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Original Article

Association between rheumatoid arthritics and osteoporosis among Chinese men, a community based study

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Abstract: Background: The main purpose of this study was to estimate the associations between rheumatoid arthritics (RA) and osteoporosis (OP) in general Chinese men. Methods: We conducted a large-scale, community-based, cross-sectional study to investigate the associations by using self-report questionnaire to access medical history. A total of 1041 men were recruited sis in this study. Multiple regression models controlling for confounding factors to include RA were performed to investigate the relationships for OP. Results: Univariate analysis indicated there was no significant association between RA and T-score (P = 0.103), however, significant association between RA and OP was reported (P = 0.005). Multiple regression analysis indicated that RA was significantly associated with OP (P = 0.013, OR = 3.191 95% CI: 1.284-7.932). The men with RA had a significant higher prevalence of OP. Conclusion: The findings indicated that RA was independently and significantly associated with OP. The prevalence of OP was less frequent in Chinese men without RA.

Keywords: Rheumatoid arthritics, osteoporosis, Chinese men, association

Introduction

Osteoporosis (OP) is a skeleton disease characterized by low bone mass and deterioration of the microarchitecture of bone tissue, which predispose the affected patients to fragility fractures commonly involving those of the spine, hip or wrist [1]. The disease is usually not diagnosed until the first fracture is manifested [1, 2]. Primary OP is an age-related condition, with reduced bone mass and increased propensity of fractures without other identifiable causes of bone loss. Among OP resultant fractures, hip fractures have mortality rate as high as 15-30% [3]. Accordingly, OP is a global public health problem, which creates a heavy burden of morbidity and economic cost to the society [4]. Rheumatoid arthritis (RA) is a chronic and progressive systemic autoimmune inflammatory disease in which the body's immune system defectively attacks the small joints. RA can result in local joint deformations such as bone erosions and joint space narrowing, and sometimes generalized bone loss [5]. The prevalence of RA is estimated to be about 0.5-1.0% in the general population [6]. The etiology of RA is incompletely understood, involving genetic factors, environmental exposures, and stochastic factors [7].

On top of classic fracture risk factors including high age, low body mass, and female gender, RA almost doubles the risk of vertebral and nonvertebral fractures due to inflammation, low levels of physical exercises, and prolonged glucocorticoid use [5, 8]. In patients with RA, a chronic inflammatory state has been shown to increase bone resorption (osteoclasts) and slow bone formation (osteoblasts) [9], and this imbalance of bone homeostasis may lead to low bone mineral density (BMD) and OP. In a study carried out in South Korea, the frequency of OP in a group of female RA patients (22.1%) was significantly higher than the healthy control group (11.4%) [10]. Despite of the reported association between OP and RA, there have been a number of controversial opinions in the literature. Kim et al. investigated the effects of disease modifying anti-rheumatic drug (DMARD) use on fracture risk in RA patients and

their study suggests that medication of RA does not consequently decrease fracture risk in OP [10]. Moreover, the relationship between the use of corticosteroids in RA and OP remains debated and unclear [11, 12].

A large amount of studies focuses on OP in female gender due to the higher incidence rate [13]. To our best knowledge, research on the correlation of RA and OP in Asian population remains limited, especially in Chinese men. In the present research, we performed the most simple and inexpensive method [14], self-reported questionnaire and association analysis to examine how OP occurrence is related to RA activity in a cohort of Chinese men. Self-reported questionnaire is a convenient and reliable method to conduct a large-scale survey and estimate the possible risk factors for common diseases. Previous reports have shown that patient self-report outcomes could provide usual clinical care of RA [15, 16]. Using this method, our research aims to provide a better insight into the relationship of OP and RA in the relatively under-investigated male population.

Methods

Study population

We performed a risk-factor study for OP using a random sample of the Chinese population. Participants were recruited from rural and urban communities in Shanghai. Participants aged 30-90 years were included in this study. More than 3,000 participants (both male were invited to a screening visit between 2011 and 2014. Written consent was obtained from all patients before the study, which was performed in accordance with the ethical standards in the Declaration of Helsinki, and approved by the Medicine Ethical Committee of the Shanghai Tongji Hospital. A total of 1041 participants with complete records were available to data analysis.

Some participants with chronic diseases and conditions that might potentially affect bone mass, structure, or metabolism were excluded. Briefly, the exclusion criteria were as follows: a history of 1) serious residual effects of cerebral vascular disease; 2) serious chronic renal disease (Glomerular filtration rate-GFR < 30 mL/min/1.73 m^2); 3) serious chronic liver disease or alcoholism; 4) significant chronic lung disease; 5) corticosteroid therapy at pharmacologic levels; 6) evidence of other metabolic or inherited bone disease, such as hyper-or hypoparathyroidism, Paget disease, osteomalacia, or osteogenesis imperfecta; 7) recent (within the past year) major gastrointestinal disease, such as peptic ulcer, malabsorption, chronic ulcerative colitis, regional enteritis, or significant chronic diarrhea; 8) Cushing syndrome; 9) hyperthyroidism; and 10) any neurologic or musculoskeletal condition that would be a non-genetic cause of low bone mass.

Data collection

All study subjects underwent complete clinical baseline characteristics evaluation, which included a physical examination and response to a structured, nurse-assisted, self-administrated questionnaire to collect information on age, gender, residential region, visit date, family history, lifestyle, dietary habits, physical activity level during leisure time, use of vitamins and medications, smoking, alcohol consumption, and self-reported therapy history. Body weight and height were measured according to a standard protocol. Smoking and alcohol consumption were categorized as never, current (smoking or consuming alcohol regularly in the past 6 months), or ever (cessation of smoking or alcohol consumption for more than 6 months). Regular exercise was defined as any kind of physical activity 3 or more times per week. Education was commonly divided into four stages: preschool, primary school, secondary school, and college.

Self-reported medical history was categorized as “no” or “yes.” HTN was defined as blood pressure ≥ 140/90 mmHg, or a history of hypertension medication. Diabetes mellitus (DM) was defined by oral glucose tolerance test (OGTT) and either HbAlc ≥ 6.5% or the use of insulin or hypoglycemic medications. The diagnosis of RA was confirmed by the American College of Rheumatology revised criteria [17]. RA was evaluated by a semi-quantitative medical history questionnaire. To determine history of rheumatoid arthritics, the participants were asked, “Did you have rheumatoid arthritics?” The possible answers were: “no” or “yes” and the answers were taken as a subjective assessment. To answer the question, the participants were required to decide one issue based on their impressions: whether or not the medical history was actually rheumatoid arthritics diagnosed by physicians.

Table 1. Clinical baseline characteristics of participants

Variable	non-RA	RA	Total	*P* value
Demographical information				
N	1041	37	1078	-
Age (mean ± sd)	64.18±9.79	64.43±8.9	64.19±9.76	0.878
Education (n, %)	281 (26.99)	12 (32.43)	293 (27.18)	0.768
Lifestyle				
Smoking (n, %)	380 (36.54)	11 (29.73)	391 (36.3	0.397
Drinking (n, %)	310 (29.84	12 (33.33)	322 (29.95%)	0.652
Exercise (n, %)	676 (64.94)	21 (56.76)	697 (64.66)	0.306
Oil	20.2±10.11	20.81±10.44	20.22±10.12	0.717
Medical history				
HTN (n, %)	476 (46.17)	14 (38.89)	490 (45.92)	0.389
CAD (n, %)	107 (10.64	1 (3.03)	108 (10.39)	0.159
DM (n, %)	100 (9.78)	3 (8.57	103 (9.74)	0.813
Gout (n, %)	37 (3.62)	1 (2.78)	38 (3.6)	0.789
Therapy history				
VC (n, %)	109 (10.47)	6 (16.22)	115 (10.67)	0.266
VD (n, %)	29 (2.79)	0 (0)	29 (2.69)	0.303
Outcomes				
T-score	-1.22±0.92	-1.47±0.82	-1.23±0.91	0.105
OP (n, %)	87 (8.36)	8 (21.62)	95 (8.81)	0.005

Note: HTN-hypertension, CAD-coronary artery disease, DM-diabetes mellitus, RA-Rheumatoid arthritis, OP-Osteoporosis.

The study outcomes

The bone mineral density (BMD g/cm^2) was measured at calcaneus by standardized quantitative ultrasound (QUS, Hologic Inc., Bedford, MA, USA) utilizing T-scores based on WHO criteria [18], which were obtained from the automated equipment. T-score refers to the ratio between patient's BMD and that of young adult population of same sex and ethnicity. T-score of > -1 was taken as normal, between -1 and -2.5 osteopenic and < -2.5 as osteoporotic.

Daily calibration was performed during the entire study period by a trained technician. The coefficients of variation of the accuracy of the QUS measurement were 0.9%. The QUS technology is less expensive, portable and also has the advantage of not using ionizing radiation, so it is safer than dual energy X-ray absorptiometry (DEXA).

Statistical analysis

Continuous variables were analyzed to determine whether they followed normal distributions, using the Kolmogorov-Smirnov Test. Variables that were not normally distributed were log-transformed to approximate a normal distribution for analysis. Results are described as mean ± SD or median, unless stated otherwise. Differences in variables between subjects grouped by RA were determined by one way analysis of variance. Among groups, differences in properties were detected by χ^2 analysis.

Univariate regression analysis was performed to determine variables associated with outcomes (T-score or OP), and to estimate confounding factors possibly disturbing the relation of RA to outcomes (T-score or OP). Multivariable regression (MR) was performed to control potential confounding factors and determine the independent contribution of variables to outcomes (T-score or OP). Results were analyzed using the Statistical Package for Social Sciences for Windows, version 16.0 (SPSS, Chicago, IL, USA). Tests were two-sided, and a *P*-value of < 0.05 was considered significant. Odds ratios (OR) with 95% confidence intervals (CI) were calculated for the relative risk of RA with the outcome of OP.

Results

Clinical characteristics of subjects

The clinical baseline characteristics of the 1041 Chinese male subjects are listed in **Table 1**. In the non-RA sample, the mean age was 64.18 years. The proportions of subjects having current smoking and alcohol habits were 36.45% and 29.84%, respectively. The prevalence of HTN in the non-RA sample, coronary artery disease (CAD), DM, Gout and OP were 46.17%, 10.64%, 9.78%, and 3.62% and 8.36%, respectively. An average T-score of -1.22 was reported in our study sample. There were no significant differences in age, smoking

Table 2. Univariate linear regression analysis for associations among variables and T-score

Variables	*β*	SE	*P* value	95% CI for B
Age	-0.009	0.003	0.002	-0.014-0.003
Smoking	-0.044	0.057	0.441	-0.157-0.068
Alcohol intake	-0.048	0.060	0.420	-0.166-0.069
Exercise	0.060	0.024	0.049	1.002-0.121
Education	0.104	0.027	< 0.001	0.052-0.156
Oil	-0.004	0.003	0.194	-0.009-0.002
HTN	0.087	0.056	0.117	-0.022-0.196
CAD	-0.085	0.092	0.359	-0.266-0.096
DM	0.060	0.095	0.523	-0.125-0.246
Gout	0.076	0.151	0.613	-0.220-0.373
Vitamin D	0.026	0.172	0.881	-0.311-0.363
RA	-0.248	0.153	0.105	-0.547-0.052

Note: HTN-hypertension, CAD-coronary artery disease, DM-diabetes mellitus, RA-Rheumatoid arthritis.

habits, exercise and education among groups according to RA (*P* value > 0.05 for all). There were significant differences in the prevalence of OP between the two groups (*P* value = 0.005).

Univariate analysis for T-score

Univariate linear regression analyses were developed to include demographical information, medical history, and lifestyle to estimate the association of various clinical factors and T-score (**Table 2**). The variables age, exercise, and education preference were significantly associated with the T-score. The comparison of T-scores among groups according to RA showed that the mean T-score was -1.22 and -1.47 in participants without RA and with RA, respectively. There were no significant differences between the two groups (*P* value = 0.105).

Univariate analysis for OP

Univariate logistic analyses were performed to evaluate associations with OP. The results indicate that age, RA, alcohol intake, exercise, education, and frequency of fish food intake were significantly associated with OP (*P* value < 0.05 for all, **Table 3**). The comparison of prevalence of OP among groups according to model 1 reported that the prevalence of OP was 8.36% and 21.62% in participants without RA and with RA, respectively. There were significant differences between the two groups (*P* value = 0.005).

Multiple variable analysis for OP

Multivariate linear regression analyses were developed to include RA and the outcome of T-score. After adjustment for relevant potential confounding factors, no significant associations were reported (*P*-value = 0.232, data not shown). Multivariate logistic regression analyses were employed to evaluate the association between RA and the OP outcome. After adjustment for relevant potential confounding factors, the multivariate logistic regression analyses detected significant associations (*P*-value = 0.013, **Table 4**). In participants with RA, the OR for OP was 3.191 in model 1 (95% CI: 1.284-7.932).

Discussion

OP in men results in considerable economic costs and heavy burden to the society, while it still generally remains unrecognized, underdiagnosed and undertreated [19]. Our extensive and community-based prevalence study in a cohort of general Chinese men has shown a significant association between RA and OP: the men with RA had a significant higher prevalence of OP (21.62% in RA group *vs* 8.36% in non-RA group, *P* = 0.005; **Table 1**) than those without RA. However, no significant association between RA and T-score (standard deviation above or below the mean for young adults, derived from measuring calcaneal BMD) was observed (-1.47±0.82 in RA group *vs* -1.22± 0.92 in non-RA group, *P* = 0.105; **Table 1**). The participants involved in our study were a random sample of Chinese men living in both rural and urban communities, covering the age ranging from 30-90 years. Our sample covered a wide range of age because the fracture risk in men displays a bimodal distribution in age: 15-45 years and after 50 years [20, 21].

Our findings were consistent with other studies reported that RA was associated with OP and individuals with RA had a higher prevalence of OP compared to those without RA [10, 22-24]. A previous study has shown that there is a higher prevalence of OP in a group of Korean female RA patients (22.1%) compared with the healthy control group (11.4%) [10]. Similarly, a cross-sectional study also revealed doubled prevalence of OP in a cohort of 394 female patients with RA compared to control group [24]. A study focusing on young patients with RA (diagnosed

Table 3. Univariate logistic regression analysis for associations among variables and osteoporosis

Variable	*β*	S.E.	*P* value	OR	95.0% CI
Age	0.072	0.013	< 0.01	1.074	1.047-1.102
Smoking	-0.245	0.143	0.066	0.783	0.616-1.006
Alcohol intake	-0.344	0.134	0.010	0.709	0.545-0.921
Excise	-0.274	0.137	0.045	0.760	0.582-0.994
Education	-0.223	0.102	0.028	0.800	0.655-0.977
Oil	0.003	0.01	0.810	1.003	0.982-1.023
HTN	-0.023	0.216	0.915	0.977	0.640-1.492
CAD	0.388	0.318	0.222	1.474	0.791-2.75
DM	0.097	0.351	0.784	1.101	0.553-2.193
Gout	-1.313	1.019	0.198	0.269	0.037-1.984
Vitamin D	0.800	0.504	0.112	2.225	0.829-5.972
RA	1.107	0.415	0.008	3.025	1.342-6.820

Note: HTN-hypertension, CAD-coronary artery disease, DM-diabetes mellitus, RA-Rheumatoid arthritis.

Table 4. Multiple variables logistic regression analysis for associations between rheumatoid arthritis and osteoporosis

Variable	*β*	S.E.	*P* value	OR	95% CI
Rheumatoid arthritis	1.160	0.465	0.013	3.191	1.284-7.932

Note: the model adjusted for age, smoking, alcohol intake, education, exercise, and medical and therapy history.

before age 50) showed that young female patients with RA, but not the male, showed increased fracture risk before age 50 years [22]. In addition, RA has been shown as a strong risk factor for vertebrate fracture (6.5-fold higher risk in severe RA compared to controls of the same age) [25]. Because OP usually remains not diagnosed until the first fracture is manifested [1, 2], the significant association of OP and RA makes early diagnose of OP possible by identifying individuals at risk and may facilitate to reduce life-threatening fractures, and this will undoubtedly relieve socioeconomic burden of the society by providing preventive interventions.

It has been reported that several mechanisms may mediate OP in RA patients, such as accumulative glucocorticoid intake, relatively low amount of physical exercise, a generalized pro-inflammatory state, in addition to the classic risk factors for OP, including low body mass, high age, and being post-menopausal in female patients [26, 27]. A significant amount of bone loss in a periarticular process was observed in early RA, and long term RA may even lead to systemic OP [28, 29]. It is suggested that there is elevated osteoclast activation and thus bone resorption in RA and this change in bone remodeling could cause OP. Several bone homeostasis mediators, such as OPG, RANK and RANKL, may be involved in RA-associated OP. For example, Xu et al. reported a lower OPG/RANKL ratio in RA patients [30]. The gene expressions of these mediators, together with the Wnt signaling pathway, were affected in RA patients. Upregulation of WNT10B, LRP6, DKK-1 and IL-17 genes were detected in the bone samples of RA patients [31]. All these studies provide potential therapeutic regimens to prevent and treat OP in RA patients. For example, inhibiting bone resorption combined with stimulating bone formation may be more potent in treating RA-associated OP [32].

Our study has provided significant clinical and therapeutic potential; however, several limitations should be acknowledged and could be addressed by future studies. Although the prevalence of RA is ~0.5-1.0% in the general population [6], our sample size of the RA group was limited. Since the participants in our study were from rural and urban communities in Shanghai ranging from 30-90 years old, data in other age groups and broader geographic representations would provide a more thorough picture about the association between OP and RA. Moreover, we used a subjective self-reported questionnaire in our study due to convenience, relatively low cost, and large-scale coverage; however, the data could be subject to individual's personal bias.

Conclusion

Our findings suggested that OP was independently and significantly associated with RA. The prevalence of OP was higher in the Chinese men with RA as compared with those without RA. Further investigation of the pathophysiological mechanisms underlying RA-associated OP may be beneficial for OP prevention and treatment.

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Disclosure of conflict of interest

None.

Abbreviations

BMD, Bone mass density; BM-MNC, Bone marrow-derived mononuclear cell; BMI, Body mass index; CAD, Coronary artery disease; CI, Confidence intervals; DM, Diabetes; DXA, Dual-energy X-ray; HTN, Hypertension; GFR, Glomerular filtration rate, OR, Odds ratios; OP, Osteoporosis; QUS, Quantitative ultrasound; RA, Rheumatoid arthritis.

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