



Gender differences in the association of cognitive impairment with the risk of hip fracture in the older population



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ABSTRACT

Objectives: To test the hypothesis that differences by gender will be observed in the association of hip fracture risk with stages of cognitive impairment; and to explore the association between Petersen's "mild cognitive impairment" (MCI) and DSM-5 "mild neurocognitive disorder" (MND).

Study design: A community sample of 4803 individuals aged 55+ years was assessed in a two-phase case-finding enquiry in Zaragoza, Spain, and was followed up for 16 years. Medical and psychiatric history was collected with standardized instruments, including the Mini-Mental Status Examination (MMSE), Geriatric Mental State (GMS), History and Aetiology Schedule, and a Risk Factors Questionnaire.

The statistical analysis included calculations of Hazard Ratios (HR) in multivariate Cox proportional hazards regression models.

Main outcome measures: Identified cases of hip fracture, validated by blind researchers.

Results: In men, hip fracture risk was increased at the "mild" (HR = 4.99 (1.39–17.91)) and at the "severe" (HR = 9.31 (1.35–64.06)) stages of cognitive impairment, indicated by MMSE performance. In contrast, in women no association could be documented at the "mild stage" (power = 89%), and the association disappeared altogether at the "severe stage" in the final multivariate statistical model (power 100%). No association observed between hip fracture and mild cognitive impairment in both men (power = 28% for P-MCI) and women (power = 44% and 19% for Petersen's MCI and DSM-5 MND, respectively).

Conclusions: Increased hip fracture risk was associated with "mild" stages of cognitive impairment in men, but not in women. To explore the potential association with the construct MCI or MND, studies with greater statistical power would be required.

1. Introduction

Hip fractures are recognized to be an important public health problem in the elderly, as they are one of the main causes of morbidity, mortality and related health-care expenditures in the geriatric

population of the western world [1]. The incidence of hip fracture is higher among women [1] and osteoporosis is considered to be the fundamental risk factor [2]. In relation to hip fracture, focused research on gender differences has been recommended to clarify the significance of epidemiological differences observed between men and women [3],

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and we have recently reported differences in risk factors: illiteracy and depression increased the risk of fractures in women, while tobacco and disability increased the risk in men [4].

Related to hip fracture and gender differences, conditions with important clinical implications in the elderly, such as cognitive impairment and dementia may also be of great interest, since epidemiological differences between men and women are also apparent: the incidence of dementia [5] and the rate of cognitive impairment [6], have been reported to be both higher in women. Cognitive difficulties increase the risk of falls [7] and the highest proportion of fractures in those aged 65 years or over result from a fall [8]. Furthermore, cognitive loss may play a role in the fragility of the bone in indirect ways [9,10]. However, there is paucity of evidence on the association of hip fractures with cognitive difficulties [11], and the association with stages of cognitive impairment, and specifically with “mild” stages has not been studied. Staging models have been very successful in different medical diseases [12], and we have recently shown that the model may be applicable to cognitive impairment [13]. In case “mild” stages of cognitive impairment are associated with hip fracture risk the interest for early prevention or treatment would be apparent. Similarly, it is also timely to explore to what extent the construct “mild cognitive impairment” (MCI), which is widely considered to be a prodromal sign of neurodegeneration [14] but also a frailty sign [15], is associated with hip fracture risk.

In view of gender differences observed in the incidence of both hip fracture and cognitive impairment; in the risk factors of hip fracture; and in the rate of cognitive impairment, the aims of the present study are, first, to test the hypothesis that differences by gender will be observed in the association between stages of cognitive impairment, even in the “mild” stage, and an increased risk of hip fracture; and, second, to explore to what extent the construct MCI is also associated with an increased risk of hip fractures.

2. Methods

2.1. General design and study population

This study was designed during the Zaragoza Dementia and Depression (ZARADEMP) Project, and the general methods have previously been reported [5]. This Project was intended to document the incidence and risk factors of somatic and psychiatric diseases in the adult population aged ≥ 55 years, in a longitudinal, five-wave epidemiological enquiry. The sample was drawn from the eligible individuals in the Spanish official census lists, and included the institutionalized individuals. It was stratified with proportional allocation by age and sex. The refusal rate was 20.5%, and 4803 individuals were ultimately interviewed at baseline (wave I, starting in 1994). The Helsinki convention principles of written informed consent, privacy, and confidentiality have been maintained throughout the Project, and the Ethics Committee of the University of Zaragoza and the Fondo de Investigación Sanitaria (FIS) approved the study, according to Spanish Law.

The design of the study included a two-phase case finding. Validated, Spanish versions of international instruments were used, including the Mini-Mental Status Examination (MMSE) [16] (cognitive performance) and the Geriatric Mental State B (GMS-B), with its cognitive section and its Automated Geriatric Examination for Computer Assisted Taxonomy (AGECAT) [17]. Other instruments were the History and Aetiology Schedule (HAS) (medical and psychiatric history data), disability scales (Katz’s Index for basic activities of daily living (bADL’s) and Lawton and Brody scale for instrumental (iADL’s)), and the European Studies of Dementia (EURODEM) Risk Factors Questionnaire (medical conditions) [5]. In phase 2, the research psychiatrists reassessed all ‘probable cases’ of dementia identified in phase 1. They administered the same assessment instruments and performed a neurological examination and medical reports were also used to help in the

diagnostic process, which was completed at the end of this phase. Dementia was diagnosed by the panel of research psychiatrists according to DSM-IV criteria. Clinically significant depression was defined as GMS-AGECAT level 3 or higher [5].

The main outcome for the present report was incident hip fractures in the study period (1994–2010).

2.2. Assessment of hip fracture

All incident hip fracture cases occurring during the study period were identified through the computerized inpatient register system in the hospitals of the health care area of Zaragoza. This register system was contrasted with the database, baseline sample of ZARADEMP Project. Two experienced, blinded and independent researchers (a general surgeon and an orthopedic/trauma surgeon) reviewed the medical records of all identified patients with hip fracture, and validated the hip fracture diagnosis, defined as follows: any fracture of the proximal femur, from the femoral head to 7 cm down the lesser trochanter. The assessment included the study of X-rays at the time of admission and discharge from hospital, and when necessary the discharge reports recorded in the medical history. Lower fractures, considered to be diaphyseal fractures, as well as pelvic, pubic or acetabular fracture cases were all excluded in this study. Other exclusion criteria were presence of high energy trauma, open fractures, non-osteoporotic pathologic fractures as malignancies or metastases, and a second hip fracture in the same patient. Non-osteoporotic fractures due to high energy trauma were identified through the computerized inpatient register by the “cause of admission”, and those due to malignancies required a more systematic assessment. The participating researchers had been trained to identify four radiologic patterns suggesting malignancies: osteolytic lesions, cortical disruption, atypical fracture patterns (like reverted sub-throchanteric) and lesser trochanter avulsions.

2.3. Assessment of stages of cognitive decline

The validated, staging system of MMSE scores [13], was used to classify the subjects as: ‘normal’ (scores 30); ‘questionable’ (scores 26–29); ‘mild’ (scores 21–25); ‘moderate’ (scores 11–20) and ‘severe’ (scores 0–10).

The researchers reviewed all the information coming from the instruments used before individuals were classified as ‘cases’ or ‘non-cases’ of cognitive impairment. For this construct, both Petersen et al. [14] (MCI) and DSM-5 “mild neurocognitive disorder” (MND) criteria were used in view that they identify different populations of individuals with cognitive difficulties (see Fig. 1) [18]. The assessment and diagnosis of both was done blind to the results of the field work by a panel of research psychiatrists (and a psychologist), following a method previously reported [18]. The cognitive and ADL’s items in the instrument used had been operationalized before to conform to the criteria in both categories of impairment. Subjective cognitive impairment was assessed by the specific questions in the GMS.

2.4. Covariates

The following covariates, assessed at baseline and defined in a previous report [4] were included in the analysis: civil status; illiterate; smoking; alcohol intake; disability; body mass index (BMI), and clinically significant depression [19].

2.5. Data analysis

Baseline cognitive measures of the sample were described as frequencies and percentages except for MMSE score, presented as mean and standard deviation (SD). Analysis was done separately for men and women. The follow-up period was considered from baseline enrollment to the first one of the following events: first incident hip fracture (day of

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