2 diabetes involve older people (2).

A large body of clinical data suggests the importance of endogenous sex hormones in the pathogenesis of type 2 diabetes, but gender-related differences seem to be relevant (3,4). In fact, high serum levels of testosterone and estradiol seem to raise the risk for type 2 diabetes in women but reduce it in men (3). Very little is known about the possible relationship between dehydroepiandrosterone and its sulfate (DHEAS) and type 2 diabetes, although DHEAS is the most abundant sex hormone in the blood. An association between low serum DHEAS concentrations and insulin resistance has been demonstrated in several animal studies (5), and an active role for DHEAS in type 2 diabetes is also supported by experimental evidence of DHEAS administration's improving glucose tolerance and sensitivity in rodents with diabetes (6,7). In humans, 3 prospective studies of the association between baseline DHEAS levels and the onset of type 2 diabetes found no significant association in women (4,8), whereas 1 study found a significant association between declining serum DHEAS levels and the onset of type 2 diabetes in men (5). All these studies were performed in middle-aged or young-old participants; however, the literature suggests that the protective effect of high serum DHEAS levels increases with age, particularly in older men (9–11).

The aim of the present study was to test whether high serum DHEAS levels were associated with any protective effect against the incidence of type 2 diabetes and to examine the possible influence of gender in a representative group of elderly men and women over a lengthy follow up (4.4 years).

Methods

Data source and subjects

The data for this analysis came from the Progetto Veneto Anziani (Pro.V.A.), an observational cohort study of the Italian population older than 65 years of age. The study population included 3099 age- and sex-stratified Caucasian participants (1854 women and 1245 men) randomly selected by using a multistage stratification method between 1995 and 1997 from 2 cities (Rovigo and Camposampiero) in the north of Italy. Sampling procedures and data-collection methods have been extensively described elsewhere (12). Trained physicians and nurses examined participants at various clinics. The present study concerns the information collected concerning the incidence of type 2 diabetes over a mean of 4.4 years (±1.2 SD) of follow up.

Among the 3099 subjects initially recruited, 537 were already diabetic at the baseline, 858 did not have their serum DHEAS levels measured at the baseline, and information regarding any type 2 diabetes at follow up was unavailable for 446 (lost to follow up or deceased). Thus, 1258 participants were included in the present analysis.

Subjects with no DHEAS measurements at the baseline did not differ from the participants included in the analysis in terms of age (74.7±7.4 vs. 74.3±6.9 years; p=0.23); percentage of females (62.4 vs. 63.3%; p=0.72); any parameters potentially associated with the onset of type 2 diabetes (i.e. they were comparable in terms of body mass index [BMI] (27.78±4.67 vs. 27.40±4.38 kg/m^2; p=0.10); fasting plasma glucose (FPG) levels (96.18±12.09 vs. 96.50±11.38 mg/dL; p=0.60); glycolated hemoglobin (A1C) levels (5.06±0.50 vs. 5.03±0.53%; p=0.20); or the percentage of those taking cortisone (2.2% vs. 2.8%; p=0.61).

The ethical committees of Padua University and the Veneto Region's Local Health Units n. 15 and n. 18 approved our study protocol, and participants gave their written informed consent to participate in the study.

Covariates

Participants were examined at the city hospitals by trained physicians and nurses. Information was collected during face-to-face individual interviews concerning their social, demographic and medical conditions. Smoking habits were dichotomized as current vs. never or former smoker (if a subject had given up smoking at least a year earlier). Regular physical activities were defined as ≥4 hours per week in the previous month of at least moderate physical activity (brisk walking, cycling, gardening, dancing or physical exercising). Alcohol drinking was categorized as yes or no during the past month. Education levels (total years of schooling) were dichotomized as <5 vs. ≥5 years. Monthly incomes were indicated as family incomes of < or ≥€500. Functional statuses were assessed using the activities of daily living score (13). Body weights and heights were measured by trained physicians, and the BMIs were calculated. Waist circumferences were measured at the midpoint between the lower margin of the last palpable rib and the top of the iliac crest, using a stretch-resistant tape; hip circumferences were calculated around the widest portion of the buttocks, with the tape parallel to the floor. Waist-to-hip ratios (WHRs) were calculated as the ratio between these 2 anthropometric parameters.

Any diseases were assessed by board-certified physicians, who examined all the clinical details collected for all participants in the study, including their clinical histories, symptoms self-reported by means of standardized questionnaires, medical and hospital records, blood tests and physical examinations. Histories of major diseases were recorded, including cardiovascular diseases (atrial fibrillation, congestive heart failure, angina or myocardial infarction, stroke or peripheral artery disease); chronic obstructive pulmonary disease, cancer or dementia. Hypertension was defined as systolic blood pressure ≥140 mm Hg, diastolic blood pressure ≥90 mm Hg or current use of antihypertensive medication (14). Depressive symptoms were assessed using the Geriatric Depression Scale, a 30-item