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Sex Differences in Spinal Osteoarthritis in Humans and Rhesus Monkeys (*Macaca mulatta*)

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Abstract

Study Design—Retrospective study of male and female spinal osteoarthritis, characterized by lateral spine thoracolumbar radiographs, in humans and nonhuman primates

Objective—To characterize differences in prevalence and vertebral distribution of spinal osteoarthritis between men and women, between male and female macaques, and between the two phylogenetically related genera.

Summary of Background Data—Naturally occurring spinal osteoarthritis manifests similarly in humans and rhesus macaques. Other types of osteoarthritis particularly of the knee and hip have revealed gender differences in humans. In regard to spinal osteoarthritis, gender differences have been noted but without consistent results. Sex differences in macaques have not been examined.

Methods—Radiographic evidence of disc space narrowing and osteophytosis was assessed using an atlas scoring method. Prevalence was determined according to sex, age, body mass (for macaques only) and spinal location (human T4-L5; macaque T8-L7).

Results—Average scores in macaques differed between the sexes, but they did not differ between men and women. The pattern of involvement along the spine was the same in male and female monkeys but differed between men and women: women had more thoracic involvement and men had more lumbar involvement. Overall, monkeys had a significantly higher prevalence of osteoarthritis than humans.

Conclusion—The appearance of sex differences in the prevalence of osteoarthritis is most likely a proxy measure for the affect of body mass. Sex differences were apparent in monkeys due to the fact that males are significantly heavier than females. No gender difference in prevalence was apparent in humans and there is substantial overlap in body mass between men and women.

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Differences in the location of osteoarthritic involvement along the spine between men and women were obscured when only average scores were examined.

Keywords

Sex differences; spinal osteoarthritis; osteophytosis; disc space narrowing; primate comparative studies

Introduction

Spinal osteoarthritis (OA) is a significant health concern affecting millions of people and incurring millions of dollars in medical and disability costs[1,2]. While risk factors for spinal OA such as age, body mass, trauma, and genetic influences have been studied, the influence of gender differences remains unclear. Studies of gender differences in OA of the hand, hip and knee[3–6] are more common due to available clinical and surgical data. Investigations relating to gender differences in spinal OA[7–13] are fewer and have reported conflicting results in prevalence and in the patterns of involvement of the vertebral regions.

Primate models, particularly those using rhesus macaques (*Macaca mulatta*, Zimmermann 1780)[14–19], have proven useful in the study of spinal OA, given that the condition manifests similarly in humans and nonhuman primates[19–21]. As with human spinal OA studies, the influence of sex differences has not been well characterized. The aim of this study was to determine whether or not sex differences are present in the occurrence and patterning of spinal OA by examining radiographic evidence in men and women and male and female macaques.

Materials and Methods

Monkeys

The sample consisted of 41 male (aged 13–30, average 21 years) and 27 female (aged 11–27, average 19 years) rhesus macaques (*M. mulatta*). Animals were housed at the Wisconsin National Primate Research Center (WNPRC) and have complete medical histories. Using these records, we calculated an average adult body mass (in kg) for each animal. Monkey ages were converted to human equivalent ages for the purpose of direct comparison to human data using 1:3.5 year human:rhesus macaque age ratio[14–16]. Animal care details were in accordance with Institutional Animal Care and Use Committee and are described in detail elsewhere[22]. These monkeys are part of an ongoing study of the effects of long-term dietary restriction on morbidity and mortality in primates[22,23]. The difference between control and dietary restriction animals was non-significant in our analyses and consequently, the two groups were combined and are discussed as a single group. The radiographs used in this analysis were randomly selected from a larger, longitudinal radiographic dataset in order to create a cross-sectional sample comparable to that available for our human subjects.

Humans

This group consisted of 173 men (aged 21–101, average 50 years) and 244 women (aged 20–82, average 51 years) randomly selected from individuals who had lateral thoracolumbar radiographs taken at a level 1 trauma center from January 1, 2000, to December 31, 2001. The radiographs were part of a standard protocol to rule-out spinal injury after a traumatic event. All study subjects were trauma-free. Institutional Review Board approval was obtained prior to examination of the human radiographs. Selection criteria for women are described elsewhere [24] and the same criteria applied to men in this study. Body mass was not available for people.

Radiographic Assessment

Lateral thoracolumbar radiographs were available for each subject. All monkey images (N=68) were obtained onsite at WNPRC and were assessed and scored by a single observer (AED), blind to the animal's age, body mass and sex. Human radiographs (N=417) were obtained from the trauma center and were scored by a single observer (PAK) blind to the subject's age. Scoring protocols were the same for all radiographs. Each vertebral level was scored for disc space narrowing (DSN), defined as a change in disc height relative to the adjacent intervertebral spaces, and osteophytosis (OST), defined by the presence of osteophytes on the anterior vertebral margins. An atlas scoring method was used: 0 for unaffected sites; 1, 2 or 3 for slight, moderate, or severe involvement, respectively, as has been applied previously[17,25].

Radiographic clarity of the more cranial thoracic vertebrae varied considerably in all subjects. In monkeys, therefore, evaluation was restricted to spaces T8/T9 through L6/L7 for DSN and vertebral bodies T8 to L7 for OST. In humans, evaluation was restricted to spaces T4/T5 through L4/L5 for DSN and bodies T5-L5 for OST. In all cases, the lumbosacral joint was not scored for DSN due to excessive variability in height and shape of the disc [26,27]. Variability in the clarity of some radiographs prohibited the scoring of some areas, resulting in variable sample sizes at individual sites. Monkey vertebral score counts ranged from 13 to 68. Human vertebral score counts ranged from 331 to 416.

Several cumulative scores were calculated. An overall average DSN and OST score was computed for each individual. Thoracic and lumbar regional scores as well as specific vertebral level scores were computed for different groups: all monkeys, all humans, and males and females by genera. No combined scores between DSN and OST were calculated.

Unilinear and multilinear regression analyses (STATA, College Station, TX) were performed with age, sex, and body mass as covariates for DSN and OST scores. Two multilinear models were examined in monkeys. The first excluded body mass measures to allow for direct comparison between the monkey and human data, while the second model included body mass. Differences between the sexes in average scores for vertebral levels were evaluated with Student's T-test. Statistical significance was established at an alpha of $p < 0.05$. Analysis of pattern differences at individual vertebral levels in OST and DSN scores between sexes was performed using MATLAB® (MathWorks, Natick, MA).

Results

Monkeys

DSN and OST were present but variable throughout the sample, with some older individuals having low scores and some younger individuals having high scores (Figure 1). The youngest female with DSN was 12 years, the youngest male 14 years. For OST, the youngest individuals of both sexes were 12 years. In univariate analyses, age, sex and body mass were all significant predictors of OA (Table 1). Males had significantly higher average overall, thoracic, and lumbar scores than females.

In a multilinear model of OA excluding body mass as a predictor, age and sex were significant and together explained 39% of the variability in DSN and 51% in OST. When body mass was included, sex was no longer a significant predictor in the model. Together age and body mass explained 47% of the variability in DSN and 62% in OST. Limiting the analysis to the thoracic or lumbar averages of DSN and OST revealed the same relationships.

Sex differences were apparent in the pattern of DSN and OST across vertebral levels (Figure 3a). The DSN curve for males included two maxima, at T12/L1 and at L6/L7. In females, there was a broad maximum spanning the lower thoracic region (T10-L1) and another at L6/L7. Males had significantly higher DSN scores at every vertebral level ($p < 0.045$) except T9-T11. The OST curves were similar for both sexes with two maxima, at T12/L1 and L6/L7. Males had significantly higher OST scores at all vertebral levels ($p < 0.037$).

Humans

As with monkeys, DSN and OST were present throughout the human sample (Figure 2). The youngest woman with DSN was 32 years, the youngest man 25years. For OST, the youngest individuals of both sexes were 22 years. In univariate analysis, there was a significant positive association between age and OA outcome, but no gender difference was apparent (Table 1).

In the multilinear analysis of DSN gender was non-significant and age explained only 8% of the variability in the model. In the multilinear analysis of OST, age and gender together explained 34% of the variability, only 1% more than that explained by age alone. In regard to thoracic or lumbar OA, age was always a significant predictor ($p<0.000$) but gender was significant only for lumbar OST ($p < 0.000$).

The pattern of OA across the spine was different in women than in men (Figure 3b). Men had higher DSN scores than women at T11/T12, and L4/L5 ($p < 0.045$). The shape of the DSN curves differed as well, where women had a minimum from T9 to L1 men exhibited a peak. Both genders showed a double maxima pattern in OST with peaks at similar locations, T7/T8 and L3/L4. Women had significantly higher scores, however, in the mid thoracic region (T6-T8, $p < 0.049$) while men had significantly higher scores in the thoracolumbar joint and lumbar regions (T11-L5, $p < 0.048$).

Inter-generic

After transforming monkey ages to human equivalents based on 1:3.5 year ratio [14–16], analysis of DSN and OST scores showed that age, sex, and species were significant predictors in unilinear ($p<0.000$) and multilinear regressions ($p<0.001$). Increasing age, maleness, and being a monkey were all positively associated with higher OA outcomes Figure 4). Together, age, sex and species explained 48% of the variation in average DSN scores and 55% of the variation in average OST scores.

The regions of greatest expression of OA were similar for males of both species with DSN and OST maxima located at the thoracolumbar and lumbosacral joints. Female monkeys and women were less similar: women showed more upper to mid-thoracic DSN and OST with significant minima at the thoracolumbar joint while female monkeys showed lower mid-thoracic DSN and OST and thoracolumbar maxima. Similarly in the lumbar region, women showed a mid lumbar maximum while female monkeys showed a minimum at the same location.

Discussion

Using demographic and radiographic data gathered from humans and rhesus macaques, we examined whether or not and, if so, how spinal OA differed between men and women, between male and female monkeys, and between the two genera. We found that average DSN and OST scores in monkeys differed between the sexes, until body mass was figured into the model and revealed that sex is likely a proxy measure for body mass. We found no sex difference in average scores in humans, likely due to the overlap in body mass in men and women but we did not have data to confirm this suspicion. The pattern of spinal

involvement did not differ between male and female macaques; however, the pattern did differ between men and women. Our results revealed greater thoracic involvement in women and greater lumbar involvement in men, aspects that were obscured by average scores.

An advantage of this study is that we were able to use consistent methodology to evaluate OA in both groups providing us with easily comparable datasets. Our study is limited in a number of ways, including the relatively small number of macaques in our study group. The macaques in this study are, however, similar to those in other studies[14–17] with larger sample sizes so it seems unlikely that their data are substantially skewed. Also, we lacked body mass data for the human subjects in this study, which made it impossible to tease apart the affect of gender from that of body mass in women and men. Lastly, because OA is so closely associated with growth and aging, which in primates follow a sigmoid curve over time, a linear regression model may not be the best fit. Using cross-sectional data, however, does not allow us to fit sigmoidal growth curves with any reliability, nor are we able to determine changes in growth rates that might affect the prevalence and severity of OA in humans and macaques. More extensive longitudinal analyses are warranted.

The relationships between body mass, body size, and sex are complex in primates. Sexual dimorphism in body size is a common trait in primates. In macaques, males are up to 60% larger than females[28], but in humans, sexual dimorphism in body size is considerably less, with men being, on average, 10% larger than women[29]. In monkeys, sex was non-significant in our multivariate analysis when mass was included, which can be attributed to the strong correlation of sex with body mass in macaques. It is possible that the significant association of sex in the univariate analysis may have functioned as a partial proxy for body mass. Although we were not able to obtain body masses for the humans, it is likely that men and women overlapped to a large degree in mass, making sex a poor predictor of mass.

In many human studies that include body mass, measures are obtained through self-reporting, which can provide unreliable, often under-estimated, measures[30]. Reliable body mass can be measured on site at the time of radiography, but even this may not be a useful metric. In nonhuman primates particularly, but also in humans, single body mass measures can reflect periods of abnormality due to illness or other temporary influences and may be less indicative of an individual's true average adult body mass and, hence, its biomechanical interactions with the musculoskeleton over time. Body mass averaged over an individual's lifetime would appear to be a better measure of how body mass and OA may interact. A cross-sectional study of humans, therefore, can never provide a measure similar to the longitudinal mass records available for our macaque subjects. Consequently, a captive monkey model may give us the most insight.

Few studies have examined spinal OA in male and female macaques. DeRousseau[16] found no sex bias in her examination of degenerative disc disease in *M. mulatta*, but noted that her sample size may have lacked the power to detect a sex difference. Colman and colleagues also looked at both male[15] and female *M. mulatta*[14], but their OA reporting differs between papers and applies only to lumbar spine prevalence. Lumbar OA in males and females was significantly and positively associated with age but the authors found no association with body mass in either study. The lack of association may be related to their use of mass at time of radiography rather than average adult body mass, as discussed above.

Gender differences in human spinal OA have been examined in several studies[7–12,31], but researchers employed various definitions and methods of evaluation. For example, Lawrence[7] focused on "disc degeneration" as a combination of several characteristics including osteophytosis, disc space narrowing, disc slippage and sclerosis. Miller and colleagues[8] defined and graded "disc generation" according to macroscopic wear to the disc

itself. Other authors have focused solely on osteophytosis, but have graded it on different scales. Nathan[31] examined OST across the entire spine and found that the pattern of involvement differed between the sexes with men having higher frequency and higher severity of OST than women. O'Neill and colleagues[9] examined OST across the thoracolumbar spine, also finding men had higher frequency and severity of OST than women, but that the patterns of vertebral involvement were similar in both sexes. These results are also similar to studies looking solely at the lumbar spine[10,11]. Snodgrass[12] looked at the thoracolumbar spine but found a positive male bias only in regard to lumbar OST. Although we cannot compare our results directly with those of other studies due to the differences in methodology, our findings do not support the general trend that men have higher levels and more severe involvement of OA (especially OST) than women. Our findings of gender differences by spinal region do, however, support those of Lawrence[7], who found women had more OST in the thoracic spine and men in the lumbar spine.

The intergeneric differences we found may be relevant to future studies of OA using the macaque model and well as to future human studies. Overall, macaques had significantly higher prevalence and severity of spinal OA compared to humans. Differences exist in the habitual orientation, curvature, and biomechanical stresses in the two spines. Macaques are anatomical quadrupeds, though they spend a substantial amount of time sitting with their spines in a vertical orientation. The human spine is habitually vertically oriented with sagittal curvature and inherent flexibility and shock absorption. It is possible that the architecture of the bipedal spine may function in a protective manner in regard to OA, explaining the lower levels of DSN and OST seen in our human study group. Further examination of vertebral bone composition, and that of osteophytes in particular, as well as possible structural and biomechanical differences in human and macaque vertebrae may help to explain intergeneric differences in spinal OA.

There are several hypotheses regarding the etiology of osteophytes as structural responses to biomechanical stresses[26,31–33]. Nathan[31] describes osteophytes as a reinforcing structural responses to spinal stress, noting that osteophytic bone is compact bone, appearing to be stronger than bone of the normal vertebral body. If osteophytes are a bony response to loading and movement related stresses, it would follow that a gender difference in OST distribution would correspond to the spinal region where gender-related stress differences are most apparent. Our data showed that men have significantly higher OST in the lumbar region and women in the thoracic. Because the lumbar spine carries the majority of weight-related spinal forces, bearing the stress of the entire upper portion of the body, it has been hypothesized that this region would be more susceptible to weight-related stresses. Miller and colleagues[8] proposed that men, based on the trunk extensor musculature as well as the size and area differences in vertebral bodies, exert maximally 1.28 times the compressive force per unit cross-sectional area than women. While standing, men exert the same or slightly less compressive stress to the lumbar spine, but maximal exertions load the male spine with up to 28% more compressive stress and 72% higher compression forces than in women. The finding that women have more OST in the thoracic region has not been examined in detail and no hypotheses as to why this should occur have been proposed as yet. Future comparative work focusing on the differences in flexibility, load balancing, and compressive forces in the spine may further our understanding of why women and men differ in the distribution of OA.

In conclusion, intergeneric differences revealed much higher prevalence and severity of OA in monkeys than in humans. In macaques, males had more prevalent and severe OA than females, but no differences were apparent in patterning across the vertebral column. In contrast, no gender effect was apparent in humans with regard to prevalence or severity of OA, but there was a significant difference in the affected areas of the spine: women had

higher thoracic involvement and men higher lumbar. These apparent differences in the manifestation of spinal OA in men and women present an area to be explored in future work.

Key Points

- Sex differences in the regional distribution and prevalence of spinal osteoarthritis were apparent in both humans and macaques, but the pattern is not the same.
- Macaque males have significantly higher prevalence than macaque females.
- Differences in prevalence between men and women appear to be regional -- men have higher lumbar involvement and women have higher thoracic involvement.
- Gender differences in humans may indicate that body mass distribution and related biomechanical stress differences pose different risk factors for men and women.

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IRB and IACUC approval were obtained for this research.

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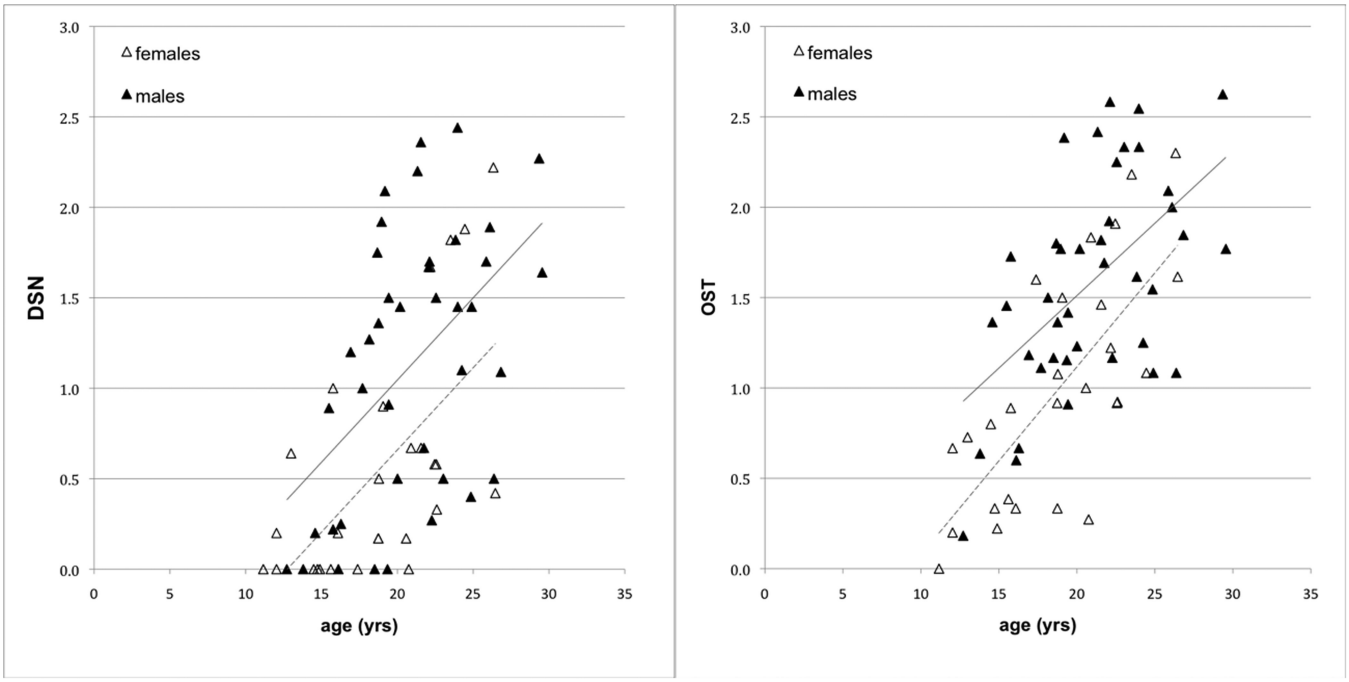


Figure 1.
Average disc space narrowing and osteophytosis scores in female (dotted trend line) and male (solid trend line) monkeys.

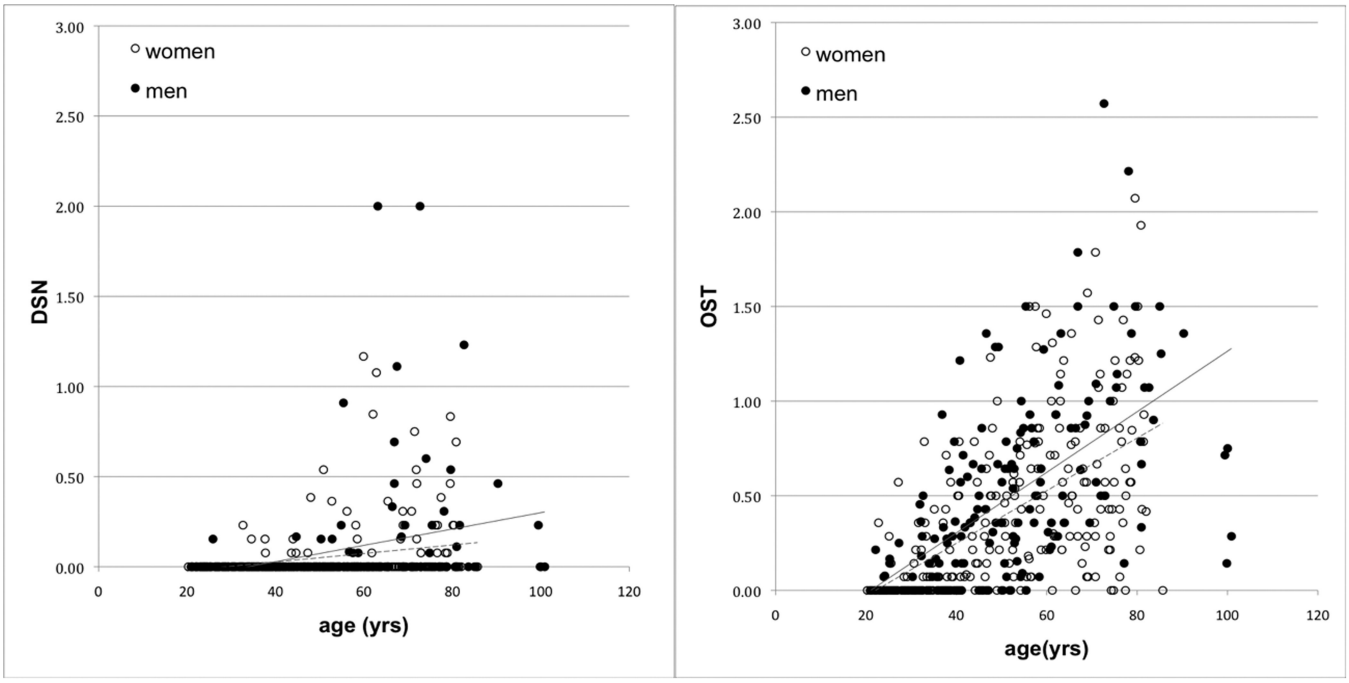
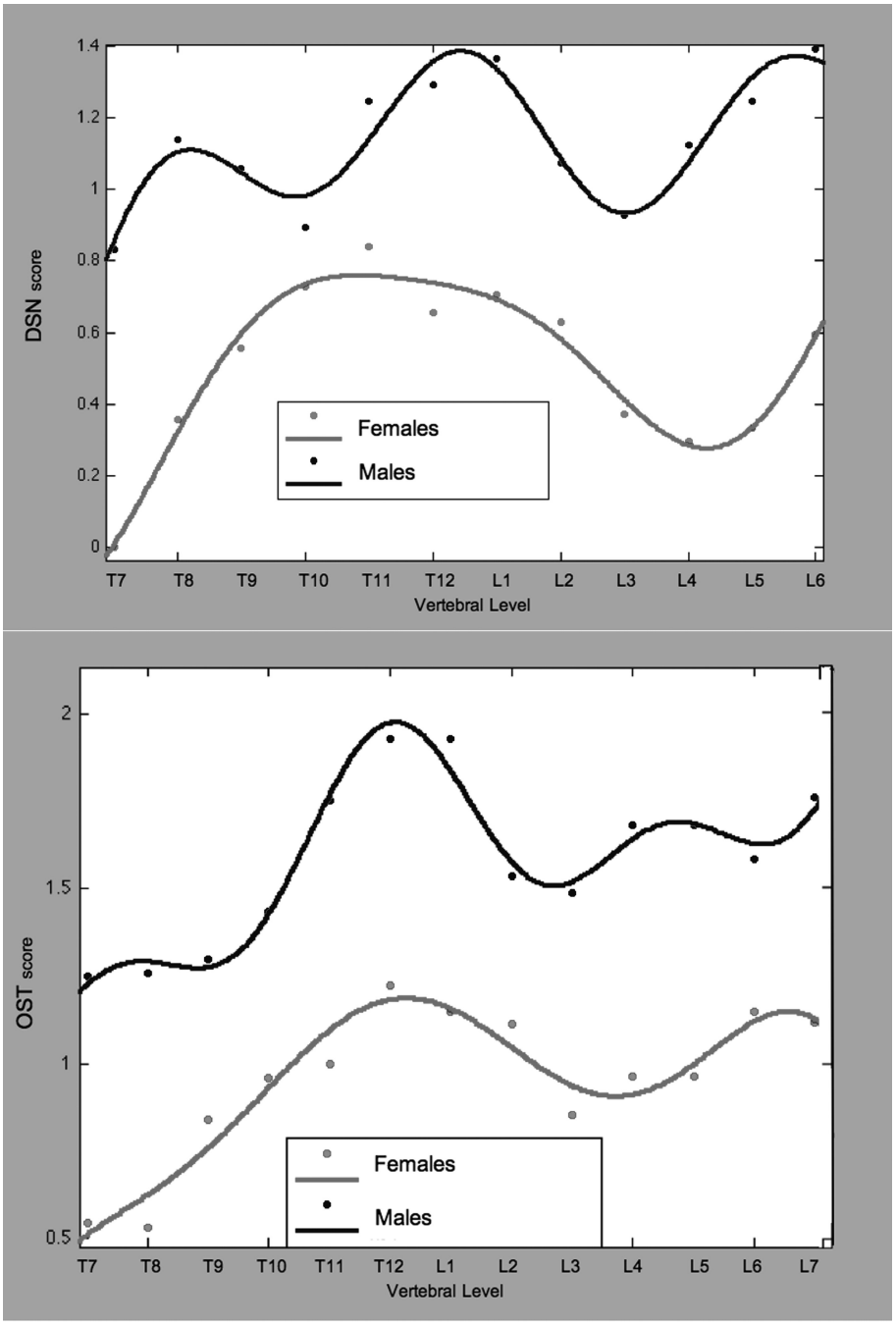


Figure 2.
Average disc space narrowing and osteophytosis scores in human women (dotted trend line) and men (solid trend line).



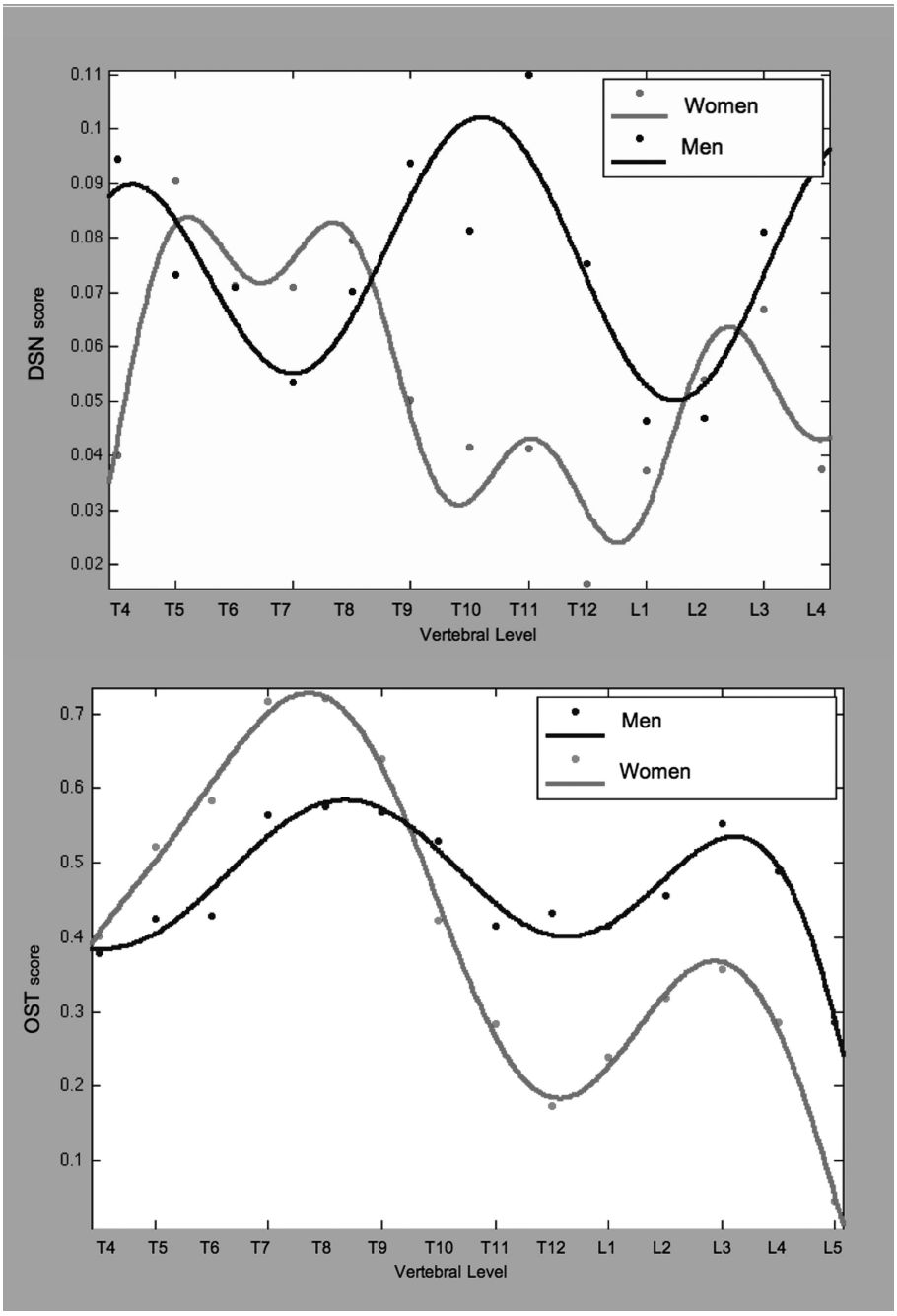


Figure 3.

a. Average disc space narrowing and osteophytosis in monkeys, by vertebral level.

b. Average disc space narrowing and osteophytosis in humans, by vertebral level.

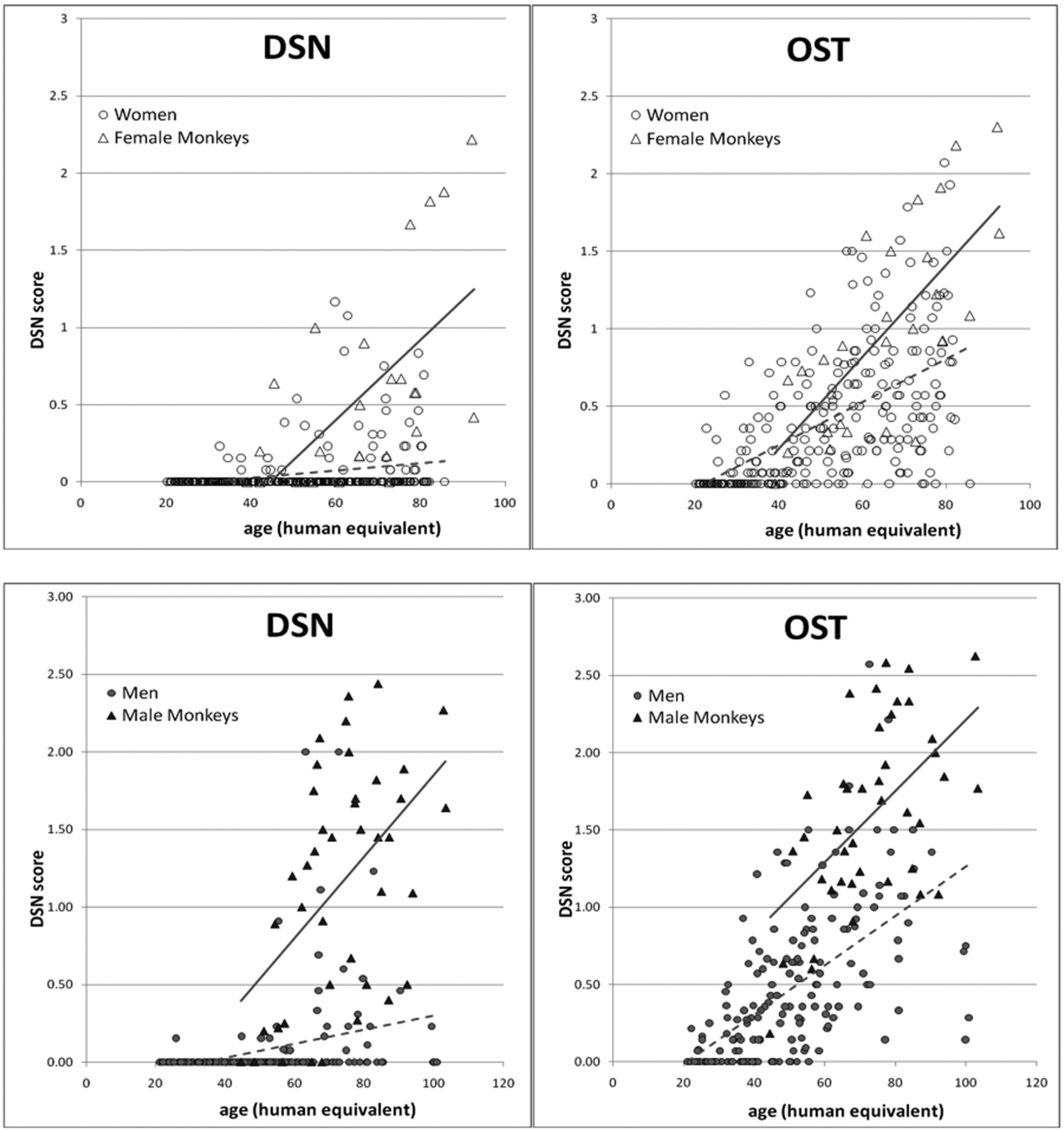


Figure 4.

Average disc space narrowing and osteophytosis score comparisons between women (dotted trend line) and female monkeys (solid trend line) above, and men (dotted trend line) and male monkeys (solid trend line) below. Monkey ages have been adjusted to represent their human equivalent based on 1:3.5yr human:monkey age ratio [14–16].

Table 1

Unilinear and multilinear regression results.

	Humans (N=417)		Macaques (n=68)	
Dependent Variables	**r^2**	**p**	**r^2**	**p**
DSN				
Univariate Analyses				
age	0.072	<0.000	0.331	<0.000
sex	0.002	<0.317	0.148	<0.001
body mass	na	na	0.180	<0.000
Multivariate Analyses				
1. full model	0.075		0.394	
age		<0.000		<0.000
sex		<0.227		<0.012
2. full model	na		0.470	
age		na		<0.000
sex		na		<0.812
body mass		na		<0.000
OST				
Univariate Analyses				
age	0.334	<0.000	0.427	<0.000
sex	0.005	<0.173	0.197	<0.000
body mass	na	na	0.255	<0.000
Multivariate Analyses				
1. full model	0.341		0.512	
age		<0.000		<0.000
sex		<0.035		<0.001
2. full model	na		0.625	
age		na		<0.000
sex		na		<0.842
body mass		na		<0.000