Osteoarthritis and Cartilage xxx (2016) 1–5

Osteoarthritis and Cartilage

OARSI OSTEOARTHRITIS RESEARCH SOCIETY INTERNATIONAL

Brief report

Relationship between circulating sex steroid hormone concentrations and incidence of total knee and hip arthroplasty due to osteoarthritis in men

S.M. Hussain †, F.M. Cicuttini †, G.G. Giles † ‡ §, S.E. Graves ‖ ¶, Y. Wang † *

† *Department of Epidemiology and Preventive Medicine, School of Public Health and Preventive Medicine, Monash University, Alfred Hospital, Melbourne, VIC 3004, Australia*
‡ *Centre for Epidemiology and Biostatistics, Melbourne School of Population and Global Health, The University of Melbourne, Carlton, VIC 3053, Australia*
§ *Cancer Epidemiology Centre, Cancer Council Victoria, Melbourne, VIC 3004, Australia*
‖ *Australian Orthopaedic Association National Joint Replacement Registry, Discipline of Public Health, School of Population Health & Clinical Practice, University of Adelaide, SA 5005, Australia*
¶ *Department of Surgery, Flinders University, SA 5042, Australia*

ARTICLE INFO

Article history:
Received 21 October 2015
Accepted 4 April 2016

Keywords:
Sex steroid hormone
Androstenedione
Osteoarthritis
Total knee replacement
Total hip replacement

SUMMARY

Objective: Few studies have examined the association between circulating sex steroid concentrations and risk of osteoarthritis (OA) in men with inconsistent results. Our aim was to examine whether concentrations of circulating sex steroid hormones were associated with the incidence of primary knee and hip arthroplasty for OA in a prospective cohort study.
Design: Two thousand four hundred and ninety four men from the Melbourne Collaborative Cohort Study (MCCS) had circulating sex steroid concentrations measured in blood samples drawn at recruitment (1990–1994) and stored in liquid nitrogen. The plasma concentrations of sex hormones, including dehydroepiandrosterone sulphate, androstenedione, testosterone, estradiol, androstanediol glucuronide, and sex hormone binding globulin, were measured. The incidence of total knee and hip arthroplasty for OA during 2001–2013 was determined by linking MCCS records to the Australian Orthopaedic Association National Joint Replacement Registry.
Results: One hundred and four men had knee and 80 had hip arthroplasty for OA over 10.7 (SD 3.8) years. Higher concentrations of androstenedione were associated with a decreased risk of total knee (hazard ratio (HR) 0.87, 95% confidence interval (CI) 0.77–0.98) and hip (HR 0.84 95% CI 0.71–1.00) arthroplasty for OA in overweight and obese men. No significant association was observed for the other measured hormones.
Conclusion: Low plasma androstenedione concentration is associated with an increased risk of both knee and hip arthroplasty for OA for overweight and obese men. While the findings need to be confirmed in other cohort studies, they suggest that circulating sex steroids may play a role in the pathogenesis of OA in men.

Introduction

Osteoarthritis (OA) is a whole joint disease of multifactorial aetiology. The gender-difference in prevalence of OA after the age of 50 years suggests a role for sex hormones in the development of OA[1]. While a number of studies have examined the association between sex hormones and risk of OA for women[2], only two studies have been conducted on men[3,4]. Higher serum testosterone (T) concentrations were associated with greater amount of cartilage volume and increased cartilage volume loss over 2 years in healthy men without knee OA[3,4]. To better understand the pathogenesis of

* Address correspondence and reprint requests to: Y. Wang, Department of Epidemiology and Preventive Medicine, School of Public Health and Preventive Medicine, Monash University, Alfred Hospital, Melbourne, VIC 3004, Australia. Tel: 61-3-9903-0353; Fax: 61-3-9903-0556.
E-mail addresses: monira.hussain@monash.edu (S.M. Hussain), flavia.cicuttini@monash.edu (F.M. Cicuttini), graham.giles@cancervic.org.au (G.G. Giles), segraves@aoanjrr.org.au (S.E. Graves), yuanyuan.wang@monash.edu (Y. Wang).

http://dx.doi.org/10.1016/j.joca.2016.04.008
1063-4584/

OA, the role of sex steroids in the development and progression of OA needs to be explored. OA could be defined using primary knee and hip arthroplasty due to severe knee and hip OA[5]. This approach is relevant to symptomatic disease burden and health economics. Our aim was to examine the relationship between circulating concentrations of sex steroids (dehydroepiandrosterone sulphate (DHEAS), androstenedione, T, estradiol (E2), androstanediol glucuronide (Ag)) and sex hormone binding globulin (SHBG), and the incidence of total knee and hip arthroplasty for OA.

Methods

Participants

The Melbourne Collaborative Cohort Study (MCCS) is a prospective cohort study of 41,514 participants (17,045 men) aged 27–75 years (99.3% aged 40–69 years) at baseline[6]. Participants were recruited via the electoral roll, advertisements and community announcements in local media during 1990–1994. The study protocol was approved by the Cancer Council Victoria's Human Research Ethics Committee.

Of the participants, 2590 (6.2%) were excluded because they: died or left Australia prior to 1 January 2001; reported at MCCS second follow-up having had any arthroplasty prior to 1 January 2001; left Australia before the recorded date of having a arthroplasty; or their first recorded procedure was a revision arthroplasty[5]. Of the remaining 38,924 participants, 15,655 were men. This current study examined 2494 men with sex steroid concentrations measured in stored plasma (Supplementary Fig. 1). There were no significant differences between those with and without hormone measurement in age (57.1 ± 8.6 vs 54.9 ± 8.7 years), body mass index (BMI; 27.3 ± 3.6 vs 27.1 ± 3.6 kg/m^2), born in Australia/United Kingdom (72.3% vs 74.0%), and socioeconomic indices for areas (SEIFA) (24.1% vs 25.6% least disadvantaged).

Demographic and anthropometric measures

At baseline, data on date of birth, country of birth (Australia, United Kingdom, Italy, or Greece), smoking, SEIFA, and co-morbidities (hypertension, diabetes, hypercholesterolemia) were collected from face-to-face interviews. Weight was measured to the nearest 0.1 kg and height measured to the nearest 1 mm using standard protocols and BMI calculated.

Plasma analysis

Plasma samples were retrieved from storage in liquid nitrogen, aliquoted into 450 AL amounts, and shipped on dry ice in batches of ~80 samples each to a laboratory where sex hormones were measured. Assignment to batches was done randomly and the proportions of cases and subcohort members were approximately equal for all batches. 10% of the samples in each batch were aliquots from pooled plasma[7]. The laboratory was blind to status of the samples. One scientist did all measurements. Samples were thawed in a warm water bath, vortexed rapidly for a few seconds, and centrifuged at 2000 rpm (210× g) for 10 min[7].

DHEAS was measured by competitive immunoassay (IMMULITE analyzer, Diagnostic Products Corporation (DPC), Los Angeles, CA) with a coefficient of variation (CV) at 2.1 Amol/L of 12.4%. T followed by E2 was measured by electro chemiluminescence immunoassay (Elecsys 2010 analyzer, Roche Diagnostics GmbH, Mannheim, Germany) with a CV for T at 36 nmol/L of 1.6% and E2 at 93 pmol/L of 11.1%. SHBG was measured by immunometric assay (IMMULITE analyzer, DPC) with a CV at 26 nmol/L of 6%. Androstenedione and Ag were analyzed by RIA (DSL-4200 and DSL-6000, respectively; TX) with a CV for androstenedione at 3.3 nmol/L of 10.7% and Ag at 21.1 nmol/L of 4.3%[7]. Plasma samples from 44 men who had given blood twice ~1 year apart were each divided into two aliquots. The two aliquots were measured in separate batches a week apart. The intra-class correlation coefficient showed good reliability[7].

Identification of total knee and hip arthroplasty

Cases with a total knee or hip arthroplasty were identified from the Australian Orthopaedic Association National Joint Replacement Registry (AOA NJRR). The Registry began data collection in Victoria in January 2001[8] and has detailed information on prostheses, patient demographics, reason for arthroplasty, whether it is primary or revision arthroplasty. Data are collected from both public and private hospitals and validated using a sequential multi-level matching process against State and Territory Health Department data[8].

Matching of MCCS participants using first name, surname, date of birth, and gender, to the AOA NJRR in order to identify those who had a joint replacement performed between 1 January 2001 and 31 December 2013 was performed using the Freely Extensible Biomedical Record Linkage system. The data linkage study was approved by the Human Research Ethics Committee of Cancer Council Victoria and Monash University.

This study examined the first total knee or hip arthroplasty with a contemporaneous diagnosis of OA[5]. If one person had multiple arthroplasties, the first recorded procedure was considered the event.

Statistical analysis

Analysis of variance (ANOVA) was used to compare means, Chi-squared test to compare proportions, and Kruskal–Wallis test to compare concentrations of sex steroids and SHBG among groups. Cox proportional hazard regression was used to estimate hazard ratios (HR) for knee or hip arthroplasty associated with each sex steroid and SHBG. Categories based on the median of each sex hormone and SHBG were created and the HRs for total knee or hip arthroplasty were investigated. As approximately 20% of men in their 60s have biochemical evidence of androgen deficiency[9], we did age-stratified analyses in the <60 years and ≥60 years age group separately. Follow-up for total knee and hip arthroplasty began on 1 January 2001, and ended at the date of arthroplasty or date of censoring. Participants were censored at the date of first arthroplasty performed for indications other than OA, the date of death, the date left Australia, or end of follow-up (31 December 2013), whichever came first. Each analysis was adjusted for age, BMI, country of birth, smoking and SEIFA[5], with further adjustment for co-morbidities. To test whether associations of steroids and SHBG with arthroplasty risk were modified by being overweight/obese (BMI ≥25 kg/m^2), interactions were fitted, and tested using the likelihood ratio test.

Tests based on Cox regression methods showed no evidence that proportional hazard assumptions were violated for any analysis. All statistical analyses were performed using Stata 12.0 (StataCorp LP., College Station, TX, USA).

Results

A total of 104 knee and 80 hip arthroplasties was identified over 10.7 (SD 3.8) years follow-up. Characteristics of study participants are presented in Table I. Men who received an arthroplasty were older, more likely to be born in Australia/United Kingdom, and had a lower plasma concentration of androstenedione compared with those who had no arthroplasty.

Please cite this article in press as: Hussain SM, et al., Relationship between circulating sex steroid hormone concentrations and incidence of total knee and hip arthroplasty due to osteoarthritis in men, Osteoarthritis and Cartilage (2016), http://dx.doi.org/10.1016/j.joca.2016.04.008