

A Case-Control Study of Risk Factors Associated to Intravertebral Spinal Disc Degeneration in Greece

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ABSTRACT

AIM: Few data exist concerning the natural history of degenerative spinal osteoarthritis (OA) and its associated risk factors. The aim of this Greek case-control study is to examine risk factors that have been previously shown or hypothesized to be correlated to spinal intravertebral disc degeneration (IDD).

MATERIALS AND METHODS: From May 2009 to December 2012, 818 matched pairs (cases and controls) were recruited and

participated in the case-control study. All clinical data were collected through a detailed interview and meticulous clinical and radiological evaluation. The severity of disease was determined by radiological Kellgren-Lawrence (K/L) grades and Lanes scores.

RESULTS: Female gender ($p=0.001$), old age ($p=0.06$), heavy bodily fatigue ($p=0.031$), lower educational level ($p=0.019$) and osteopenia or osteoporosis ($p=0.005$ and $p=0.0005$, respectively) were significantly associated to increased risk of spinal intravertebral disc degeneration. In the female subgroup population, menopause was a significant risk factor ($p=0.012$) breast feeding, on the contrary, was protective and associated to a decreased probability of IDD ($p=0.013$). No significant difference was found between the two groups as far as smoking status was concerned.

CONCLUSIONS: Systemic risk factors play a role in the aetiology of spinal IDD in Greece. Female sex, overweight, heavy bodily fatigue, lower educational level and decreased bone density statuses are strongly associated with the diagnosis of symptomatic disease.

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Key words: Case-control; Intravertebral disc degeneration; Risk factors

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INTRODUCTION

Osteoarthritis (OA) is a highly prevalent, disabling and complex disease^[1-4], difficult to diagnose and define. The Subcommittee on Osteoarthritis of the American College of Rheumatology (ACR) Diagnostic and Therapeutic Criteria Committee defined OA as 'A

heterogeneous group of conditions that lead to joint symptoms and signs which are associated with defective integrity of articular cartilage, in addition to related changes in the underlying bone at the joint margins^[2].

The concept that binds the heterogeneous disease labelled as OA is the pathological one: focal areas of loss of articular cartilage within synovial joints, associated with hypertrophy of bone (osteophytes and subchondral bone sclerosis)^[5-6]. These pathological changes, when severe, produce all radiological changes (loss of joint space and osteophytes)^[7]. A Kellgren & Lawrence radiological OA score of 2-4 is still the most widely used definition of radiological OA in epidemiological studies^[8].

This pathological phenomenon can occur in any joint^[1-4]. Still, no internationally agreed standard definition criteria for spine osteoarthritis exist^[1-3,7].

Although there are no official classification criteria for osteoarthritis of the spine, intravertebral disc degeneration (IDD) is often characterized by narrowing of the disc space, disc height loss and the presence of osteophytes, seen at plain radiographs that often precedes facet joint osteoarthritis^[9-10]. IDD cannot be defined as real OA because the facet joints are the only synovial joints in the spine and used as a proxy for OA of the spine, in particular when imaging with computed tomography and/or magnetic resonance imaging are not available. A recent nomenclature, providing further insight of the DD (Disc Degeneration) disease suggests that it consists not only of disc narrowing and osteophytes, but of disc herniation and black discs as well^[10].

A discussion of all potential risk factors contributing to the disease evolution emphasizes the role of genetic, systemic and local factors; however the results depend enormously on the site of the joint involved^[11,12]. Age, race, sex, obesity and body mass index (BMI), tobacco use, occupational status and physical activity have been traditionally evaluated, though with often inconsistent results and both positive and null associations. Overweight at young age, as well as BMI above 25 kg/m² has been significantly correlated to lumbar disc degeneration^[11-12]. A clear, significant and independent association of bone mineral density at the hip and lumbar spine with lumbar IDD has been also suggested^[13]. No clear associations have been demonstrated with smoking, occupational exposures, heavy physical activity or hormonal replacement therapy use^[11].

The epidemiology of osteoarthritis differs significantly depending on the subjects' race; between Caucasian and Asian populations significant differences have been observed^[14]. Data on the prevalence of spinal disc degeneration in population-based studies from European countries are limited. In Greece, no such study has ever been performed^[15].

The aim of this study is to examine risk factors that have been previously shown or hypothesized to be correlated to IDD of the spine. We examined age, sex, weight, height, as well as BMI, smoking, family, educational and hormonal status, occupational exposure and/or work overload, presence and severity of back pain, degree of physical activity and duration of breast-feeding, as well as presence or absence of osteoporosis in an adult case-control study in Greece.

MATERIALS AND METHODS

We performed a case-control study from May 2009 to December 2012. Patients were recruited at the Palliative Care Unit of Aretaieion University Hospital, in Athens, from urban, suburban and rural areas. From a total of 930 subjects eligible for the study, a remaining 818 matched pairs (cases and controls) agreed to be interviewed. Of the

471 cases, 70 patients were excluded because of incomplete data on their history. The final sample consisted of 401 cases (141 men and 260 women) and 417 (223 men and 194 female) controls. Patients and controls were matched for age and sex. All controls eligible to participate were thoroughly evaluated for the absence of spinal IDD. Only subjects with absence of pain reported at the spine and with negative imaging of the vertebrae were considered as controls. More specifically, all controls had normal plain radiographs of the spine. No disc space narrowing, loss of disc height, disc bulging/prominence or osteophytes was seen. Furthermore, during the study period none of the control subjects developed pain or neurological symptoms/signs suggesting the presence of previous subclinical disc prolapse/herniation. Whenever a potential subject evaluated as a control had a suspicious spinal plain X-ray, he/she were immediately excluded from the analysis. As a result, a total of 56 potential controls (36 females and 20 males, mean age 60.4 years) were excluded.

At initial evaluation, patients with secondary osteoarthritis and other chronic rheumatic disorders were excluded. Exclusion criteria included (1) major congenital or developmental diseases and bone dysplasias; (2) major local factors such as severe scoliosis; (3) certain metabolic diseases associated with joint disease such as hemochromatosis and Wilson's disease; (4) inflammatory joint disease such as rheumatoid arthritis, ankylosing spondylitis or other autoimmune disorders; (5) other bone diseases such as morbus Paget, history of Perthe's disease or osteochondritis; (6) intra-articular fractures, earlier trauma or surgery to the spine and (7) patients with crystal deposition arthropathies, uncontrolled diabetes mellitus and/or pathological thyroid conditions. Patients with an underlying malignancy or aged ≥ 75 , and non-Greek, non-Caucasian origin were also excluded.

Age was self reported. Height and weight were measured with participants wearing indoor clothing and without shoes. Body mass index (BMI) was calculated as weight in kilograms divided by length in meters squared (kg/m²) and was subsequently expressed as World Health Organization BMI class groups^[16].

Controls and cases were questioned in detail regarding their educational level and occupation, socioeconomic status, medical history and life style habit. A detailed physical and neurological examination was performed. All measurements took place and questions were asked by the palliative care experts (physicians and research nurses) at the initial extensive interview as part of the baseline measurements. Each individual patient completed the Greek Brief Pain Inventory (G-BPI) tool^[17].

Different job categories were identified according to an expert judgment of job titles by Schellart^[18]. The category of physically demanding work was characterized by lifting of heavy objects, handling of heavy tools, stooping frequently in combination with standing or walking. Examples of occupations in this category were jobs in construction work, the agricultural sector and industry. As a result, the interviewer asked cases and controls their occupation and classified them into three major categories: physically demanding manual jobs, non-manual jobs and house-working. Manual workers (construction, farming) were classified in the first category, office workers and/or retired in the second, while housewives in the third one^[18]. Occupational exposure was defined on the work overload and cases or controls working in the first and third category were considered as so (Table 2). Cases and controls exercising regularly for at least 6 months^[19] were considered as having a degree of physical activity, when compared to those without any form of exercise (presence versus absence of physical activity).

The bone density status was obtained for all cases and controls,

both males and females. It was subsequently classified as normal or as presence of osteoporosis or osteopenia. For bone mineral density measurements (BMD), dual-energy X-ray Absorptiometry (DXA) method measurements was used (Hologic Explorer, Bedford, Massachusetts, USA). Daily calibration using phantom was accomplished. A-P lumbar spine (L1-4 vertebrae) and hip BMD measurements were calculated. According to the World Health Organization (WHO) classification system, T-score ≥ -1.0 is considered as normal, while a T-score ≤ -2.5 is considered as osteoporosis and between -1 and -2.5 as osteopenia (such criteria are related to both women and men >50 years)^[20]. For female subjects, in particular, nullparity versus multiparity and prior breast-feeding was recorded. Information about total lifetime breast-feeding history was obtained and its total length (all number of breast-fed children included) was subsequently categorized as following: 3 months, 4-11 months, 12-23 months and 24 months^[21].

Kellgren-Lawrence (K/L) grade represents disease severity, as reflected on plain radiographs^[8]. The scale scoring system is with ascending severity and a score ≥ 2 depicts radiographically osteoarthritis in the particular vertebrae. Based solely on radiographic findings, osteoarthritis can be classified as: 0=absent, 1=doubtful, 2=minimal, 3=moderate and 4=severe. Osteoarthritis of the spine can be defined as pain or stiffness on most days (50%) of the prior month in addition to a score of two in at least one disc or one apophyseal joint^[22]. Unfortunately, despite the fact that IDD has been recently examined using the gold standard imaging method of Magnetic Resonance Imaging (MRI) of the spine and facet joint osteoarthritis by Computed Tomography, such imaging modalities were not available for the total population of our study cohort. As a result, only plain X-rays were used for evaluation and analysis.

Furthermore, all available spine levels (cervical and/or lumbar on the lateral radiography) were scored for the presence and severity of osteophytes (anterior) and disc space narrowing, using the system by Lane *et al.*^[23]. This system grades both osteophytes and disc space narrowing on a scale from 0 to 3, which 0=none, 1=mild, 2=moderate, and 3=severe. The Lane atlas is one of the systems recommended in a recent review on existing grading scales^[23].

All spinal radiographs, for both cases and controls, were scored by a single reader, a blinded individual palliative care expert physician trained to score the radiographs with both the initial Kellgren-Lawrence criteria, as well as the subsequent grading by Lane *et al.* The palliative care expert was trained in a rheumatology clinic in order to do so and was blinded to the participants' clinical data. A random selection of 40 spinal radiographs (5%) was evaluated by another independent trained reader, a trained radiologist on orthopedic diagnosis, in order to obtain the inter-observer reproducibility^[21,24]. The interclass correlation coefficient for both osteophytes and disc space narrowing indicated a good reproducibility. We, as others previously^[21,24], used the two different definitions of intervertebral disc degeneration proposed in the study of de Schepper *et al.*, i.e. 'narrowing' and 'osteophytes'. 'Narrowing' was defined as disc space narrowing (grade ≥ 1) at two or more vertebral levels, and 'osteophytes' as the presence of osteophytes (grade ≥ 2) at two or more vertebral levels^[21,24].

For both patients and controls, further examinations were performed, whenever necessary. For the patient cohort, further imaging was performed on an individual basis, in particular whenever invasive treatment measures were to be undertaken. All control subjects evaluated in our study had radiological findings similar to those of pediatric populations and the grading of IDD was 0. As mentioned previously, 40 control subjects (5%) were randomly

selected and re-evaluated by another independent trained radiologist. These subjects were submitted, additionally, to a spinal MRI (cervical/lumbar). None of the harmless imaging findings, suggested in the nonneclature by Fardon *et al.*^[10] such as minor bulging of the annuli, age related desiccation, anterior and lateral marginal vertebral body osteophytes, prominence of disc material beyond one end plate as a result of luxation of one vertebral body relative to the adjacent vertebral body were found in our asymptomatic control cohort.

The protocol for research work was approved by the Human Ethics Committee of Aretaieion University Hospital and conforms to the provisions of the declaration of Helsinki.

Statistical analysis

Age, weight, height, BMI and G-BPI score, (and number of children for female subjects) were analyzed as continuous variables, whereas family/marital status, smoking and hormonal status, level of education, occupation, work overload, physical activity and bone density status, (along with prior breast-feeding or not for female subjects), were recorded as categorical variables. For the evaluation of the BMI, an additional categorical classification was preformed. Data was expressed as mean \pm standard deviation (S.D for continuous variables and as percentages for categorical data). The Kolmogorov—Smirnov test was utilized for normality analysis of the parameters.

Univariate analyses were made by using the chi-square test or alternatively the Fisher exact test to analyze the relation between the outcome variable and the qualitative variables. The Student t-test was used to analyze the relation between the outcome variable and the quantitative measures.

All potential risk factors, whether or not they demonstrated significant associations in univariate analysis were included in the multivariate model, and the Enter method was used. Goodness of fit was evaluated using the Hosmer-Lemeshow statistic. The odds ratio (OR) of relapse was then estimated in a multivariable logistic regression model, and ORs and their 95% confidence intervals (95% CI) were presented. All tests are two-sided, a p -value of <0.05 was used to denote statistical significance. All analyses were carried out using the statistical package SPSS version 17.00 (Statistical Package for the Social Sciences, SPSS Inc., Chicago, Ill., USA).

RESULTS

Results of univariate analysis are demonstrated in Tables 1 and 2. People with IDD of the spine were older, with higher BMI, lower height and a higher level of pain than those without the disease ($p<0.01$). The percent of occupational exposure due to a physically demanding manual work was higher in the patient group ($p<0.005$). Furthermore, patients with IDD did not exercise regularly, when compared to controls ($p=0.0005$). Considering bone density status, osteoporosis or osteopenia was more frequent in cases ($p=0.0005$). This is probably due to the higher percentage of women in the group of patients with spinal IDD (64.8%, vs 46.5% in the control group) ($p<0.005$).

No statistically significant difference was found between the two groups as far as marital status, smoking status and level of education is concerned. When BMI was analyzed as a categorical variable, statistical significance between patients and controls was found only for obese subjects. 33.2% of cases were obese, when compared to 25.9% of controls ($p<0.05$).

40.5% of male patients and 32.1% of female patients had 'osteophytes' at two or more vertebral levels. Furthermore, 'disc

narrowing' was depicted in 26.6% of males and 55.4% of female cases. Mean values of K/L and Lane criteria were 3, thus, suggesting that the disease had an increased severity. Absence of radiological findings was reported in both the male and female control cohort (mean K/L and Lane criteria values were 0). The 40 control subjects randomly selected for further radiological evaluation of the spine (cervical/lumbar) had no MR imaging findings of DD disease.

Multivariate analysis revealed that female gender ($p=0.001$), high BMI ($p=0.06$), as well as the presence of osteopenia or osteoporosis ($p=0.005$ and $p=0.0005$, respectively) were significantly associated to increased risk of spinal IDD (Table 3). Occupational work overload, in particular manual, physically demanding jobs tended to show a statistical significant correlation to IDD ($p=0.031$), but did not reach it in the final analysis. Similar results were noticed with educational status, since subjects with a lower educational level showed a trend to present with IDD ($p=0.019$)

Analysis in the subgroup of male and female subjects

In males, the percent of occupational exposure and work overload was higher in the group of patients ($p<0.005$) (Table 2). The final enter logistic regression multivariate analysis demonstrated that, severe occupational exposure ($p=0.077$) and lower educational level ($p=0.036$) tended to be significantly associated to increased risk of IDD (Table 3).

In females, cases were older, with higher BMI, and higher weight than those without IDD ($p<0.01$) (Table 1).The percent of female subjects with severe occupational exposure, even due to house

working, and menopause was higher in the IDD group ($p<0.005$) (Table 2). The bone density analysis revealed that osteoporosis or osteopenia was more frequent in cases than in controls (36.3% versus 21.1%, $p<0.0005$) (Table 2). Furthermore, the percent of breast feeding women was lower in the group of patients (77.3%), when compared to controls (84.5%) ($p=0.050$) (Table 2).The final enter logistic regression multivariate analysis in females showed that BMI ($p=0.035$), bone status (osteopenia or osteoporosis) ($p=0.028$ and $p=0.0005$, respectively), and menopause ($p=0.012$) were significantly associated with an increased risk of IDD. On the contrary, breast feeding ($p=0.013$) was associated with decreased probability of IDD in females. All other variables did not reach statistical significance.

Pain analysis

The percentage of controls with positive family history and pain was zero.

Analysis of pain (G-BPI) was performed only in the patients' subgroup. Back pain was reported by all cases average pain was severe (mean values >6). Cases experienced the worst pain in the whole spine ($p=0.004$). Pain was worse at the time of physical examination ($p<0.0005$) and interrupted the patients' general activity and sleep in an important level ($p<0.0005$ and $p=0.033$, respectively). Increased, as well as worst pain levels, were found to be significantly correlated to advanced age ($p<0.001$). Older people also reported a worse interference of pain to general activity and sleep ($p<0.0001$). Female sex was significantly correlated to worse pain during initial examination ($p<0.01$), as well as to the worst interference of pain

Table 1 Univariate correlation of age, BMI, height, weight and number of children (quantitative variables) with the presence/absence of spinal IDD.

	Total population			Male population			Female population		
	IDD (n=401)	Control (n=417)	p-value	IDD (n=141)	Control (n=223)	p-value	IDD (n=260)	Control (n=194)	p-value
Age	58.49±11.47	56.02±12.67	0.004	55.07±11.76	55.53±13.15	0.734	60.34±10.89	56.58±12.11	0.001
BMI	28.10±4.58	27.36±4.52	0.021	27.86±3.81	27.65±4.02	0.616	28.22±4.95	27.03±5.03	0.012
Height	1.67±0.09	1.70±0.10	0.0005	1.76±0.07	1.76±0.108	0.731	1.62±0.06	1.63±0.07	0.800
Weight	78.10±14.87	78.34±15.91	0.823	85.95±13.89	85.02±14.33	0.543	73.84±13.62	70.65±14.09	0.016
Number of Children	---	---	---	---	---	---	1.77±0.95	1.72±1.00	0.580

BMI: Body Mass Index; IDD: Intervertebral Disc Degeneration.

Table 2 Univariate correlation of occupational exposure, physical activity, smoking, educational, marital and bone density statuses (qualitative variables) for both cases and controls, analyzed by gender.

		Total population			Male population			Female population		
		IDD (n=401)	Control (n=417)	p-value	IDD (n=141)	Control (n=223)	p-value	IDD (n=260)	Control (n=194)	p-value
Gender	male	141(35.2%)	223 (53.5%)	0.0005	---	---	---	---	---	---
	female	260 (64.8%)	194 (46.5%)		---	---		---	---	
Occupation	manual	161 (40.1%)	190 (45.6%)	0.0005	102 (72.3%)	150 (67.3%)	0.351	59 (22.7%)	40 (20.6%)	0.105
	non manual	95 (23.7%)	132 (31.7%)		39 (27.7%)	73 (32.7%)		56 (21.5%)	59 (30.4%)	
	houseworks	145 (36.2%)	95 (22.8%)		---	---		145 (55.8%)	95 (49.07%)	
Occupational exposure	no	285 (71.1%)	322 (77.2%)	0.045	62(44.0%)	136(61.0%)	0.002	223 (85.8%)	186 (95.9%)	0.0005
	yes	116 (28.9%)	95 (22.8%)		79(56%)	87(39%)		37 (14.2%)	8 (4.1%)	
Physical activity	yes	339(84.5%)	409(98.1%)	0.0005	22 (15.6%)	4(1.8%)	0.0005	220(84.6%)	190(97.9%)	0.0005
	no	62 (15.5%)	8(1.9%)		119(84.4%)	219(98.2%)		40 (15.4%)	4(2.1%)	
Smoking	never	258 (64.3%)	264 (63.3%)	0.787	61 (43.3%)	116 (52.0%)	0.263	197 (75.8%)	148 (76.3%)	0.557
	current	101 (25.2%)	113 (27.1%)		56 (39.7%)	76 (34.1%)		45 (17.3%)	37 (19.1%)	
	ex	42 (10.5%)	40 (9.6%)		24 (17.0%)	31 (13.9%)		18 (6.9%)	9 (4.6%)	
Family status	unmarried	84 (20.9%)	76 (18.2%)	0.334	24 (17.0%)	38 (17.0%)	0.985	60 (23.1%)	38 (19.6%)	0.420
	married	317 (79.1%)	341 (81.8%)		117 (83.0%)	185 (83.0%)		200 (76.9%)	156 (80.4%)	
Education	elementary	188 (46.9%)	179 (42.9%)	0.102	60 (42.6%)	95 (42.6%)	0.274	128 (49.2%)	84 (43.3%)	0.103
	high School	145 (36.2%)	132 (31.7%)		54 (38.3%)	71 (31.8%)		91 (35.0%)	61 (31.4%)	
	university	68 (17.0%)	106 (25.4%)		27 (19.1%)	57 (25.6%)		41 (15.8%)	49 (25.3%)	
Osteoporosis	no	273 (68.1%)	375 (99.3%)	0.0005	136 (96.5%)	222(99.6%)	NA	137 (52.7%)	153 (78.9%)	0.0005
	osteopenia	44 (11.0%)	19 (4.6%)		2 (1.5%)	0(0.0%)		42 (16.2%)	19 (9.8%)	
	osteoporosis	84 (20.9%)	23 (5.5%)		3 (2.0%)	1(0.4%)		81 (20.1%)	22 (11.3%)	
Breast feeding	no	---	---	---	---	---	---	59 (22.7%)	30 (15.5%)	0.050
	yes	---	---		---	---		201 (77.3%)	164 (84.5%)	
Menopause	no	---	---	---	---	---	---	46 (17.7%)	71 (36.6%)	0.0005
	yes	---	---		---	---		214 (82.3%)	123 (63.4%)	

IDD: Intervertebral Disc Degeneration.

Table 3 Multivariable logistic regression of risk factor variables.

	Reference category	Total population			Male population			Female population		
		OR	95%CI	p-value	OR	95%CI	p-value	OR	95%CI	p-value
Age	---	1.01	0.99-1.02	0.263	1.01	0.99-1.03	0.347	1.00	0.96-1.02	0.408
Gender	Male	2.02	1.34-3.04	0.001	---	---	---	---	---	---
BMI	---	1.03	1.00-1.07	0.050	1.00	0.95-1.06	0.864	1.05	1.00-1.09	0.035
Occupation				0.279						0.762
Non-manual	Manual	1.36	0.81-2.26	0.244	1.47	0.74-2.95	0.274	0.98	0.47-2.05	0.952
Housework		1.46	0.88-2.44	0.146	---	---	---	0.82	0.48-1.42	0.482
Occupational exposure	No	1.56	0.74-3.28	0.239	2.64	0.90-7.74	0.077	---	---	---
Family Status	Unmarried	0.87	0.59-1.27	0.459	0.93	0.50-1.72	0.820	1.16	0.68-1.97	0.597
Smoking				0.256			0.371			0.289
Current	Never	1.26	0.88-1.80	0.216	1.35	0.83-2.19	0.222	1.25	0.72-2.16	0.427
Ex		1.43	0.86-2.37	0.171	1.40	0.74-2.67	0.303	1.99	0.80-4.96	0.140
Education				0.089			0.086			0.769
High School	Elementary	1.56	1.08-2.25	0.019	1.80	1.04-3.11	0.036	1.02	0.63-1.64	0.937
University		1.13	0.65-1.98	0.668	1.16	0.52-2.55	0.717	0.78	0.36-1.69	0.528
Bone Density				0.0005						0.0005
Osteopenia	Normal	2.40	1.30-4.42	0.005	---	---	---	2.04	1.08-3.87	0.028
Osteoporosis		3.68	2.12-6.37	0.0005	---	---	---	3.85	2.14-6.94	0.0005
Breast feeding	No	---	---	---	---	---	---	0.48	0.27-0.86	0.013
Menopause	No	---	---	---	---	---	---	2.39	1.21-4.71	0.012

OR: Odds Ratio; CI: Confidence Interval.

with physical activity ($p < 0.001$) and sleep ($p < 0.01$). No statistical significance was found between all G-BPI subscales and the patients' BMI and smoking status. Statistically significant association was found between obese smoking patients pain significantly interfered in their general activity ($p = 0.027$).

DISCUSSION

In the present Greek case-control study, we, for the first time, sought to examine parameters that have been previously shown or hypothesized to be correlated to spinal IDD.

In this study, age and overweight were strongly associated with the diagnosis of spinal IDD. Furthermore, shorter stature subjects with a decreased bone density were at an increased risk. We found an association of occupational exposure with highly demanding manual work, all with the absence of regular physical activity in both women and men. Breast-feeding in the female population showed a negative association with regard to the risk of disc degeneration.

Before proceeding to interpret these findings, we considered and tried to eliminate all potential sources of bias. We recruited patients who were referred for consultation to the Palliative Care Unit, of Aretaieion University Hospital. All medical records of both cases and matched controls were thoroughly re-evaluated by the attending palliative care physicians. Cases had back pain and evidence of structural changes seen on plain conventional X-rays, whereas controls were included in the analysis only if the absence of pain was followed by completely negative radiographic findings of plain spine X-rays. No disc space narrowing, loss of disc height, disc bulging/prominence or osteophytes was seen. Furthermore, the 40 control subjects randomly selected for further radiological evaluation of the spine (cervical/lumbar) had no MR imaging findings of DD disease^[10]. Thus, controls had no evidence of radiographic disease, regardless of age. Trained readers, blinded to all the participants' clinical data, scored the plain spinal radiographs for the presence and severity, as well as the absence of the degeneration.

Even though aging is not sufficient for the development of osteoarthritis and most people have some degree of radiographic disease, even in younger ages, it is still the strongest risk factor for osteoarthritis in all joints, including the spine. Reports have long recognized the aging process to be the strongest risk factor for bony degeneration, particularly within the vertebra^[4,7,24-26]. However, the mechanism by which age increases the susceptibility

to joint degeneration is still largely unknown. Age-related changes in articular cartilage likely play a role. They could be related, to an alteration within the collagen network cross-linking resulting from the advanced glycation end products, a decreased response of chondrocytes to repair stimuli and/or altered levels of cartilage oligomeric protein and hyaluronic acid^[5]. Yet other less cartilage-oriented mechanisms could also be implicated, such as decreased proprioception and muscle strength or unstable articulation with aging^[7,11,21,24-26]. The results of our study are comparable to those of others, reporting a strong relationship between increasing age and the presence of IDD.

Overweight was also found to be a significant risk factor. Obesity as reported in the literature represents a significant predictor and BMI represents the most useful parameter of its evaluation^[16]. Several studies have directly examined the obesity – caused mechanical bone changes occurring in the knee and in the articular cartilage. Our results on the association between obesity and IDD are in agreement with those in other Caucasian populations^[25]. Epidemiologic surveys and other population based studies have showed that IDD was clearly associated with obesity in both weight bearing and non-weight bearing joints^[27-31]. The results of a comparative study conducted by Yoshimura and colleagues^[14], suggested that a higher BMI was associated with an excess risk of osteophytosis. The same results were also found in the Oulu Back Study (OBS)^[31]. Another report has shown that for every 5kg of weight gain, there is a commensurate 36 increased risk for developing osteoarthritis^[32]. The only results that are not completely in accordance with ours and those previously reported are those of the Chingford Study^[7]. While higher BMI showed a trend toward predicting progression for degenerative features, the results did not reach statistical significance.

Previous studies also have suggested that distinct occupational risk factors exist for osteoarthritis. Our results concerning the association of spinal IDD to heavy physically demanding work in Greece are in accordance with those already reported in the literature^[31-35]. Thus, current evidence would suggest that disc degeneration is more common in those who perform heavy physical work^[36]. Still, occupational overload can present a potential confounder^[12]. The Chingford study does not associate physical activity and occupational exposure to progressive disc degeneration^[7].

It is well recognized that estrogen deficiency has an important role in osteoporosis^[37], although the underlying mechanism for this remains unclear. The Framingham study concluded that estrogen

intake in women had a modest but non-significant protective effect on both radiographic osteoarthritis and severe osteoarthritis of the hip^[38]. In addition, women with osteoarthritis of the spine were more likely to have osteoporosis by WHO classification at the femoral neck and total hip than those without spinal osteoarthritis. Our results are in agreement with those in the Italian population and those from the Chingford Study^[17,39-40]. On the contrary, the results of an epidemiological study conducted by Yoshimura and colleagues revealed that osteoporosis reduced the risk of subsequent osteoarthritis at the spine in women, but not in men^[14,41]. Pye and colleagues^[42] using a sample of 500 men and women examined osteophytes, disc space narrowing and endplate sclerosis at 4 lumbar discs with radiographs and showed that BMD increased with increasing grades for all radiographic features in both sexes. They concluded that their data can support the hypothesis that degenerative disc disease is inversely linked to osteoporosis. In the contrary, a large study performed in the United Kingdom in female twins supported a clear, significant and independent association of BMD at hip and lumbar spine with IDD, which in part was genetically mediated^[13].

In the current study we observed that, breast-feeding was inversely associated with the risk of intravertebral disc degeneration. There is a marked paucity of epidemiologic and population-based data on spinal osteoarthritis and breast-feeding. There is only one study available in the literature, associating breast-feeding to the risk of rheumatoid arthritis. Its results suggest that breast-feeding is associated with a slightly lower risk for the development of rheumatoid arthritis^[43].

Based upon the findings of the current study, smoking does not appear to convey a clinically significant level of protection against the development of IDD. These findings corroborate to those of previous studies indicating no association between smoking and osteoarthritis^[44-45]. Unlike, in a topic review, chronic cigarette consumption was found with significant adverse effects on the human spinal column^[44-45]. In the Framingham Study, smoking was reported to have a mild protective effect on the development of osteoarthritis^[38]. Thus, results are controversial and the association between smoking and the risk of spinal osteoarthritis is suggested as weaker than the association between smoking and knee/hip osteoarthritis.

Our multivariate analysis revealed that lower educational level tended to be associated to an increased risk of IDD, in the male patient population in particular. Low educational attainment is linked to pain and disability in osteoarthritis, and represents a strong predictor of its prevalence and potential progression^[46]. Behavioural risk factors such as health-seeking behaviour, diet, access to and utilisation of health services, self-efficacy, stress level and income may be related to educational level^[47]. Furthermore, lower educational level might be linked to heavier work occupation and physically demanding jobs, as well as to the absence of normal physical exercise.

Studying risk factors for symptomatic osteoarthritis is challenging. While pain in osteoarthritis has long been considered chronic, it is not necessarily constant^[48]. Because of methodological and logistical difficulties, few studies are conducted to examine the dynamic relationship between risk factors and pain fluctuation^[49]. We have found an association between levels of diffuse pain of the spine and older age, as well as female sex.

One of the limitations of our study is that CT^[50] and/or MRI^[10] imaging modalities of the vertebra were not available for all participants of our study. Such imaging represents nowadays the gold standard for assessing the disease (disc degeneration and facet joint

osteoarthritis, respectively). MRI is the gold-standard for grading the DD disease^[10]. Schneiderman *et al* proposed a 4-grading scheme to classify IDD^[51]. Pfirrmann and Boss proposed a 5-grades scheme according to the signal characteristics of the disc^[52]. Samartzis *et al*^[53] in a large population-based study used the Schneiderman grading scheme; these investigators have also shown that IDD was significantly correlated to overweight or obese patients. Recently enough, another grading scheme was suggested and developed that incorporates disc structure and brightness, presence or absence of Modic changes, presence or absence of a high intensity zone, and reduction in disc height (disc height less than 5 mm)^[54]. Despite these literature reports, controversy still exists and radiologists state that a vertebral disc prolapse, when assessed by MRI, represents a different entity^[55-56].

Unfortunately, due to its high cost, we were unable to screen patients and controls with spinal MRIs. Patients were submitted to an MRI on an individual basis only, in particular whenever invasive treatment measures were to be undertaken. Control subjects had an MRI (cervical/lumbar) performed only in an effort to exclude selection biases. Nevertheless, none of the signs suggesting DD, as described in the nomenclature of 2014^[10], were seen in the 40 control subjects randomly selected and submitted to a MR imaging of their spine. Still, our results can not be undermined: a large literature from the past decade is available, including both cross-sectional and longitudinal studies, using plain radiographs for assessing lumbar disc degeneration^[21]. Such radiological literature evidence was used as a basis in our report. Further studies, using MRI scans, might be necessary in our country to better evaluate the grading of DD.

We have tested all available predictors of spinal osteoarthritis in a case-control study in Greece. We have chosen to examine putative risk factors, some believed to be potential biologically causative agents, all previously examined in other populations. Interestingly enough, our results for Greek Caucasians are in accordance with those for other patients: age, overweight and decreased bone density were strongly associated with the diagnosis of symptomatic spinal osteoarthritis, while an association of occupational exposure and heavy bodily fatigue has been proved.

AUTHOR CONTRIBUTION AND ADHERENCE TO ETHICAL RECOMMENDATIONS

All authors contributed to the acquisition and analysis of data. The protocol for research work was approved by the Human Ethics Committee of Aretaieion University Hospital and conforms to the Ethical Provisions of the Declaration of Helsinki.

Help to the collection and assembly of data, as well as administrative support was provided by Mrs Parpa and Tsilika. Dr Liva, Dr Panagiotou and Professor Mystakidou contributed to the conception and design of the study, as well as the interpretation of data. Provision of study patients and statistical expertise was given by Dr Liva and Dr Panagiotou. Dr Liva and Dr Panagiotou authored the manuscript, while Professor Mystakidou was responsible for the drafting, critical revision and final approval of the article. Furthermore, she is responsible for the integrity of the all the data presented in the analysis. Professor Mystakidou also takes the responsibility for the integrity of the work as a whole.

CONFLICT OF INTERESTS

There are no conflicts of interest with regard to the present study.

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