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The relationship between hormone replacement therapy and symptomatic spine osteoarthritis : A nationwide health survey analysis of the elderly Korean population

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Title:

The relationship between hormone replacement therapy and symptomatic spine osteoarthritis

: A nationwide health survey analysis of the elderly Korean population

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Abstract

Objectives

To identify the effect of hormone replacement therapy (HRT) on symptomatic spine osteoarthritis (OA).

Methods and design

Cross-sectional study of a nationwide survey was performed.

Setting

This study collected data from the fifth Korean National Health and Nutrition Examination Survey (KNHANES V-5; 2010–2012).

Participants

After excluding ineligible respondents, the total number of participants in this study was 4,265 females. All participants reported symptoms and disabilities related to spine OA. In addition, plain radiographs of the spine were taken of all patients.

Primary and secondary outcome measures

Demographic and lifestyle variables was compared between HRT and non-HRT group.

In addition, radiographic examination and symptom assessment was performed to determine the existence of spine OA.

Results

In terms of demographic factors, marital status, education, income, and HRT were significantly related to spine OA morbidity. A risk analysis of related factors showed significant effects of HRT and age on spine OA (odds ratios: 0.717 and 1.257, $P<0.05$). Nevertheless, in the HRT group, smokers had a significantly increased risk of spine OA ($P<0.05$). The spine OA group exhibited a significantly lower prevalence

of HRT. In addition, the HRT group demonstrated a lower incidence of symptomatic spine OA. Calculated risks for compromised morbidity with HRT to incidence of spine OA were 0.717 (odds ratio). The duration of HRT was also related to the risk of spine OA. The group that had been taking medication for more than one year showed significantly decreased risks (odds ratio: 0.686) compared to patients with less than one year of medication (odds ratio: 0.744; $P<0.05$).

Conclusion

Women receiving HRT showed a significantly lower prevalence of spine OA. Hormone replacement therapy was closely related to spine OA morbidity.

Key words: Osteoarthritis, Spine, Hormone replacement therapy

Strength and limitations of this study

-Study included a large cross-sectional population and utilized sophisticated statistical methods, which may enhance the significance of the result.

-Study included analysis of demographic and lifestyle variables as well as radiographic examination and symptom assessment, which may enhance the significance of the result.

-Cross-sectional study design prevented establishing causal relationships between HRT and OA.

-More sophisticated diagnostic tools, such as magnetic resonance imaging or computed tomography, may be needed to evaluate the precise status of patient joints. -The prevalence or etiology of OA may also be influenced by ethnic or environmental factors, which may decrease the generalizability of our study.

Introduction

Menopause is a particularly influential period during which women adapt to a new biological state. Women in the postmenopausal period tend to have lower estradiol and serotonin concentrations and high levels of follicle stimulating hormone.[1-4] Hormone replacement therapy (HRT) has shown several benefits for elderly females because it minimizes symptoms related to estrogen deficiency.[1, 3-8] However, few studies have investigated the effects of hormonal therapy on the musculoskeletal system. Recently, more people are experiencing degenerative osteoarthritis (OA), which can occur in several mobile joints of the body, including the spine. The objective of this study was to estimate the association between hormonal factors and spine OA in a Korean population. We analyzed a large cross-sectional population using data from the Korea National Health and Nutrition Examination Survey (KNHANES) to determine the relationship between HRT and symptomatic spine OA.

Methods

Study population

The study design was cross-sectional using three years of data from the Fifth Korean National Health and Nutrition Examination Survey (KNHANES-V: 2010–2012). The KNHANES is a nationwide health and nutrition survey that is conducted regularly. The number of participants who completed both the health interview and health examination surveys was 25,534 (Figure 1). We excluded men (n=11,616), pre-menopausal women (n=9,372) and those with missing data for variables included in the analysis (n=281). The remaining 4,265 participants had undergone physical and laboratory examinations, including a radiographic examination of the spine. In addition, health interview data were retrieved, including demographic and lifestyle variables. All participants provided informed consent, and the Korea Centers for Disease Control and Prevention Institutional Review Board approved this study (2010-02CON-21-C, 2011-02CON-06-C, 2012-01EXP-01-2C).

Radiographic examination and symptom assessment

Anteroposterior and lateral pain radiographic examinations of the lumbar spine were taken using a SD3000 Synchro Stand (Accele Ray, Switzerland). Radiographic changes of each joint were independently assessed by two radiologists using the Kellgren/Lawrence (KL) grading system as follows: Grade 0, no visible features of OA, doubtful/questionable osteophytes; Grade 1, minimal, definitive small osteophytes; and Grade 2, definitive moderate osteophytes or subchondral bone cysts and sclerosis with or without foraminal stenosis.[9] The presence of radiographic OA was defined as a KL grade of 2 or more. If the grades given by the

two radiologists differed, the higher grade was accepted. The concordance rate regarding the KL grade within one grade for the same case was 94.76%. In addition, all patients described their joint-related symptoms (e.g., spine), and these symptoms were scored. Participants who had experienced arthritic pain for more than one month in the past three months were asked to report the pain's intensity regardless of whether they used medication using a numeric rating scale (NRS) ranging from 0–10.

Demographic and lifestyle variables

HRT was defined as more than one year of regular hormone medication intake. Exogenous hormone-related factors included oral contraceptive (OC) use duration and HRT starting age and duration. Demographic variables were age, gender, monthly household income, marital status, current residence, education level, smoking status (never smoker, past smoker or current smoker), alcohol consumption (g/d), and physical activity (low, moderate or high). Household income was calculated as the monthly household income divided by the square root of the number of members. Education was classified by years of schooling (<6 years, 7–9 years, 10–12, and >12 years). Marital status was stratified into three groups: never married, married and living with a spouse, or married but living alone due to divorce or the death of a spouse. Respondents who had smoked more than 100 cigarettes in their lifetime were classified as smokers and placed into the smoker group. Physical activity was quantified according to the Korean version of the International Physical Activity Questionnaire. Body weight and height were obtained, and the body mass index was calculated by dividing the body weight in kg by the height^2 in m^2. Waist circumference was measured between the lower costal margin and the iliac crest.

We defined obesity as a body mass index ≥25.

Statistical analyses

Statistical analyses were conducted using SAS survey procedures (version 9.3; SAS Institute, Cary, NC, US) in a manner that reflected the sampling weights and provided nationally representative estimates. The characteristics of patients with spine OA were compared with those of participants without spine OA using two independent sample *t*-tests, a one-way analysis of variance for continuous variables and Chi-square tests for categorical variables. Multivariate logistic regression analyses were conducted to investigate the relationship between parameters. A *p*-value <0.05 was considered statistically significant.

Results

The relationship between demographic factors and spine OA

We defined spine OA as definite osteoarthritis on plain radiographs with related spinal pain. The mean age of the study population was 64.3 ± 0.2 (50–94) years. In terms of demographic factors, marital status, education, income, and HRT were significantly related to spine OA morbidity (Table 1, $P<0.05$). A risk analysis of related factors showed significant effects of HRT and age on spine OA (odds ratios: 0.717 and 1.257, respectively, Table 2, $P<0.05$). However, in the HRT group, smokers showed a significantly increased risk of spine OA (odds ratio (OR): 11.3) compared to nonsmokers (Table 3).

Relationship between HRT and spine OA

The HRT group had a lower prevalence of spine OA ($P<0.05$). In addition, the spine OA group showed a significantly lower rate of HRT (Table 4, $P<0.05$). Calculated risks for compromised morbidity were 0.717 (odds ratio) compared to the control group (Table 5). Solitary radiographic spine OA or solitary symptom groups also showed a lower percentage of HRT than controls (ORs: 0.723 and 0.916, respectively); however, the radiographic OA plus symptom group demonstrated the lowest percentage of HRT with a significantly higher morbidity (OR: 0.717, $P<0.05$). The duration of HRT was also related to the risk of spine OA; the >1 year of medication group had a significantly decreased risk (OR: 0.686) compared to the <1 year of medication group (OR: 0.840).

Discussion

Osteoarthritis involves degenerative changes in soft tissue, subchondral bone and hyaline cartilage, which lead to serious joint disability.[5, 10-14] Estrogen deficiency is related to the occurrence and progression of OA. Beginning in early menopause, the number of patients suffering from OA dramatically increases.[1-6, 10, 15, 16] The association between estrogen and OA has been verified in a murine model, and research on both estrogen deficiency and complement in articular cartilage has been conducted in animal models.[17] In many experimental animal studies, ovariectomy was reported to induce OA, while the estrogen complement delayed cartilage degeneration.[6, 8, 18-21] Estrogens act on estrogen receptors distributed throughout articular cartilage, the synovial membrane and ligaments and are thought to be related to degenerative changes. The positive effect `` women of the same age not receiving HRT. Moreover, patients receiving long-term HRT have a lower risk of knee and hip OA on plain radiographs compared to women who do not take HRT.[2, 3, 5, 13, 17]

In this study, age, marital status, educational level, and income were significantly related to osteoarthritis morbidity. However, BMI and body composition factors were not associated with spine OA. Previous studies have reported that joint pain is associated with several socio-demographic factors, such as gender, advanced age, low education level, smoking, and occupation.[10, 14] In particular, we found

significant relationships between factors in the female group and a higher prevalence of OA. It appears that the female population is more prone to OA, and this association may be related to hormonal influences, especially in an elderly population. Yang et al. reported that estrogens act on estrogen receptors distributed in articular cartilage, the synovial membrane and ligaments, which are thought to be related to degenerative changes.[17] They found that estrogen replacement therapy reduced the severity of OA in this experimental model. In our study, the HRT group showed a significantly lower prevalence of spine OA. The spine OA group also had a significantly lower rate of HRT. We therefore assumed that HRT might influence the incidence of spine OA. We found a positive, long-term effect of HRT, suggesting that estrogen deficiency may be a cause of OA and highlighting the need for further studies on the effects of estrogen on cartilage and bone. Although we could not determine cause and effect relationships, HRT may prevent OA. We hypothesized that HRT may have a positive effect on the development of radiographic spinal OA. Accordingly, spinal pain decreased along with a lowered prevalence of radiographic spinal OA. The duration of hormonal therapy also showed a significant relationship with the incidence of spine OA, which suggests the importance of continuous HRT in elderly females.

In the present study, smoking was not significantly related to spine OA morbidity, whereas smoking did impact the increased prevalence of spine OA, especially in the HRT group. However, the association between the risk of OA and smoking is still unclear. Some studies have reported that smoking is a protective factor against severe OA. In contrast, observational studies have concluded that smoking has no protective effect on the progression of OA.[7, 23-28] Nevertheless, smokers

prescribed HRT showed a significantly increased risk of OA compared to nonsmokers taking HRT, although the use of HRT had a protective effect on OA in the present study and also in some previous studies. These data showed that smoking may have a hazardous effect on joint cartilage that could eliminate the protective effect of OA used by HRT.

This study has several limitations. First, the cross-sectional study design prevented us from establishing causal relationships between HRT and OA. In this study, we could not match the OA site and spinal pain origin. We used a cross-sectional nationwide health survey with a brief health interview regarding pain related to each joint (e.g., the hip, knee and spine). Therefore, we could not clarify the relationship between spine OA and pain that was spinal in origin. Future prospective studies will be required to determine causal relationships. Second, the use of a single 11-point NRS did not allow us to evaluate the exact intensity of the respondents' acute and chronic pain, including functional impairment. In addition, more sophisticated diagnostic tools, such as magnetic resonance imaging or computed tomography, may be needed to evaluate the precise status of patient joints. Third, we cannot confirm or generalize our results to other populations because of ethnic differences between countries. The prevalence or etiology of OA may also be influenced by ethnic or environmental factors, which may decrease the generalizability of our study. Despite these limitations, our study included a large cross-sectional population and utilized sophisticated statistical methods. In addition, we found a significantly lower prevalence of spine OA in patients receiving HRT. We believe that our results will be helpful to physicians treating OA

In conclusion, HRT was closely related to spine OA morbidity. Populations receiving HRT showed a significantly lower prevalence of spine OA, and the duration of HRT was significantly related to OA spine prevalence.

Figure legends

Figure 1

A flow chart showing the inclusion and exclusion of participants according to the study's criteria.

Author contributions

All authors made substantial contributions to sections (1), (2) and (3) described below:

(1) Study conception and design, data acquisition, or data analysis and interpretations- **JHP**, **JYH**

(2) Drafting of the manuscript or revising it critically for important intellectual content- **KDH**, **SWH**

(3) Final approval of the version to be submitted- **EMC**, **JYH**

Conflict of interest

There are no conflicts of interest to report.

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Data sharing statement

Fifth Korean National Health and Nutrition Examination Survey (KNHANES-V: 2010–2012) data is available to any researchers under approval of IRB.

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Table 1. Parameter comparison between spine OA patients and the control group.

	No Osteoarthritis		Osteoarthritis		P-value
	N	%	N	%	
Smoking	154	6.1% (0.6)	38	4.5% (0.9)	0.1340
Drinking (heavy)	15	0.5% (0.2)	3	0.3% (0.2)	0.4693
High activity	527	15.1% (0.8)	104	12.1% (1.3)	0.0608
Urban residence	2410	71.0% (2.4)	639	69.6% (3.0)	0.5131
With spouse	2262	67.7% (1.1)	547	58.3% (2.1)	**<0.0001**
High education	788	22.0% (1.0)	150	14.7% (1.5)	**<0.0001**
Low income	1181	33.9% (1.1)	378	42.8% (2.0)	**<0.0001**
Contraceptive	760	21.2% (0.9)	202	21.6% (1.6)	0.8115
HRT	503	13.5% (0.7)	85	8.2% (1.1)	**0.0002**
BMI ≥25	1246	24.2% (0.1)	336	24.4% (0.1)	0.0593
WC ≥85	2018	82.3% (0.2)	542	83.0% (0.3)	0.0673

An age-adjusted logistic regression model was used.
(P<0.05 indicated statistical significance; (): standard error)
N: Absolute number in a group
BMI: Body mass index (kg/m^2)
WC: Waist circumference (cm)

Table 2. Risk analysis of spine OA with other related factors.

	OR	95% CI	P-value
Age (per 5 y)	1.257	1.194–1.323	**<0.0001**
Smoking	0.711	0.454–1.114	0.1367
Drinking (heavy)	0.853	0.220–3.308	0.8182
High activity	0.892	0.676–1.178	0.4197
Urban residence	1.077	0.870–1.332	0.4960
With spouse	1.031	0.837–1.269	0.7746
High education	0.912	0.693–1.201	0.5127
Low income	0.999	0.816–1.222	0.9889
Contraceptive	1.037	0.838–1.283	0.7359
HRT	0.717	0.527–0.976	**0.0344**
BMI ≥25	1.094	0.926–1.291	0.2920
WC ≥85	0.975	0.811–1.172	0.7884

An age-adjusted logistic regression model was used.
(P<0.05 indicated statistical significance; (): standard error)

Table 3. Prevalence and risk analysis for spine OA with smoking in the HRT group.

	Nonsmokers		Smokers		P-value
	N	%	N	%	
	475	83.5% (1.8)	17	98.4% (1.7)	**0.025**
Odd		1		11.32 (1.31–17.90)	**0.027**

Age, BMI, WC, drinking, and exercise were adjusted.
(P<0.05 indicated statistical significance; (): standard error, 95% CI)

Table 4. The prevalence of hormone therapy according to spinal pain and radiographic OA.

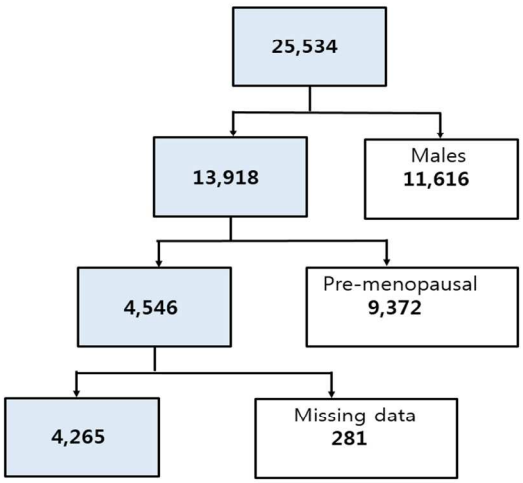
	No HRT		HRT		P-value
OA	N	%	N	%	
Grade 0	696	19.8% (1.0)	184	30.2% (2.4)	**<0.0001**
Grade 1	1454	40.8% (1.0)	253	46.5% (2.5)	
Grade 2	1527	39.4% (1.1)	151	23.3% (2.1)	
Sx	1302	34.7% (1.1)	162	26.0% (2.2)	**0.0005**
OA + Sx	819	21.0% (1.1)	85	13.1% (2.1)	**<0.0001**

An age-adjusted logistic regression model was used.
(P<0.05 indicated statistical significance; (): standard error)
OA: Participants with only radiological findings;
Sx: Respondents with only symptoms;
OA+Sx: Patients with both symptoms and radiological findings.

Table 5. Risk analysis of spine OA with hormone therapy.

HRT	OR	95% CI	P-value
OA	0.723	0.563–0.929	**0.011**
Sx	0.916	0.723–1.159	0.464
OA + Sx	0.717	0.527–0.976	**0.034**

An age-adjusted logistic regression model was used.
(P<0.05 indicated statistical significance; (): standard error)
OA: Participants with only radiological findings;
Sx: Patients with only symptoms;
OA+Sx: Respondents with both symptoms and radiological findings.



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STROBE Statement

Checklist of items that should be included in reports of observational studies

Section/Topic	Item No	Recommendation	Reported on Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	3
Objectives	3	State specific objectives, including any prespecified hypotheses	3
Methods			
Study design	4	Present key elements of study design early in the paper	4
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	4
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	4-6
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	4-6
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	4-6
Data sources/measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	4
Bias	9	Describe any efforts to address potential sources of bias	4-6
Study size	10	Explain how the study size was arrived at	4
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	5-6
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	4-6
		(*b*) Describe any methods used to examine subgroups and interactions	4-6
		(*c*) Explain how missing data were addressed	4-6
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	4-6
		(*e*) Describe any sensitivity analyses	4-6

Section/Topic	Item No	Recommendation	Reported on Page No
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	7
		(b) Give reasons for non-participation at each stage	7
		(c) Consider use of a flow diagram	7
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	7
		(b) Indicate number of participants with missing data for each variable of interest	7
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	7
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	7
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	7
		Cross-sectional study—Report numbers of outcome events or summary measures	7
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	7
		(*b*) Report category boundaries when continuous variables were categorized	7
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	7
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	7
Discussion			
Key results	18	Summarise key results with reference to study objectives	8
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	10
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	9
Generalisability	21	Discuss the generalisability (external validity) of the study results	8-11
Other Information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	12

**Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.*

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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The relationship between hormone replacement therapy and spinal osteoarthritis : A nationwide health survey analysis of the elderly Korean population

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Title:

The relationship between hormone replacement therapy and spinal osteoarthritis: A nationwide health survey analysis of the elderly Korean population

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Abstract

Objectives

To identify the effects of hormone replacement therapy (HRT) on spinal osteoarthritis (OA).

Methods and design

A cross-sectional study of a nationwide survey was performed.

Setting

This study collected data from the fifth Korean National Health and Nutrition Examination Survey (KNHANES V-5; 2010–2012).

Participants

After excluding ineligible respondents, the total number of participants in this study was 4,265 females. All participants reported symptoms and disabilities related to spinal OA. In addition, plain radiographs of the spine were taken of all patients.

Primary and secondary outcome measures

Demographic and lifestyle variables were compared between the HRT and non-HRT groups. In addition, radiographic examination and symptom assessment were performed to determine the existence of spinal OA.

Results

Demographic factors, marital status, education, income, and HRT all correlated with a decrease in spinal OA morbidity. A risk analysis of related factors showed that HRT and age had significant effects on spinal OA (odds ratios: 0.717 and 1.257, $P<0.05$). Nevertheless, in the HRT group, smokers had a significantly increased risk of spinal OA ($P<0.05$). In addition, the HRT group demonstrated a lower prevalence of spinal OA. The calculated risk for compromised morbidity with HRT compared to the

prevalence of spinal OA was 0.717 (odds ratio). The duration of HRT was also related to the risk for spinal OA. The group that had been taking HRT for more than one year showed significantly decreased risk (odds ratio: 0.686) compared to patients with less than one year of HRT (odds ratio: 0.744; $P<0.05$).

Conclusion

Women receiving HRT showed a significantly lower prevalence of spinal OA. HRT also correlated with a decrease in spinal OA morbidity.

Key words: Osteoarthritis, Spine, Hormone replacement therapy

Strength and limitations of this study

-This study analyzed a large cross-sectional population and used sophisticated statistical methods, which could enhance the significance of the results.

-The study included analysis of demographic and lifestyle variables as well as radiographic examinations and symptom assessment, which could enhance the significance of the results.

-The cross-sectional study design precluded establishment of a causal relationship between HRT and OA.

-More sophisticated diagnostic tools, such as magnetic resonance imaging or computed tomography, might be needed to evaluate the precise status of patient joints.

-The prevalence or etiology of OA could also be influenced by ethnic or environmental factors, which could decrease the generalizability of our results.

Introduction

Menopause is a particularly influential period during which women adapt to a new biological state. Women in the postmenopausal period tend to have low estradiol and serotonin concentrations and a high level of follicle stimulating hormone.[1-4] Hormone replacement therapy (HRT) has shown several benefits for elderly females because it minimizes symptoms related to estrogen deficiency.[1,3-8] However, few studies have investigated the effects of hormone therapy on the musculoskeletal system. Imada et al. performed a case-control study of the influence of oophorectomy on the development of degenerative spondylolisthesis. They reported that the abrupt decrease in estradiol level caused by oophorectomy could be a predisposing factor in degenerative spondylolisthesis at L4/5.[9] Recently, more people have begun experiencing degenerative osteoarthritis (OA), which can occur in several mobile joints of the body, including the spine. We hypothesized that HRT might prevent the onset of degenerative spinal disease and therefore might contribute to the prevention of low back pain.[10] The objective of this study was to estimate the associations between hormonal factors and spinal OA in a Korean population. We analyzed a large cross-sectional population using data from the Korea National Health and Nutrition Examination Survey (KNHANES) to determine the relationship between HRT and spinal OA.

Methods

Study population

The study design was cross-sectional, using three years of data from KNHANES-V (2010–2012), a nationwide health and nutrition survey that is conducted regularly. The number of participants who completed both the health interview and health examination surveys was 25,534 (Figure 1). We excluded men (n=11,616), pre-menopausal women (n=9,372) and those with missing data for variables included in the analysis (n=281). The remaining 4,265 participants underwent physical and laboratory examinations, including a radiographic examination of the spine. In addition, health interview data were retrieved, including demographic and lifestyle variables. All participants provided informed consent, and the Korea Centers for Disease Control and Prevention Institutional Review Board approved this study (2010-02CON-21-C, 2011-02CON-06-C, 2012-01EXP-01-2C).

Radiographic examination and symptom assessment

Anteroposterior and lateral plain radiographic examinations of the lumbar spine were taken using a SD3000 Synchro Stand (Accele Ray, Switzerland). Radiographic changes in each joint were independently assessed by two radiologists using the Kellgren/Lawrence (KL) grading system as follows: Grade 0, no visible features of OA, doubtful/questionable osteophytes; Grade 1, minimal, definitive small osteophytes; and Grade 2, definitive moderate osteophytes or subchondral bone cysts and sclerosis with or without foraminal stenosis.[11] The presence of radiographic OA was defined as a KL grade of 2 or more. If the grades given by the two radiologists differed, the higher grade was accepted. The concordance rate for

KL grades within one grade for the same case was 94.76%. In addition, all patients described their joint-related symptoms (e.g., spine), and those symptoms were scored. Participants who reported experiencing arthritic pain for more than one of the past three months were asked to report the pain intensity using a numeric rating scale (NRS) ranging from 0–10, regardless of whether they used medication.

Demographic and lifestyle variables

HRT was defined as use of more than one year of regular hormone medication. Exogenous hormone-related factors included oral contraceptive (OC) use duration and HRT starting age and duration. Demographic variables were age, gender, monthly household income, marital status, current residence, education level, smoking status (never smoker, past smoker, or current smoker), alcohol consumption (g/d), and physical activity (low, moderate, or high). Household income was calculated as the monthly household income divided by the square root of the number of members. Education was classified by years of schooling (<6 years, 7–9 years, 10–12 years, and >12 years). Marital status was stratified into three groups: never married, married and living with spouse, and divorced/widowed. Respondents who had smoked more than 100 cigarettes in their lifetime were classified as smokers and placed into the smoker group. Physical activity was quantified according to the Korean version of the International Physical Activity Questionnaire. Body weight and height were obtained, and the body mass index was calculated by dividing the body weight in kg by the height^2 in m^2. Waist circumference was measured between the lower costal margin and the iliac crest. We defined obesity as a body mass index ≥25.

Statistical analyses

Statistical analyses were conducted using SAS survey procedures (version 9.3; SAS Institute, Cary, NC, US) in a manner that reflected the sampling weights and provided nationally representative estimates. The characteristics of patients with spinal OA were compared with those of participants without spinal OA using two independent sample *t*-tests, a one-way analysis of variance for continuous variables, and Chi-square tests for categorical variables. Multivariate logistic regression analyses were conducted to investigate the relationships between parameters.

Results

The relationships between demographic factors and spinal OA

We defined spinal OA as definite osteoarthritis on plain radiographs with related spinal pain. The mean age of the study population was 64.3 ± 0.2 (50–94) years. The total numbers of participants with spinal OA and HRT were 904 and 588, respectively, out of 4,265 total participants. We found no spinal OA in 3,361 participants, regardless of HRT status. In terms of demographic factors, marital status, education, income, and HRT correlated with a decrease in spinal OA morbidity (Table 1). A risk analysis of related factors showed that HRT had significant effects on spinal OA (odds ratio (OR): 0.717, Table 2). However, in the HRT group, smokers showed a significantly increased risk of spinal OA (OR: 11.3) compared to nonsmokers (Table 3).

Relationship between HRT and spinal OA

The HRT group had a lower prevalence of spinal OA. In addition, the spinal OA group showed a significantly lower rate of HRT (Table 4). Calculated risks for compromised morbidity were 0.717 (OR) compared to the control group (Table 5). The solitary radiographic spinal OA and solitary symptom groups also showed a lower percentage of HRT than controls (OR: 0.723 and 0.916, respectively); however, the radiographic OA plus symptom group had the lowest percentage of HRT and significantly higher morbidity (OR: 0.717). The duration of HRT was also related to the risk of spinal OA: the >1 year of medication group had a significantly decreased

risk (OR: 0.686) compared to the <1 year of medication group (OR: 0.840).

Discussion

Osteoarthritis involves degenerative changes in soft tissue, subchondral bone, and hyaline cartilage that lead to serious joint disability.[5,12-16] Estrogen deficiency is related to the occurrence and progression of OA. Beginning in early menopause, the number of women who suffer from OA increases dramatically.[1-6,12,17,18] The association between estrogen and OA has been verified in a murine model, and research on both estrogen deficiency and complement in articular cartilage has been conducted in animal models.[19] In many experimental animal studies, ovariectomy was reported to induce OA, whereas estrogen complement delayed cartilage degeneration.[6,8,20-23] Estrogens act on estrogen receptors distributed throughout the articular cartilage, synovial membrane, and ligaments and are thought to be related to degenerative changes. In addition, Gruber et al. suggested the expression and localization of estrogen receptor-beta in the annulus cells of human intervertebral discs. They provided evidence of ER beta gene expression in human intervertebral disc cells in vivo and in vitro. Culturing annulus cells in the presence of 17-beta-estradiol significantly increased cell proliferation.[24] Baron et al. investigated the effects of menopause and HRT on the intervertebral discs and reported that estrogen-replete women appear to maintain higher intervertebral discs than untreated post-menopausal women.[25] Moreover, patients receiving long-term HRT have a lower risk of knee and hip OA on plain radiographs than women who do not take HRT.[2,3,5,15,19]

In this study, age, marital status, education level, and income all significantly correlated with OA morbidity. However, BMI and body composition factors were not associated with spinal OA. Previous studies have reported that joint pain is associated with several socio-demographic factors, such as gender, advanced age, low education level, smoking, and occupation.[10,14] In particular, we found significant relationships between factors in the female group and higher prevalence of OA. It appears that the female population is more prone to OA, and this association could be related to hormonal influences, especially in an elderly population. Wang et al. reported increased low back pain prevalence in females than males, especially after menopause. They reported that higher low back pain prevalence in school age girls compared to school age boys is likely caused by psychological factors, female hormone fluctuation, and menstruation. Compared with young and middle-aged subjects, a further increase in low back pain prevalence in females compared with males was noted after menopause.[26] In our study, the HRT group showed a significantly lower prevalence of spinal OA. We therefore assume that HRT can influence the prevalence of spinal OA. We found a positive, long-term effect of HRT, suggesting that estrogen deficiency could be a cause of OA and highlighting the need for further studies on the effects of estrogen on cartilage and bone. Although we could not determine cause and effect relationships, HRT might prevent OA. We hypothesized that HRT has a protective effect on the development of spinal OA. In accordance with our hypothesis, both spinal pain and prevalence of radiographic spinal OA were lower in the HRT group. The duration of hormonal therapy also showed a significant relationship with prevalence of spinal OA, which suggests the importance of continuous HRT in elderly females.

In the present study, smoking was not significantly related to spinal OA morbidity, but it was correlated with an increased prevalence of spinal OA, especially in the HRT group. However, the association between the risk of OA and smoking is still unclear. Some studies have reported that smoking is a protective factor against severe OA. In contrast, observational studies have concluded that smoking has no protective effect on the progression of OA.[7,25,27-33] In any case, smokers prescribed HRT showed a significantly increased risk of OA compared to nonsmokers taking HRT, even though the use of HRT had an overall protective effect against OA. These data show that smoking could have a hazardous effect on joint cartilage that could eliminate the protective effect of HRT for OA.

This study has several limitations. First, the cross-sectional study design prevented us from establishing causal relationships between HRT and OA. In this study, we could not match the OA site and spinal pain origin. We used a cross-sectional nationwide health survey with a brief health interview regarding pain related to each joint (e.g., hip, knee, and spine). Therefore, we could not clarify the relationship between spinal OA and pain with a spinal origin. Future prospective studies will be required to determine causal relationships. Second, the use of a single 11-point NRS did not allow us to evaluate the exact intensity of the respondents' acute and chronic pain, including functional impairment. In addition, more sophisticated diagnostic tools, such as magnetic resonance imaging or computed tomography, might be needed to evaluate the precise status of patient joints. Third, the prevalence and etiology of OA might be influenced by ethnic or environmental factors, which could decrease the generalizability of our study. In addition, the relatively small number of smokers in the

HRT group could dilute the significance of that result. Despite these limitations, our study analyzed a large cross-sectional population and used sophisticated statistical methods. We found a significantly lower prevalence of spinal OA in patients receiving HRT. We believe that our results will be helpful to physicians treating OA

In conclusion, populations receiving HRT showed a significantly lower prevalence of spinal OA, and the duration of HRT was significantly related to spinal OA prevalence.

Figure legends

Figure 1

A flow chart showing the inclusion and exclusion of participants according to study criteria.

Author contributions

All authors made substantial contributions to sections (1), (2), and (3) as described below:

(1) Study conception and design, data acquisition, and data analysis and interpretation- **JHP**, **JYH**

(2) Drafting of the manuscript or revising it critically for important intellectual content- **KDH**, **SWH**

(3) Final approval of the version to be submitted- **EMC**, **JYH**

Conflict of interest

There are no conflicts of interest to report.

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Data sharing statement

Fifth Korean National Health and Nutrition Examination Survey (KNHANES-V: 2010–2012) data are available to any researchers under approval of an IRB.

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Table 1. Parameter comparison between spinal OA patients and the control group.

	No Osteoarthritis	Osteoarthritis	P-value
	N = 3361	**N** = 904	
Smoking	6.1% (0.6)	4.5% (0.9)	0.1340
Drinking (heavy)	0.5% (0.2)	0.3% (0.2)	0.4693
High activity	15.1% (0.8)	12.1% (1.3)	0.0608
Urban residence	71.0% (2.4)	69.6% (3.0)	0.5131
With spouse	67.7% (1.1)	58.3% (2.1)	**<0.0001**
High education	22.0% (1.0)	14.7% (1.5)	**<0.0001**
Low income	33.9% (1.1)	42.8% (2.0)	**<0.0001**
Contraception	21.2% (0.9)	21.6% (1.6)	0.8115
HRT	13.5% (0.7)	8.2% (1.1)	**0.0002**
BMI ≥25	24.2% (0.1)	24.4% (0.1)	0.0593
WC ≥85	82.3% (0.2)	83.0% (0.3)	0.0673

An age-adjusted logistic regression model was used.
(P<0.05 indicates statistical significance; (): standard error)
N: Number in a group
BMI: Body mass index (kg/m^2)
WC: Waist circumference (cm)

Table 2. Risk analysis of spinal OA with other related factors.

	OR	95% CI	P-value
Age	**1**		
Smoking	0.711	0.454–1.114	0.1367
Drinking (heavy)	0.853	0.220–3.308	0.8182
High activity	0.892	0.676–1.178	0.4197
Urban residence	1.077	0.870–1.332	0.4960
With spouse	1.031	0.837–1.269	0.7746
High education	0.912	0.693–1.201	0.5127
Low income	0.999	0.816–1.222	0.9889
Contraception	1.037	0.838–1.283	0.7359
HRT	0.717	0.527–0.976	**0.0344**
BMI ≥25	1.094	0.926–1.291	0.2920
WC ≥85	0.975	0.811–1.172	0.7884

An age-adjusted logistic regression model was used.
(P<0.05 indicates statistical significance; (): standard error)

Table 3. Prevalence and risk analysis for spinal OA with smoking in the HRT group.

	Nonsmokers	Smokers	P-value
Spine OA	83.5% (1.8)	98.4% (1.7)	**0.025**
Odds	**1**	11.32 (1.31–17.90)	**0.027**

Age, BMI, WC, drinking, and exercise were adjusted.
(P<0.05 indicates statistical significance; (): standard error, 95% CI)

Table 4. The prevalence of hormone therapy according to spinal pain and radiographic OA.

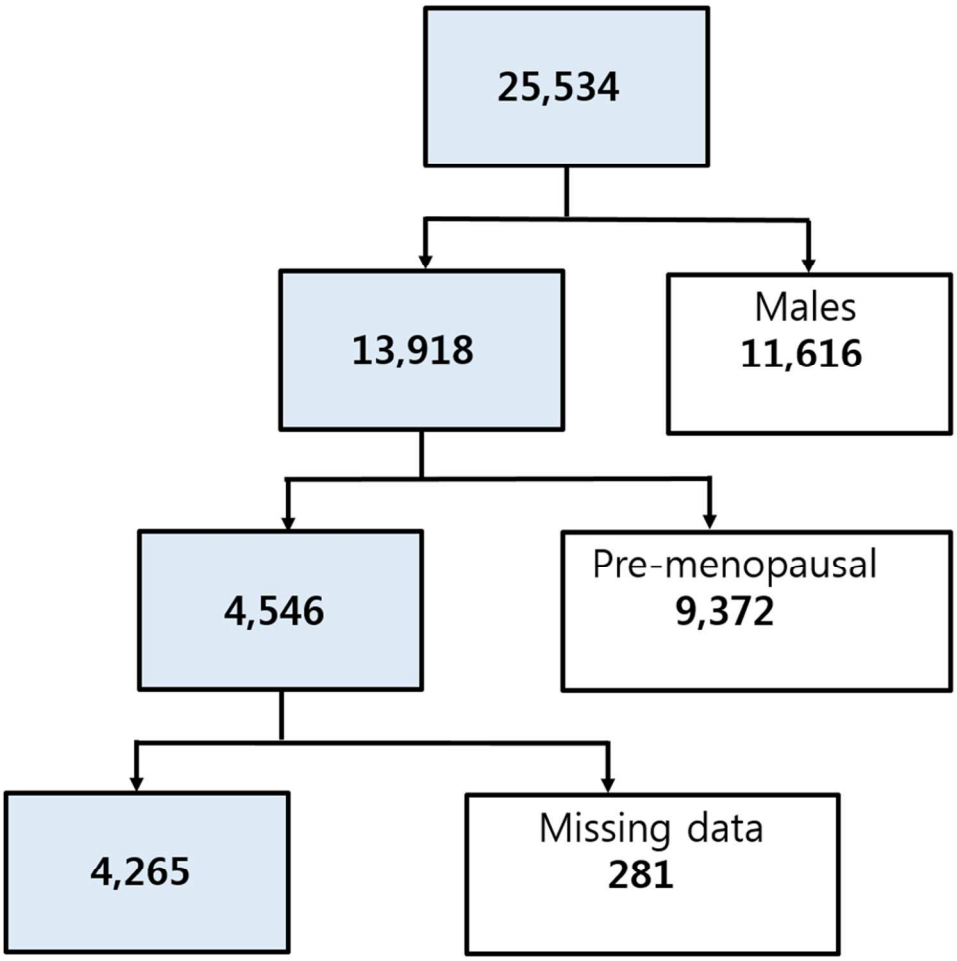
	No HRT		HRT		P-value
OA	**N**	%	**N**	%	
Grade 0	696	19.8% (1.0)	184	30.2% (2.4)	**<0.0001**
Grade 1	1454	40.8% (1.0)	253	46.5% (2.5)	
Grade 2	1527	39.4% (1.1)	151	23.3% (2.1)	
Sx	1302	34.7% (1.1)	162	26.0% (2.2)	**0.0005**
OA + Sx	819	21.0% (1.1)	85	13.1% (2.1)	**<0.0001**

An age-adjusted logistic regression model was used.
(P<0.05 indicates statistical significance; (): standard error)
OA: Participants with only radiological findings;
Sx: Participants with only symptoms;
OA+Sx: Participants with both symptoms and radiological findings.

Table 5. Risk analysis of spinal OA with hormone therapy.

HRT	OR	95% CI	P-value
OA	0.723	0.563–0.929	**0.011**
Sx	0.916	0.723–1.159	0.464
OA + Sx	0.717	0.527–0.976	**0.034**

An age-adjusted logistic regression model was used.
(P<0.05 indicates statistical significance; (): standard error)
OA: Participants with only radiological findings;
Sx: Participants with only symptoms;
OA+Sx: Participants with both symptoms and radiological findings.



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STROBE Statement

Checklist of items that should be included in reports of observational studies

Section/Topic	Item No	Recommendation	Reported on Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	3
Objectives	3	State specific objectives, including any prespecified hypotheses	3
Methods			
Study design	4	Present key elements of study design early in the paper	4
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	4
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	4-6
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	4-6
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	4-6
Data sources/measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	4
Bias	9	Describe any efforts to address potential sources of bias	4-6
Study size	10	Explain how the study size was arrived at	4
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	5-6
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	4-6
		(*b*) Describe any methods used to examine subgroups and interactions	4-6
		(*c*) Explain how missing data were addressed	4-6
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	4-6
		(*e*) Describe any sensitivity analyses	4-6

Section/Topic	Item No	Recommendation	Reported on Page No
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	7
		(b) Give reasons for non-participation at each stage	7
		(c) Consider use of a flow diagram	7
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	7
		(b) Indicate number of participants with missing data for each variable of interest	7
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	7
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	7
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	7
		Cross-sectional study—Report numbers of outcome events or summary measures	7
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	7
		(*b*) Report category boundaries when continuous variables were categorized	7
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	7
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	7
Discussion			
Key results	18	Summarise key results with reference to study objectives	8
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	10
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	9
Generalisability	21	Discuss the generalisability (external validity) of the study results	8-11
Other Information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	12

**Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.*

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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The relationship between hormone replacement therapy and spinal osteoarthritis : A nationwide health survey analysis of the elderly Korean population

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Title:

The relationship between hormone replacement therapy and spinal osteoarthritis: A nationwide health survey analysis of the elderly Korean population

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Abstract

Objectives

To identify the effects of hormone replacement therapy (HRT) on spinal osteoarthritis (OA).

Methods and design

A cross-sectional study of a nationwide survey was performed.

Setting

This study collected data from the fifth Korean National Health and Nutrition Examination Survey (KNHANES V-5; 2010–2012).

Participants

After excluding ineligible respondents, the total number of participants in this study was 4,265 females. Participants were asked to report symptoms and disabilities related to spinal OA. In addition, plain radiographs of the spine were taken of all patients.

Primary and secondary outcome measures

Demographic and lifestyle variables were compared between the HRT and non-HRT groups. In addition, radiographic examination and symptom assessment were performed to determine the existence of spinal OA.

Results

Marital status, education, income, and HRT were correlated with spinal OA. A risk analysis of related factors showed that HRT and age had effects on spinal OA (odds ratios: 0.717 and 1.257). Nevertheless, in the HRT group, smokers had a increased risk of spinal OA. In addition, the HRT group demonstrated a lower prevalence of spinal OA. The calculated risk for compromised morbidity with HRT compared to the

prevalence of spinal OA was 0.717 (odds ratio). The duration of HRT was also related to the risk for spinal OA. The group that had been taking HRT for more than one year showed decreased risk (odds ratio: 0.686) compared to patients with less than one year of HRT (odds ratio: 0.744; $P<0.05$).

Conclusion

Women receiving HRT showed a lower prevalence of spinal OA. HRT also correlated with a decrease in spinal OA morbidity.

Key words: Osteoarthritis, Spine, Hormone replacement therapy

Strength and limitations of this study

-This study analyzed a large cross-sectional population and used sophisticated statistical methods, which could enhance the significance of the results.

-The study included analysis of demographic and lifestyle variables as well as radiographic examinations and symptom assessment, which could enhance the significance of the results.

-The cross-sectional study design precluded establishment of a causal relationship between HRT and OA.

-More sophisticated diagnostic tools, such as magnetic resonance imaging or computed tomography, might be needed to evaluate the precise status of patient joints.

-The prevalence or etiology of OA could also be influenced by ethnic or environmental factors, which could decrease the generalizability of our results.

Introduction

Menopause is a particularly influential period during which women adapt to a new biological state. Women in the postmenopausal period tend to have low estradiol and serotonin concentrations and a high level of follicle stimulating hormone.[1-4] Hormone replacement therapy (HRT) has shown several benefits for elderly females because it minimizes symptoms related to estrogen deficiency.[1,3-8] However, few studies have investigated the effects of hormone therapy on the musculoskeletal system. Imada et al. performed a case-control study of the influence of oophorectomy on the development of degenerative spondylolisthesis. They reported that the abrupt decrease in estradiol level caused by oophorectomy could be a predisposing factor in degenerative spondylolisthesis at L4/5.[9] Recently, more people have begun experiencing degenerative osteoarthritis (OA), which can occur in several mobile joints of the body, including the spine. We hypothesized that HRT might prevent the onset of degenerative spinal disease and therefore might contribute to the prevention of low back pain.[10,11] The objective of this study was to estimate the associations between hormonal factors and spinal OA in a Korean population. We analyzed a large cross-sectional population using data from the Korea National Health and Nutrition Examination Survey (KNHANES) to determine the relationship between HRT and spinal OA.

Methods

Study population

The study design was cross-sectional, using three years of data from KNHANES-V (2010–2012), a nationwide health and nutrition survey that is conducted regularly. The KNHNES is conducted annually by the Korean Centers for Disease Control for civilians, and a survey of spine osteoarthritis was included. The KNHNES is a nationally representative database on health and nutrition, and the subjects were selected from stratified, multistage probability samples of Korean households based on gender, age, and geographical area.The number of participants who completed both the health interview and health examination surveys was 25,534 (Figure 1). We excluded men (n=11,616), pre-menopausal women (n=9,372) and those with missing data for variables included in the analysis (n=281). The remaining 4,265 participants underwent physical and laboratory examinations, including a radiographic examination of the spine. In addition, health interview data were retrieved, including demographic and lifestyle variables. All participants provided informed consent, and the Korea Centers for Disease Control and Prevention Institutional Review Board approved this study (2010-02CON-21-C, 2011-02CON-06-C, 2012-01EXP-01-2C).

Radiographic examination and symptom assessment

Anteroposterior and lateral plain radiographic examinations of the lumbar spine were taken using a SD3000 Synchro Stand (Accele Ray, Switzerland). Radiographic changes in each joint were independently assessed by two radiologists using the Kellgren/Lawrence (KL) grading system as follows: Grade 0, no visible features of OA, doubtful/questionable osteophytes; Grade 1, minimal, definitive small

osteophytes; and Grade 2, definitive moderate osteophytes or subchondral bone cysts and sclerosis with or without foraminal stenosis.[12] The presence of radiographic OA was defined as a KL grade of 2 or more. If the grades given by the two radiologists differed, the higher grade was accepted. The concordance rate for KL grades within one grade for the same case was 94.76%. In addition, all patients described their joint-related symptoms (e.g., spine), and those symptoms were scored. Participants who reported experiencing arthritic pain for more than one of the past three months were asked to report the pain intensity using a numeric rating scale (NRS) ranging from 0–10, regardless of whether they used medication.

Demographic and lifestyle variables

HRT was defined as use of more than one year of regular hormone medication. Exogenous hormone-related factors included oral contraceptive (OC) use duration and HRT starting age and duration. Demographic variables were age, gender, monthly household income, marital status, current residence, education level, smoking status (never smoker, past smoker, or current smoker), alcohol consumption (g/d), and physical activity (low, moderate, or high). Household income was calculated as the monthly household income divided by the square root of the number of members. Education was classified by years of schooling (<6 years, 7–9 years, 10–12 years, and >12 years). Marital status was stratified into three groups: never married, married and living with spouse, and divorced/widowed. Respondents who had smoked more than 100 cigarettes in their lifetime were classified as smokers and placed into the smoker group. Physical activity was quantified according to the Korean version of the International Physical Activity Questionnaire. Body weight and height were obtained, and the body mass index was calculated by

dividing the body weight in kg by the height^2 in m^2. Waist circumference was measured between the lower costal margin and the iliac crest. We defined obesity as a body mass index ≥25.

Statistical analyses

Statistical analyses were conducted using SAS survey procedures (version 9.3; SAS Institute, Cary, NC, US) in a manner that reflected the sampling weights and provided nationally representative estimates. The characteristics of patients with spinal OA were compared with those of participants without spinal OA using two independent sample *t*-tests, a one-way analysis of variance for continuous variables, and Chi-square tests for categorical variables. Multivariate logistic regression analyses were conducted to investigate the relationships between parameters.

Results

The relationships between demographic factors and spinal OA

We defined spinal OA as definite osteoarthritis on plain radiographs with related spinal pain. The mean age of the study population was 64.3 ± 0.2 (50–94) years. The total numbers of participants with spinal OA and HRT were 904 and 588, respectively, out of 4,265 total participants. We found no spinal OA in 3,361 participants, regardless of HRT status. In terms of demographic factors, marital status, education, income, and HRT correlated with a decrease in spinal OA morbidity (Table 1). A risk analysis of related factors showed that HRT had significant effects on spinal OA (odds ratio (OR): 0.717, Table 2). However, in the HRT group, smokers showed a significantly increased risk of spinal OA (OR: 11.3) compared to nonsmokers (Table 3).

Relationship between HRT and spinal OA

The HRT group had a lower prevalence of spinal OA. In addition, the spinal OA group showed a significantly lower rate of HRT (Table 4). Calculated risks for compromised morbidity were 0.717 (OR) compared to the control group (Table 5). The solitary radiographic spinal OA and solitary symptom groups also showed a lower percentage of HRT than controls (OR: 0.723 and 0.916, respectively); however, the radiographic OA plus symptom group had the lowest percentage of HRT and significantly higher morbidity (OR: 0.717). The duration of HRT was also related to the risk of spinal OA: the >1 year of medication group had a significantly decreased

risk (OR: 0.686) compared to the <1 year of medication group (OR: 0.840).

Discussion

Osteoarthritis involves degenerative changes in soft tissue, subchondral bone, and hyaline cartilage that lead to serious joint disability.[5,13-17] Estrogen deficiency is related to the occurrence and progression of OA. Beginning in early menopause, the number of women who suffer from OA increases dramatically.[1-6,13,18,19] The association between estrogen and OA has been verified in a murine model, and research on both estrogen deficiency and complement in articular cartilage has been conducted in animal models.[20] In many experimental animal studies, ovariectomy was reported to induce OA, whereas estrogen complement delayed cartilage degeneration.[6,8,21-24] Estrogens act on estrogen receptors distributed throughout the articular cartilage, synovial membrane, and ligaments and are thought to be related to degenerative changes. In addition, Gruber et al. suggested the expression and localization of estrogen receptor-beta in the annulus cells of human intervertebral discs. They provided evidence of ER beta gene expression in human intervertebral disc cells in vivo and in vitro. Culturing annulus cells in the presence of 17-beta-estradiol significantly increased cell proliferation.[25] Baron et al. investigated the effects of menopause and HRT on the intervertebral discs and reported that estrogen-replete women appear to maintain higher intervertebral discs than untreated post-menopausal women.[26] Moreover, patients receiving long-term HRT have a lower risk of knee and hip OA on plain radiographs than women who do not take HRT.[2,3,5,16,20]

In this study, age, marital status, education level, and income all significantly correlated with OA morbidity. However, BMI and body composition factors were not associated with spinal OA. Previous studies have reported that joint pain is associated with several socio-demographic factors, such as gender, advanced age, low education level, smoking, and occupation.[10,15] In particular, we found significant relationships between factors in the female group and higher prevalence of OA. It appears that the female population is more prone to OA, and this association could be related to hormonal influences, especially in an elderly population. Wang et al. reported increased low back pain prevalence in females than males, especially after menopause. They reported that higher low back pain prevalence in school age girls compared to school age boys is likely caused by psychological factors, female hormone fluctuation, and menstruation. Compared with young and middle-aged subjects, a further increase in low back pain prevalence in females compared with males was noted after menopause.[27] In our study, the HRT group showed a significantly lower prevalence of spinal OA. We therefore assume that HRT can influence the prevalence of spinal OA. We found a positive, long-term effect of HRT, suggesting that estrogen deficiency could be a cause of OA and highlighting the need for further studies on the effects of estrogen on cartilage and bone. Although we could not determine cause and effect relationships, HRT might prevent OA. We hypothesized that HRT has a protective effect on the development of spinal OA. In accordance with our hypothesis, both spinal pain and prevalence of radiographic spinal OA were lower in the HRT group. The duration of hormonal therapy also showed a significant relationship with prevalence of spinal OA, which suggests the importance of continuous HRT in elderly females.

In the present study, smoking was not significantly related to spinal OA morbidity, but it was correlated with an increased prevalence of spinal OA, especially in the HRT group. However, the association between the risk of OA and smoking is still unclear. Some studies have reported that smoking is a protective factor against severe OA. In contrast, observational studies have concluded that smoking has no protective effect on the progression of OA.[7,26,28-34] In any case, smokers prescribed HRT showed a significantly increased risk of OA compared to nonsmokers taking HRT, even though the use of HRT had an overall protective effect against OA. These data show that smoking could have a hazardous effect on joint cartilage that could eliminate the protective effect of HRT for OA.

This study has several limitations. First, the cross-sectional study design prevented us from establishing causal relationships between HRT and OA. In this study, we could not match the OA site and spinal pain origin. We used a cross-sectional nationwide health survey with a brief health interview regarding pain related to each joint (e.g., hip, knee, and spine). Therefore, we could not clarify the relationship between spinal OA and pain with a spinal origin. Future prospective studies will be required to determine causal relationships. Second, the use of a single 11-point NRS did not allow us to evaluate the exact intensity of the respondents' acute and chronic pain, including functional impairment. In addition, more sophisticated diagnostic tools, such as magnetic resonance imaging or computed tomography, might be needed to evaluate the precise status of patient joints. Third, the prevalence and etiology of OA might be influenced by ethnic or environmental factors, which could decrease the generalizability of our study. In addition, the relatively small number of smokers in the

HRT group could dilute the significance of that result. Despite these limitations, our study analyzed a large cross-sectional population and used sophisticated statistical methods. We found a significantly lower prevalence of spinal OA in patients receiving HRT. We believe that our results will be helpful to physicians treating OA

In conclusion, populations receiving HRT showed a significantly lower prevalence of spinal OA, and the duration of HRT was significantly related to spinal OA prevalence.

Figure legends

Figure 1

A flow chart showing the inclusion and exclusion of participants according to study criteria.

Author contributions

All authors made substantial contributions to sections (1), (2), and (3) as described below:

(1) Study conception and design, data acquisition, and data analysis and interpretation- **JHP**, **JYH**

(2) Drafting of the manuscript or revising it critically for important intellectual content- **KDH**, **SWH**

(3) Final approval of the version to be submitted- **EMC**, **JYH**

Conflict of interest

There are no conflicts of interest to report.

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Data sharing statement

Fifth Korean National Health and Nutrition Examination Survey (KNHANES-V: 2010–2012) data are available to any researchers under approval of an IRB.

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Table 1. Parameter comparison between spinal OA patients and the control group.

	No Osteoarthritis	Osteoarthritis	P-value
	N = 3361	**N** = 904	
Smoking	6.1% (0.6)	4.5% (0.9)	0.1340
Drinking (heavy)	0.5% (0.2)	0.3% (0.2)	0.4693
High activity	15.1% (0.8)	12.1% (1.3)	0.0608
Urban residence	71.0% (2.4)	69.6% (3.0)	0.5131
With spouse	67.7% (1.1)	58.3% (2.1)	**<0.0001**
High education	22.0% (1.0)	14.7% (1.5)	**<0.0001**
Low income	33.9% (1.1)	42.8% (2.0)	**<0.0001**
Contraception	21.2% (0.9)	21.6% (1.6)	0.8115
HRT	13.5% (0.7)	8.2% (1.1)	**0.0002**
BMI ≥25	24.2% (0.1)	24.4% (0.1)	0.0593
WC ≥85	82.3% (0.2)	83.0% (0.3)	0.0673

An age-adjusted logistic regression model was used.
(P<0.05 indicates statistical significance; (): standard error)
N: Number in a group
BMI: Body mass index (kg/m^2)
WC: Waist circumference (cm)

Table 2. Risk analysis of spinal OA with other related factors.

	OR	95% CI	P-value
Age	**1**		
Smoking	0.711	0.454–1.114	0.1367
Drinking (heavy)	0.853	0.220–3.308	0.8182
High activity	0.892	0.676–1.178	0.4197
Urban residence	1.077	0.870–1.332	0.4960
With spouse	1.031	0.837–1.269	0.7746
High education	0.912	0.693–1.201	0.5127
Low income	0.999	0.816–1.222	0.9889
Contraception	1.037	0.838–1.283	0.7359
HRT	0.717	0.527–0.976	**0.0344**
BMI ≥25	1.094	0.926–1.291	0.2920
WC ≥85	0.975	0.811–1.172	0.7884

An age-adjusted logistic regression model was used.
(P<0.05 indicates statistical significance; (): standard error)

Table 3. Prevalence and risk analysis for spinal OA with smoking in the HRT group.

	Nonsmokers	Smokers	P-value
Spine OA	83.5% (1.8)	98.4% (1.7)	**0.025**
Odds	**1**	11.32 (1.31–17.90)	**0.027**

Age, BMI, WC, drinking, and exercise were adjusted.
(P<0.05 indicates statistical significance; (): standard error, 95% CI)

Table 4. The prevalence of hormone therapy according to spinal pain and radiographic OA.

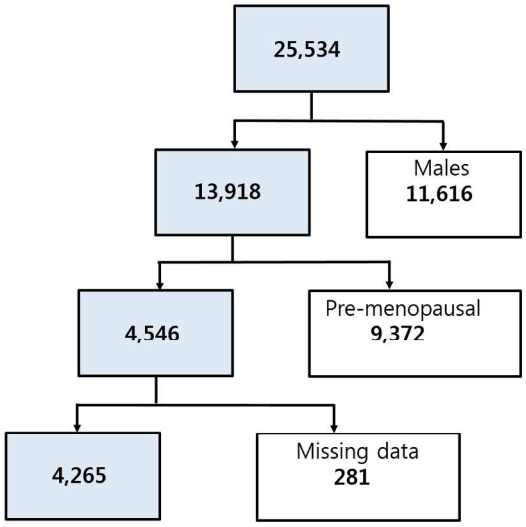
	No HRT		HRT		P-value
OA	**N**	%	**N**	%	
Grade 0	696	19.8% (1.0)	184	30.2% (2.4)	**<0.0001**
Grade 1	1454	40.8% (1.0)	253	46.5% (2.5)	
Grade 2	1527	39.4% (1.1)	151	23.3% (2.1)	
Sx	1302	34.7% (1.1)	162	26.0% (2.2)	**0.0005**
OA + Sx	819	21.0% (1.1)	85	13.1% (2.1)	**<0.0001**

An age-adjusted logistic regression model was used.
(P<0.05 indicates statistical significance; (): standard error)
OA: Participants with only radiological findings;
Sx: Participants with only symptoms;
OA+Sx: Participants with both symptoms and radiological findings.

Table 5. Risk analysis of spinal OA with hormone therapy.

HRT	OR	95% CI	P-value
OA	0.723	0.563–0.929	**0.011**
Sx	0.916	0.723–1.159	0.464
OA + Sx	0.717	0.527–0.976	**0.034**

An age-adjusted logistic regression model was used.
(P<0.05 indicates statistical significance; (): standard error)
OA: Participants with only radiological findings;
Sx: Participants with only symptoms;
OA+Sx: Participants with both symptoms and radiological findings.



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STROBE Statement

Checklist of items that should be included in reports of observational studies

Section/Topic	Item No	Recommendation	Reported on Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	3
Objectives	3	State specific objectives, including any prespecified hypotheses	3
Methods			
Study design	4	Present key elements of study design early in the paper	4
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	4
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	4-6
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	4-6
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	4-6
Data sources/measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	4
Bias	9	Describe any efforts to address potential sources of bias	4-6
Study size	10	Explain how the study size was arrived at	4
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	5-6
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	4-6
		(*b*) Describe any methods used to examine subgroups and interactions	4-6
		(*c*) Explain how missing data were addressed	4-6
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	4-6
		(*e*) Describe any sensitivity analyses	4-6

Section/Topic	Item No	Recommendation	Reported on Page No
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	7
		(b) Give reasons for non-participation at each stage	7
		(c) Consider use of a flow diagram	7
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	7
		(b) Indicate number of participants with missing data for each variable of interest	7
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	7
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	7
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	7
		Cross-sectional study—Report numbers of outcome events or summary measures	7
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	7
		(*b*) Report category boundaries when continuous variables were categorized	7
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	7
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	7
Discussion			
Key results	18	Summarise key results with reference to study objectives	8
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	10
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	9
Generalisability	21	Discuss the generalisability (external validity) of the study results	8-11
Other Information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	12

**Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.*

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.