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Contribution of lumbar spine pathology and age to paraspinal muscle size and fatty infiltration

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ABSTRACT

Study Design: Retrospective chart analysis of 199 individuals aged 18-80 years scheduled for lumbar spine surgery.

Objective: The purpose of this study was to quantify changes in muscle cross sectional area (CSA) and fat signal fraction (FSF) with age in men and women with lumbar spine pathology and compare them to published normative data.

Summary of Background Data: Pathological changes in lumbar paraspinal muscle are often confounded by age-related decline in muscle size (CSA) and quality (fatty infiltration). Individuals with pathology have been shown to have decreased CSA and fatty infiltration of both the multifidus and erector spinae muscles, but the magnitude of these changes in the context of normal aging is unknown.

Methods: Individuals aged 18-80 years who were scheduled for lumbar surgery for diagnoses associated with lumbar spine pain or pathology were included. Muscle CSA and FSF of the multifidus and erector spinae were measured from preoperative T2-weighted magnetic resonance images at the L4 level. Univariate and multiple linear regression analyses were performed for each outcome using age and gender as predictor variables. Statistical comparisons of univariate regression parameters (slope and intercept) to published normative data were also performed.

Results: There was no change in CSA with age in either gender ($p>0.05$), but women had lower CSA's than men in both muscles ($p<0.0001$). There was an increase in FSF with age in erector spinae and multifidus muscles in both genders ($p<0.0001$). Multifidus FSF values were higher in women with lumbar spine pathology than published values for healthy controls ($p=0.03$), and slopes tended to be steeper with pathology for both muscles in women ($p<0.08$) but not in men ($p>0.31$).

Conclusions: Lumbar muscle fat content, but not CSA changes with age in individuals with pathology. In women, this increase is more profound than age-related increases in healthy individuals.

Key Words: Lumbar Spine Pathology; Fatty Infiltration; Magnetic Resonance Imaging; Age; Cross Sectional Area

Level of Evidence: 3

INTRODUCTION

Low back pain (LBP) is highly prevalent in the United States, with approximately 65-85% of the general population experiencing some low back pain within their lifetime(1). Although most LBP is considered self-limiting in nature, recent evidence suggests that a high proportion of individuals develop recurrent symptoms, leading to poor functional outcomes and increased health care utilization(1, 2). Changes in muscle size and fat content are often associated with LBP symptoms and lumbar spine pathology (3, 4), however, the magnitude of these pathological changes are confounded by natural age-related changes such as sarcopenia, fatty infiltration, and decreased torque production (5). Muscle physiological cross sectional area is commonly used as an indicator for muscle force production capacity (6), and cross sectional area (CSA) has been quantified using Magnetic Resonance Imaging (MRI) region of interest segmentation analyses(7). Measures of total muscle size or volume in isolation do not take into account fatty infiltration, which is associated with aging and pathology (8). Since fatty infiltration in muscle decreases the proportion of contractile tissue capable of producing force, it is important to understand how muscle size and fatty infiltration change, both with age, and in the presence of pathology. Understanding muscle loss in the presence of lumbar spine pathology requires an understanding of how muscle loss occurs with aging. If pathology yields unique rates of muscle loss, new strategies for resolving muscle loss should be a clinical goal for functional improvement, since standard exercise strategies do not appear to reverse these changes in this population (9) (10-12).

Prior literature suggests that LBP and pathology alters CSA and fatty infiltration, with most studies demonstrating decreases in muscle size and increases in fatty infiltration in those with symptoms compared to their healthy counterparts(13-15). However, the extent of these morphological changes is unclear when considering physiological declines observed with normal aging(16-18). Effects of aging and pathology on muscle size and quality have been observed in other musculoskeletal regions, such as the rotator cuff and thigh muscles. In the rotator cuff, there is evidence that muscle size

decreases more with age in individuals with tears compared to those with no known pathology(19). Similarly, fatty infiltration seems to be more pronounced in individuals with rotator cuff tears compared to healthy controls across a spectrum of ages (20). There is also evidence of age-related decreases in CSA and increases in fatty infiltrate in the thigh muscles, although no comparisons have been made to pathological conditions in this muscle region(5, 21). Currently there is no information on the differential effect of age and pathology on changes in the lumbar musculature. The purpose of this study was to determine the relationship between age and muscle CSA and fatty infiltrate in men and women with LBP or pathology who were scheduled to undergo lumbar spine surgery, and compare these relationships to published normative data on fatty infiltrate in healthy individuals. The overall goal of this work is to begin to uncouple the effects of pain/injury and age on atrophic changes in lumbar spine musculature. We hypothesize that muscle size and quality will decline with age, and this decline will be more pronounced in patients with lumbar spine pathology.

METHODS

Study Participants

Magnetic Resonance Images (MRI) from 236 patients were screened based on an initial chart query using current procedural terminology (CPT) codes for lumbar spine surgical procedures from 2005-2015 at the University of California San Diego hospital database. Individuals were included in this screen if they were between 18-80 years of age, and were undergoing a surgical procedure of the lumbar spine. Patients were excluded from the analyses if they did not have a concurrent diagnosis (ICD-9) or procedural code associated with lumbar spine related symptoms, or did not have imaging of the lumbar spine. Surgical and diagnosis codes included in the query and initial screening are listed in Table 1. From the initial 236 patients queried, 37 patients were excluded from the analyses; 17 patients were excluded due to existence of instrumentation at the L4 level affecting MR signal intensity analyses, 7 were excluded due to CPT codes unrelated to LBP or degenerative pathology (i.e. skin

mass, neoplasm), and 9 were excluded due to analytical limitations (i.e. T2 images not available, motion artifact), and 4 were excluded due to acute trauma with lumbar vertebral fracture from a motor vehicle accident. After screening and exclusions, a total of 199 patients were retained for analysis (Figure 1). This study was approved by the local institutional review board (IRB #071983).

MRI acquisition and measurements

Regions of interest from T2-weighted axial magnetic resonance images taken from a single slice estimated to be closest to the midlevel of the L4 vertebra were used to measure muscle CSA and fat content with custom written Matlab software (Mathworks, Natick MA). For CSA measurements, regions of interest for both multifidus and erector spinae muscles were seeded and segmented bilaterally using Osirix software (22), based on fascial plane separations using the facet joint as a landmark between the multifidus and erector spinae, and the lumbosacral fascia posteriorly(23) (Figure 2a). Pixels were identified as either fat or muscle by fitting a two term Gaussian model to the histogram of pixel intensities from segmented regions of interest, and finding the intersection of the Gaussian distributions (Figure 2b). Pixel values above the intersection were classified as fat, and pixels below were classified as muscle. Fat content was measured using the fat signal fraction (FSF) and was calculated with the following equation(24):

$$FSF = \frac{npixels_{fat}}{npixels_{fat}+npixels_{muscle}}$$

Statistical analysis

Measures of CSA and FSF were averaged between left and right muscle regions of interest for the multifidus and erector spinae muscles separately. Age was analyzed as a continuous variable, and sex was analyzed as a dichotomous variable. Differences in demographic characteristics between genders were analyzed using independent t-tests for continuous variables, and chi square tests for categorical variables. Separate linear regression analyses were performed for CSA and FSF

measurements with both age and gender as predictor variables in a single model. Univariate regressions between age and CSA or FSF were then performed for each gender for comparison to data from a healthy cohort. Parameter estimates and intercepts from the univariate regression analyses were compared to healthy subjects from Crawford et al using independent t-tests ((25) personal correspondence). All statistical analyses were performed using SAS software (SAS 9.3, SAS Institute, Cary NC). Statistical significance was set at $p<0.05$ and trends were defined as $p<0.1$.

RESULTS

Mean (SD) patient age was 58.7 (13.5) years with no significant differences in age between men and women ($p=0.79$). There were a larger proportion of women (n=116, 58.2%) compared to men (n=83, 41.8%). The most common preoperative lumbar diagnoses were radiculopathy (42.2%), non-specific LBP (26.1%), and spinal stenosis (10.6%). All other related diagnoses were categorized as "other" and accounted for 21.1% of the cases. There were no differences in types of diagnoses between genders (Table 2). Similarly, there were no differences in age across the diagnostic categories ($p=0.35$). Linear regression model results demonstrated no effect of age on muscle CSA (β = -0.0002 and -0.0118 for multifidus and erector spinae respectively, $p>0.59$), but a significant gender effect for multifidus (β = -2.26, $p<0.0001$) and erector spinae muscle CSA (β =-3.19, $p<0.0001$) where men displayed a larger CSA for both spine muscles (Figure 3c-d). Age and gender were significant predictors of FSF in the multifidus (age β = 0.004, gender β = 0.0600; $p<0.0001$) whereas only age predicted FSF in the erector spinae (Age β = 0.0040, $p<0.0001$, gender β = 0.0201; $p=0.15$) muscle (Figure 3a-b). Women displayed more FSF than men in the multifidus, and older ages were associated with higher FSF in both muscles.

In the univariate gender stratified analyses, none of the variance in CSA was explained by age in either gender or muscle group ($r^2<0.003$, $p>0.84$). For FSF, age accounted for approximately 33% of the variance in FSF in the multifidus ($p<0.0001$), and 32% in the erector spinae in women

($p<0.0001$). In men, age accounted for 22% of the variance in FSF in the multifidus ($p<0.0001$) and 14% in the erector spinae ($p=0.0005$). In a sub-analysis, we compared the gender-stratified univariate regression estimates between age and FSF from our study with a previous study that reported normative values for healthy individuals aged 20-62 years (25). There was a trend towards a steeper slope in women with pathology compared to women without pathology for both multifidus ($p=0.08$) and erector spinae muscles ($p=0.08$), such that women with pathology displayed more age-related increases in FSF (Figure 4b,d). For men, there were no significant differences in slopes between healthy and pathological populations ($p>0.28$). When comparing intercepts between healthy and pathological populations, men with pathology tended to display higher intercepts in both multifidus ($p=0.06$) and erector spinae muscles ($p=0.05$) (Figure 4a,c), and women with pathology had a higher intercept only in the multifidus ($p=0.03$). Compared to a healthy population, men with pathology display overall more FSF in both multifidus and erector spinae muscles, and women display more FSF in the multifidus (Table 3). Recognizing that differences in age range between the population in the current study and the healthy cohort may affect the results, we also performed sub-comparisons using only patients under the age of 65 (N=129), yielding similar main effects of age and sex. However, trends observed between intercepts for healthy and pathological groups in the erector spinae were lost ($p<0.17$), as well as the difference in intercept between healthy and pathological women for the multifidus ($p=0.29$). The trend for a difference between intercepts for multifidus FSF in men became significant ($p=0.04$). All other results remained consistent with the full cohort comparison.

Due to differences in analytical methods for measuring muscle size, comparisons between normal and pathological trajectories for CSA were not performed (Figure 4).

DISCUSSION

The results of this study demonstrate that there is no significant effect of age on changes in CSA of either multifidus or erector spinae muscles in individuals with lumbar spine pathology,

however there are significant increases in paraspinal muscle FSF with age in both genders. When compared to prior published data on healthy individuals across a smaller age range, overall levels of FSF are higher in individuals with pathology across all ages. Additionally, a trend towards a more pronounced increase in FSF with age is seen in women with pathology, but not in men. Finally, men with pathology tend to display higher FSF values compared to a healthy population for both muscles and women with pathology tend to have higher FSF values in the multifidus only. When limiting comparisons to include only those under 65 years of age, men displayed higher FSF values for the multifidus only, and women did not display higher FSF values in either muscle when compared to the healthy cohort, although the trends towards a more pronounced increase in FSF with age in women were retained for both muscles.

CSA and FSF in healthy and pathological populations

Direct comparisons of CSA values from the current study to prior literature are limited by variation in segmentation methodology, such as considering the erector spinae and multifidus muscles as one unit, as well as data reporting methods such as normalization to vertebral body size, which we did not measure in this study. One study using similar segmentation methods in patients with LBP ranging from 18-60 years old reported average CSA values of 10.1(1.5) cm^2 and 18.5 (3.9) cm^2 at the L4 level for the multifidus and erector spinae muscles respectively, which is consistent with the data from the current study (7). To our knowledge, no data exists on CSA values in healthy individuals that are methodologically consistent with and directly comparable to values from the current study. When comparing levels of fatty infiltrate in the lumbar multifidus for individuals with and without LBP, Fischer et al reported mean FSF percentage values of 20.1% (range 4.3-73.4%) in individuals with chronic LBP symptoms (26), and Crawford, et al. reported mean (SD) FSF values at the L4 level in a healthy population of 21.2 (9.3)% in females and 15.3 (5.3)% in males (25). The previously reported values for mean FSF percentages are substantially lower than in the current study, for which mean FSF percentages in the multifidus were 45.3 (11.8)% in men and 51.6 (10.7)% in women with pathology in

the multifidus. The higher percentage of fatty infiltrate may be due to differences in fat fraction calculation methodology; where Fischer et al calculated fat fraction based on a single voxel measurement placed in the center of the muscle, our calculations included the entire muscle region. Additionally, differences in definition of the muscular region of interest can also influence these percentages, since the FSF values from the healthy comparison cohort were calculated based on volumetric, not cross sectional ROI's with potentially different muscular border definitions. We chose the posterior border for our ROI based on anatomical observations in normal healthy people that the multifidus muscle compartment is encapsulated posteriorly by the lumbosacral fascia, although there is no current consensus on standardized methodology for defining ROI's of these muscles.

Contributions of Age to CSA and FSF

In the current study, the results indicate that across a broad age range, age contributes to changes in FSF, but not CSA, in individuals with lumbar spine pathology. This is consistent with Fortin, et al who reported no associations between CSA and age (27), and Crawford et al, who reported no associations between muscle volume and age(25), but in conflict with a number of other studies (28-30). In one study that investigated lumbar spine muscle volume and fatty infiltrate across a young and old group of healthy individuals of similar body weight, age explained 18-36% of the variance in multifidus and erector spinae FSF unilaterally using T1-weighted MRI pixel intensity analyses (32). Interestingly, when variance results of the current study were compared to variances from the healthy cohort, age explained a larger variance in FSF in individuals with pathology than healthy individuals in women, but not in men, even when comparisons were limited to similar age ranges. This suggests that pathology may have some differential effect across genders. Importantly, though age accounts for approximately 30% of the variance in FSF for individuals with lumbar spine pathology, absolute levels of fatty infiltrate are still substantially higher than healthy individuals, especially in women, indicating that the presence of spine pathology dramatically increases the amount of muscle loss. This may suggest that changes in muscle quality and size are a result of muscle degenerative processes related

specifically to pathology, instead of simple disuse atrophy that is associated with aging. This has implications for rehabilitative management strategies in these individuals, as traditional exercise approaches have not been shown to reverse degenerative muscle changes(12, 34). Investigating the underlying mechanisms responsible for pathological versus age related changes may help uncouple these patterns, and are likely relevant in understanding the potential for functional differences in muscle between the populations.

LIMITATIONS

There were several limitations in this study. First, data was collected from retrospective chart reviews, so additional meaningful patient demographics such as duration of symptoms and body mass index were not consistently available across all subjects. Additionally, the MR images were only analyzed from a slice at a single level in an effort to standardize CSA across individuals. However, this may not have been the location of pain or structural pathology in many of the patients, as degree of spinal stenosis or other degenerative changes were not quantified from the images. Additionally, a single slice image taken from the L4 vertebrae may not be generalizable to changes across the entire lumbar spine. However, previous literature suggests that data from L4 are highly correlated with overall fat fraction of the entire lumbar spine (although these fat fractions were based on muscular volume, not CSA, at the L4 level) (25), and that pathological changes in the lumbar spine that are associated with a specific structural abnormality are often seen at the L4-5 or L5-S1 levels (35, 36), making this a logical choice for a single image analysis location. Methodologically, FSF values are also affected by changes in signal intensity as a result of inflammation. Although no patients reported specific inflammatory diseases, mild lumbar inflammation may result in overestimation of FSF values. Additionally, information on weight was only included in the charts of a subset of patients, and may be an additional confounder to CSA and FSF given their associated changes with age. However in a subset of individuals whose weight data was available (N=164), there was still no significant effect of age on

CSA when weight was accounted for in the model ($p>0.86$), and there were no differences in the magnitude of the age effect on FSF.

CONCLUSIONS

This retrospective study examined the contribution of age to muscle size and quality in a large cohort men and women undergoing surgery for lumbar spine pathology. The results indicate that individuals with pathology demonstrate similar CSA's, but larger overall levels of fatty infiltrate, compared to healthy controls across all ages. Although CSA is greater in men than women, it does not decline with age, whereas fatty infiltrate increases with age and pathology in both muscles. In women, the rate of increase in fatty infiltrate with age tends to be greater than their healthy counterparts. The larger volume of fat likely reduces the functional capacity of these important stabilizing muscles in the lumbar spine. Further research is required to elucidate the underlying mechanisms of age versus pathology related changes in muscle quality and their functional implications.

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FIGURE LEGENDS

Figure 1. Flow diagram of participant screening, exclusion, and analysis.

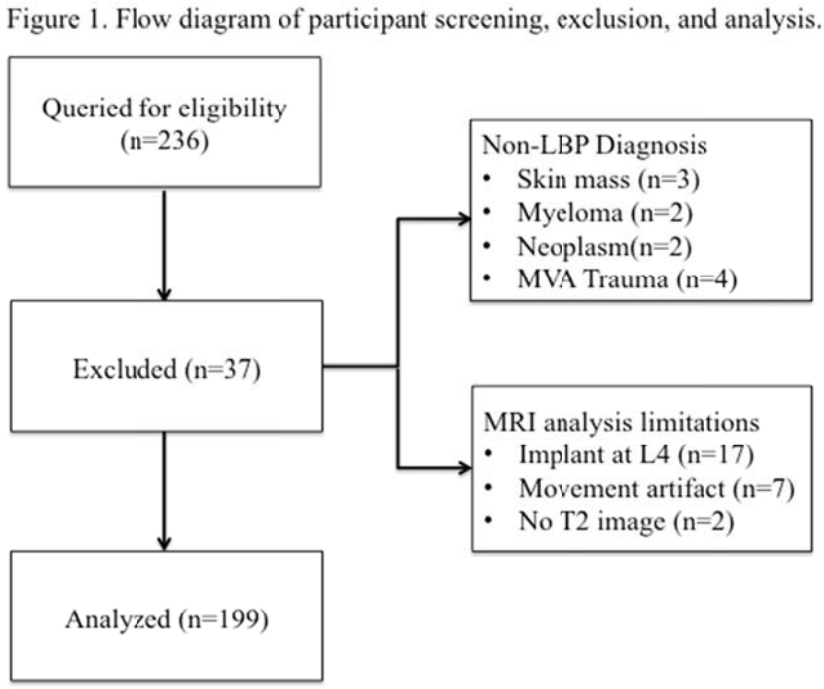

Figure 2. MR image segmentation for CSA and FSF analysis. Panel 2A depicts regions of interest for multifidus (M) and erector spinae (E) muscles, bordered anteriorly by the lamina and spinous process, and posteriorly by the lumbosacral fascia. Panel 2B depicts a representative histogram of pixel intensities across a spectrum of fat and muscle. Thresholds were defined on a patient-by-patient basis as the intersection between the Gaussian distribution of fat and water (x).

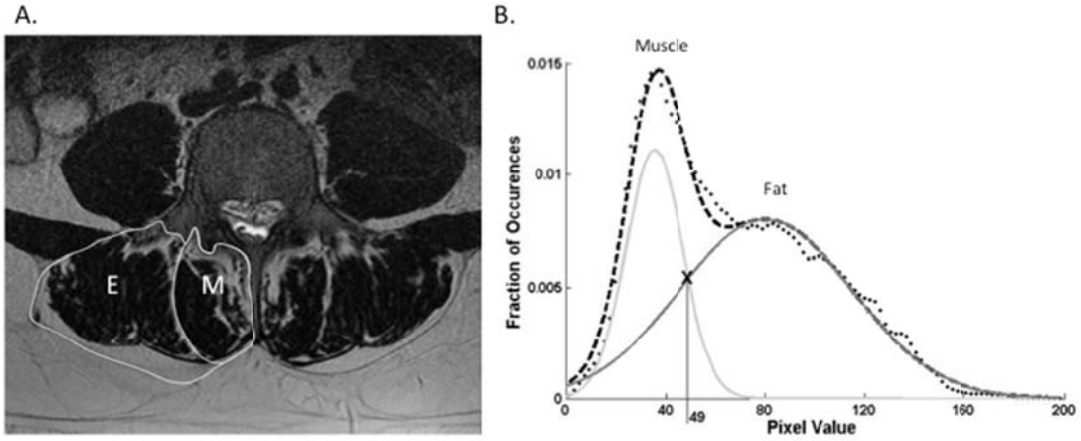

Figure 3. Regression plots for men (black) and women (grey) for multifidus (FSF in Panel A, CSA in Panel C) and erector spinae (FSF in Panel B, CSA in Panel D). There was a significant effect of gender in both FSF and CSA for the multifidus ($p<0.0001$), and in CSA ($p<0.001$) but not FSF ($p=0.17$) for the erector spinae. There was a significant effect of age for both muscles in FSF only ($p<0.0001$).

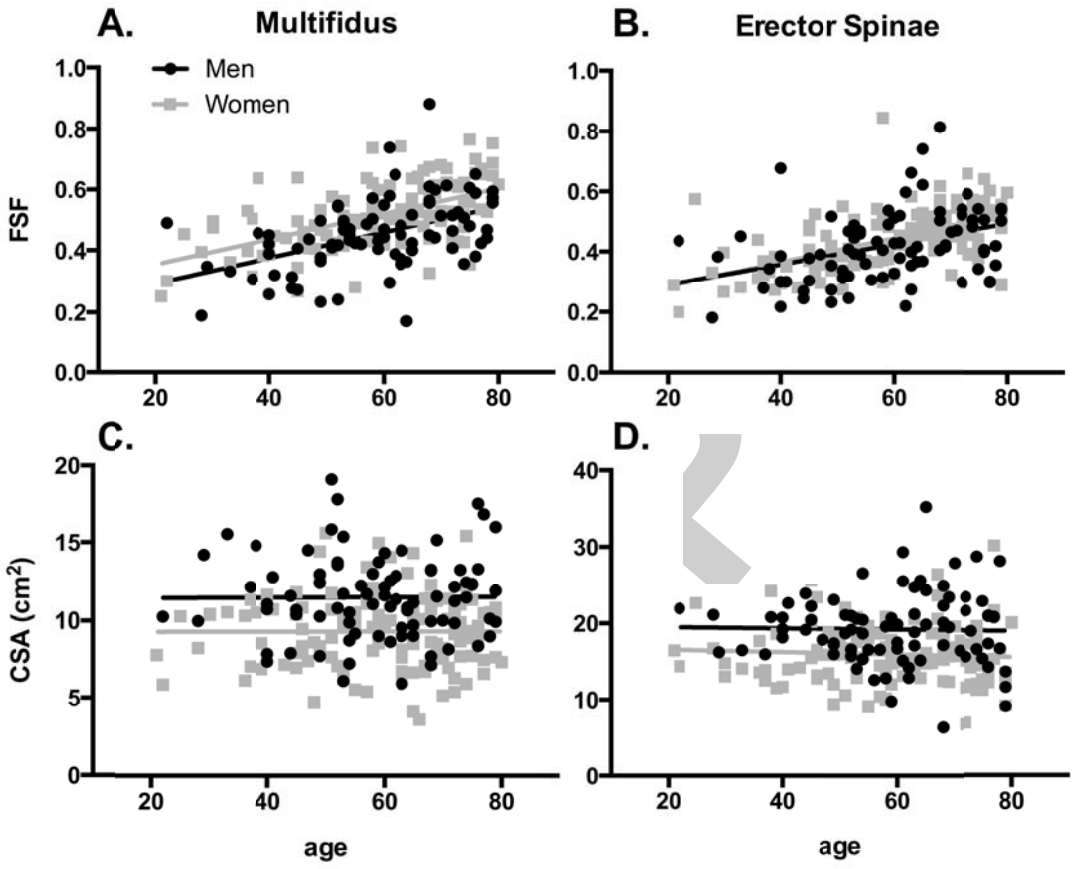

Figure 4. Univariate regression plots for multifidus FSF in men (A) and women (B) and erector spinae (C, D). Regression lines from healthy individuals from Crawford, et al. are superimposed using a dotted line for comparison. (*) indicates $p<0.05$ between regression intercepts of healthy and pathological populations. A trend for a difference between the intercepts (#) was seen for both muscles in men ($p=0.06$), and between slopes (+) both muscles in women ($p=0.08$).

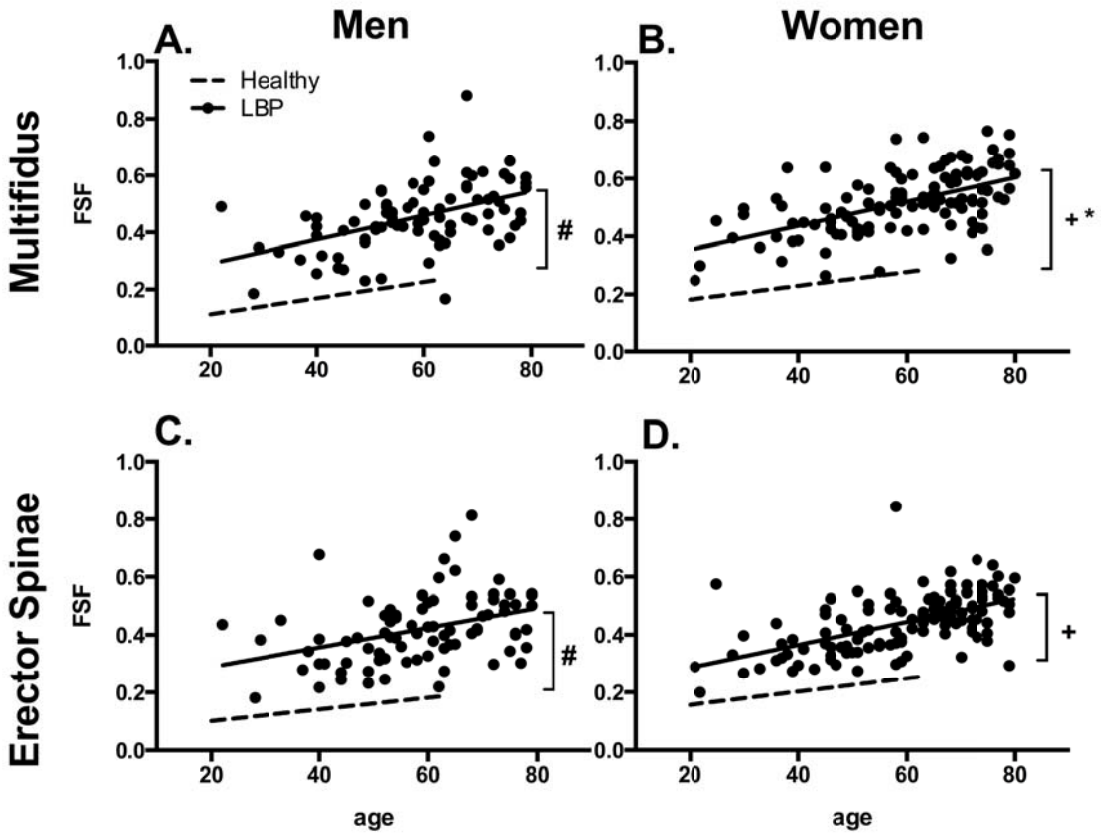

Table 1. Surgical and diagnostic codes used for inclusion criteria in chart queries.

Surgical Codes	Description	ICD-9 code	Diagnosis
22585	Fusion of additional interspaces	719.45	Pain in joint, pelvic region and thigh
22612	Posterolateral lumbar fusion	721.3	Lumbosacral spondylosis without myelopathy
22614	Posterolateral lumbar fusion, additional segments	722.52	Degeneration of lumbar or lumbosacral intervertebral disc
22630	Posterior Interbody Fusion, Lumbar	724.02	Spinal stenosis, lumbar region, without neurogenic claudication
22633	Combined fusion, posterolateral fusion, with posterior interbody fusion	724.03	Spinal stenosis, lumbar region, with neurogenic claudication
22634	Combined fusion, posterolateral fusion, with posterior interbody fusion (each additional interspace/segment)	724.2	Lumbago
63005	Laminectomy without facetectomy, foraminotomy or discectomy, lumbar, except for spondylolisthesis	724.4	Sciatica
63012	Laminectomy with removal of abnormal facets and/or pars interarticularis with decompression, for spondylolisthesis, lumbar	724.5	Thoracic or lumbosacral neuritis or radiculitis, unspecified
63017	Laminectomy without facetectomy, foraminotomy or discectomy, lumbar, except for spondylolisthesis (more than 2 vertebral segments)	729.5	Backache, unspecified
63030	Laminotomy (hemilaminectomy), including partial facetectomy, foraminotomy and/or excision of herniated disc, lumbar	782	Backache, unspecified
63035	Laminotomy (hemilaminectomy), including partial facetectomy, foraminotomy and/or excision of herniated disc, lumbar (each additional interspace)		
63042	Laminotomy (hemilaminectomy), including partial facetectomy, foraminotomy and/or excision of herniated disc, re-exploration, lumbar		
60344	Laminotomy (hemilaminectomy), including partial facetectomy, foraminotomy and/or excision of herniated disc, re-exploration, lumbar (each additional interspace)		
63047	Laminectomy, facetectomy and foraminotomy, lumbar		

Table 2. Patient demographic characteristics.

	Female (n=120)	Male (n=83)	P value
Patients (%), n=203	59.1	40.9	0.011
Age, y (SD)	58.6 (13.3)	59.1(14.2)	0.79
Diagnosis (% of total)			
Non-specific LBP	15.3	10.8	0.89
Radiculopathy	25.6	17.2	0.88
Stenosis	4.9	5.4	0.82
Other	13.3	7.4	0.86
CSA (cm^2)			
Multifidus	9.29 (2.38)	11.49 (2.69)	<0.0001
Erector Spinae	15.92 (3.96)	19.20 (4.70)	<0.0001
FSF			
Multifidus	0.52 (0.11)	0.45 (0.12)	<0.0001
Erector Spinae	0.44 (0.10)	0.42 (0.12)	0.17

*LBP = Low back pain, CSA = Cross Sectional Area, FSF = Fat Signal Fraction

Table 3.

Multifidus	**Normal (N=80)**		**Pathological (N=199)**		
	slope	**intercept**	**slope**	**intercept**	**p**
Men	0.003 (0.001)		0.004 (0.008)		0.28
		0.056 (0.028)		0.205 (0.488)	0.06
Women	0.002 (0.001)		0.004 (0.006)		0.08
		0.134 (0.049)		0.269 (0.389)	0.03
Erector Spinae					
Men	0.002 (0.001)		0.003 (0.009)		0.31
		0.061 (0.025)		0.220 (0.517)	0.05
Women	0.002 (0.001)		0.004 (0.006)		0.08
		0.110 (0.052)		0.205 (0.368)	0.10

*Values are represented as mean (SD), normal values are based on personal correspondence with Crawford et al (25).