European Spine Journal (2020) 29:1175–1180
https://doi.org/10.1007/s00586-020-06370-2

ORIGINAL ARTICLE

Is fractal dimension a reliable imaging biomarker for the quantitative classification of an intervertebral disk?

Junchao Ma[1] · Ruifeng Wang[1] · Yong Yu[1] · Xiaotong Xu[1] · Haifeng Duan[1] · Nan Yu[1]

Received: 1 August 2019 / Accepted: 7 March 2020 / Published online: 17 March 2020

Abstract

Purpose This study aimed to explore the feasibility of the fractal method used in decoding disk heterogeneity, hoping to find a reliable imaging biomarker for the quantitative and continuous grading of intervertebral disks (IVDs).

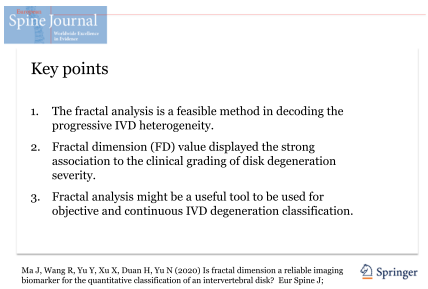
Methods Totally, 180 IVDs in 65 low back pain patients (29 males, 36 female, 28–69 years) were examined with MRI. Each IVD was manually segmented on axial slice (at the mid-height layer of the disk). All disks were visually evaluated regarding degeneration grade, using Pfirrmann classification, by two experienced radiologists. Fractal dimension (FD) of the IVD was calculated from the defined regions of interest and correlated with Pfirrmann grade.

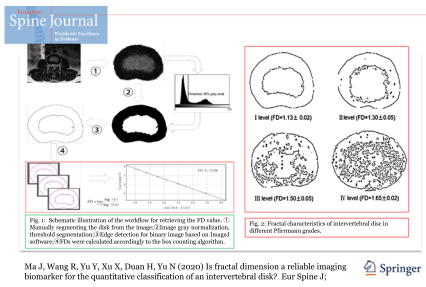
Results Fractal dimension differed significantly between any two groups ($P < 0.01$). The mean FDs for the four grades were as follows: Pfirrmann 1: 1.13 ± 0.02; Pfirrmann 2: 1.30 ± 0.05; Pfirrmann 3: 1.50 ± 0.05; and Pfirrmann 4: 1.65 ± 0.02. The well-hydrated IVDs displayed low fractal dimension. Degenerated IVDs displayed increased fractal dimension caused by disk heterogeneity, where the fractal dimension was shown to correlate strongly with Pfirrmann grade.

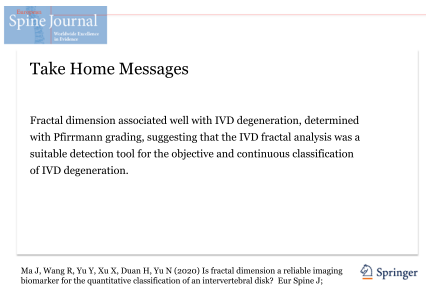
Conclusions Fractal dimension associated well with IVD degeneration, determined with Pfirrmann grading, suggesting that the IVD fractal analysis was a suitable detection tool for the objective and continuous classification of IVD degeneration.

Graphic abstract

These slides can be retrieved under Electronic Supplementary Material.







Keywords Fractal dimension · Classification · MRI · Intervertebral disks · Degeneration

Introduction

The most common cause of chronic disability is low back pain (LBP), which seriously affects the quality of life of patients and brings a heavy burden to society [1, 2]. Disk degeneration is the main cause of LBP.

Magnetic resonance imaging (MRI) is considered to be the best imaging method for evaluating intervertebral disk (IVD) degeneration and is of great significance for the

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s00586-020-06370-2) contains supplementary material, which is available to authorized users.

✉ Nan Yu
yunan0512@sina.com

[1] Department of Radiology, The Affiliated Hospital of Shaanxi University of Chinese Medicine, 2# Weiyang Western Road, Xianyang 712000, China

diagnosis and classification of IVD. Pfirrmann et al. [3] proposed a grading system focusing on the signal intensity of the nucleus pulposus (NP) and the structural morphology in sagittal T2-weighted MRI images. The Pfirrmann classification system is based on the visual interpretation of MRI images. The qualitative classification of IVD degeneration was affected by the subjective influence of observers. The Pfirrmann classification system is still the most widely used clinical grading method because of its simple evaluation procedure and low time and examination cost. With the development of the new technology of MRI, quantitative methods for detecting the degeneration of IVDs have been developed in recent years, including the measurement of T1, T1r, and T2 relaxation times and apparent diffusion coefficients [4, 5]. These methods provide additional information about the biochemical composition and structural integrity of IVDs. However, this is not free of cost. These methods require specific image acquisition protocols and have relatively long acquisition times, which limit their clinical application. Therefore, it is necessary to explore a simple and low-cost detection technology for the quantitative classification of IVDs. The texture analysis provides the basis for solving the aforementioned problems [6]. They do not need a special acquisition protocol while still maintaining the ability to convert qualitative data into quantitative data.

Waldenberg et al. [7] used the histogram analysis to quantitatively classify IVDs, suggesting that the IVD histogram analysis was a suitable tool for objective and continuous IVD degeneration classification. However, the histogram analysis is a first-order texture feature analysis, which may not fully explain the complex pathophysiological phenomenon during disk degeneration. In the process of IVD degeneration, a series of pathological changes (clefts, tears, and granular material) significantly increase the heterogeneity of the disk. Fractal dimension (FD) reflects the ability of the space occupied by complex shapes. It is a measure of the irregularity of complex shapes [8–10]. It is speculated that the heterogeneity of IVD signals during disk degeneration can be quantitatively described using the FD.

This study aimed to explore the feasibility of the fractal method used in decoding disk heterogeneity, hoping to find a reliable imaging biomarker for the quantitative and continuous grading of IVDs.

Materials and methods

MRI datasets and qualitative grading

One hundred and ninety-five lumbar disks from 65 patients (29 male and 36 female; 28–69 years; median 38 years) with nonspecific LBP were analyzed. In this study, the mid-height of L3/4, L4/5, and L5/S1 disks was selected for analysis, and the location line passed through the center of the nucleus as parallel as possible (Fig. 1). Data were acquired using a 3.0-Tesla MRI scanner (Magnetom Skyra, Siemens Healthcare, Erlangen, Germany), and a fast relaxation fast spin echo imaging sequence with the following acquisition parameters: repetition time, 3500 m/s; echo time, 90 m/s; 256 × 256 matrix; section thickness, 4 mm; and intersection gap, 0.5 mm. The exclusion criteria were as follows: lumbar trauma, previous lumbar surgery, infection, tuberculosis, tumors, or other serious lumbar diseases such as ankylosing spondylitis, patients with in vivo metal implants or pacemakers, and claustrophobia. After approval by the local ethics committee, informed consent was obtained from all participants.

For the Pfirrmann classification of IVDs, high-quality sagittal images of T2WI (repetition time 3800 ms, echo time 108 ms, 256 × 192 matrix, section thickness 4 mm, and intersection gap 0.8 mm) were obtained. Two experienced radiologists independently reviewed the images and classified each one of the 195 disks into one of the five classes of degeneration severity. When the two observers disagreed, they finally settled their differences through consultation. Severely degenerated IVDs with collapsed disk spaces were excluded from assessment because the new classification system was designed to classify relatively early degenerative disks and possible partial volume effect caused by endplates in the slice is needed to be avoided. Therefore, only grade 1–4 disks were analyzed in this study.

Disk degeneration quantification

Disk segmentation, data processing, and fractal-based quantification

The mid-height layer of disks was selected (Fig. 1, red location line). The axial disk image was imported into the ImageJ software for image preprocessing and FD calculation. The process included the following steps. (1) A manual method was used for segmenting the disk from the image. (2) Image conversion to 8-bit: the grayscale of IVD images was normalized (window width 255 and window level 128). The binary images of the disks were obtained (threshold: 65% gray level). (3) Edge detection for binary images was performed based on ImageJ software. (4) The images were further analyzed using the ImageJ software (Wayne Rasband, National Institutes of Health, MD, USA) together with the FracLac plug-in (A. Karperien–Charles Sturt University, Australia). FD were calculated accordingly to the box-counting algorithm as the slope of the regression line for the log–log plot of the scanning box size and the count from a box-counting scan. A representation of the process is shown in Fig. 1.

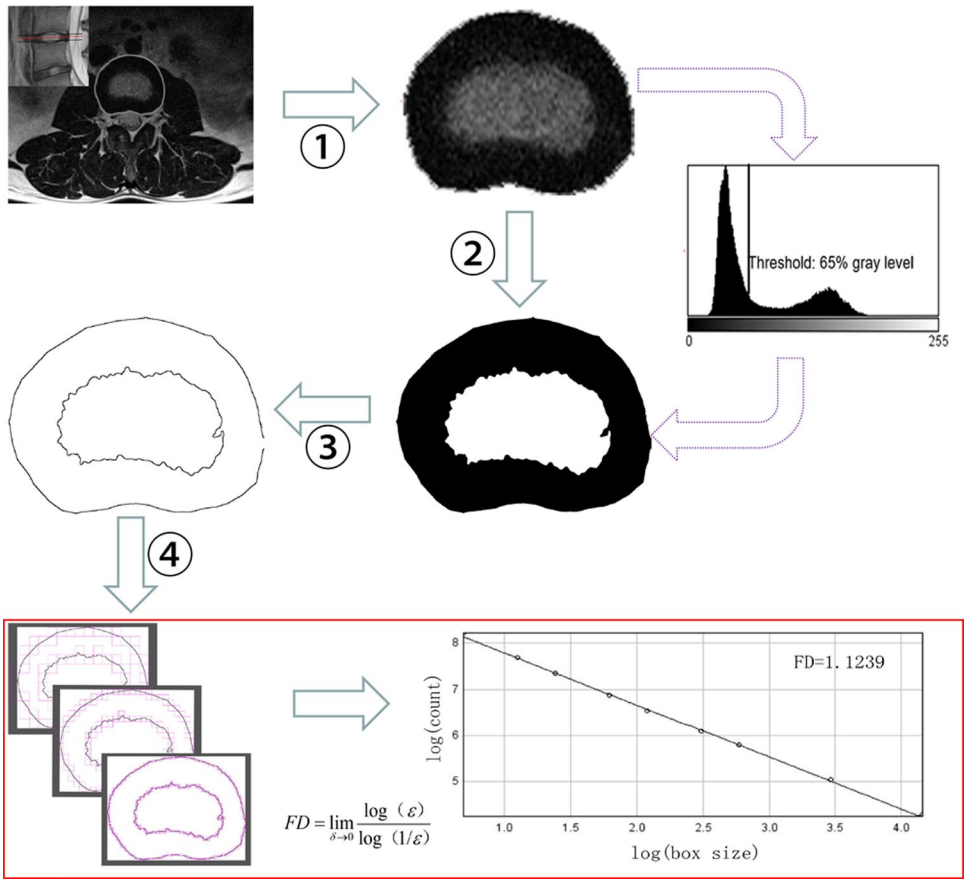


Fig. 1 Schematic illustration of the workflow for retrieving the fractal dimension. ① Manually segmenting the disk from the image; ② image gray normalization, threshold segmentation; ③ edge detection for binary image based on imageJ software; ④ FDs were calculated accordingly to the box-counting algorithm

Statistical analysis

The Mann–Whitney *U* test was performed to examine statistical significance between the FD value and Pfirrmann grade. Statistical significance was defined as $P < 0.01$. All values were given as mean ± one standard deviation. Cohen's kappa statistics was employed for evaluating intra/interobserver agreement on the Pfirrmann scale. To test the effect of manual disk segmentation on the FDs, the FD was calculated twice by the two radiologists. The intraclass correlation coefficients were calculated between these measurements to test their repeatability (intra/interobserver agreement).

Table 1 Intraobserver and interobserver agreement

Category rated	Pfirrmann's sagittal T2-weighted	
	Agreement (%)	κ
Intraobserver		
1 versus 2	95.4	0.88
Interobserver		
1	92.0	0.80
2	89.7	0.73

Results

Pfirrmann classification and intraobserver and interobserver agreements

Of the 195 disks in 65 patients, 15 Pfirrmann grade five disks were excluded, and 180 disks were finally evaluated and divided into four Pfirrmann groups. Intraobserver and interobserver agreements are summarized in Table 1. In both intraobserver and interobserver agreements, kappa values for the Pfirrmann classification were interpreted as substantial agreement. The two radiologists' consensus distribution was as follows: 24 disks were assigned as Pfirrmann 1, 75 disks as Pfirrmann 2, 48 disks as Pfirrmann 3, and 33 disks as Pfirrmann 4.

Fractal characteristics of IVDs (Pfirrmann 1 to Pfirrmann 4) (Fig. 2)

In the degenerative process, two main changes occurred in the fractal characteristics of IVDs. First, the distinction between NP and annulus fibrosus (AF) became rough and irregular. In the normal disk (Pfirrmann 1), the distinction between NP and AF was clear and regular. When it came to a severely degenerative disk (Pfirrmann 4), the

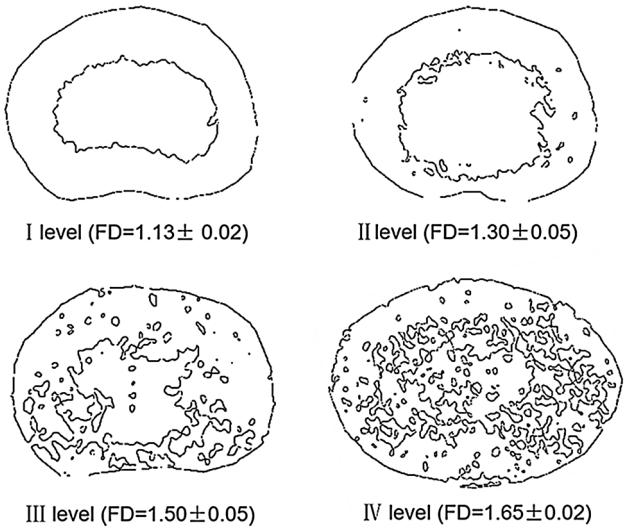


Fig. 2 Fractal characteristics of intervertebral disk in different Pfirrmann grades. As disk degeneration advances, the distinction between NP and AF was lost and more and more "island-like" structure in AF were detected

distinction between NP and AF was lost (detailed characteristics in Fig. 2). Second, the signal heterogeneity in the AF presented mainly as an "island-like" structure in the annulus (Fig. 3). This structure was related to the signal heterogeneity in the AF. Some of the structures were shown as the previously reported high-intensity zones (HIZs, 35 disks). Besides these zones, a diffuse "island-like" structure in the annulus corresponded to a slightly higher signal intensity in the annulus. This diffuse "island-like" structure could not be fully visualized in MRI images.

Correlation between the FD value and Pfirrmann grade

The mean FDs for the four grades were as follows: Pfirrmann 1: 1.13 ± 0.02; Pfirrmann 2: 1.30 ± 0.05; Pfirrmann 3: 1.50 ± 0.05; and Pfirrmann 4: 1.65 ± 0.02. Statistically significant differences were found between any two groups ($P < 0.01$; Table 2). The FD displayed a strong association with the clinical grading of disk degeneration severity, where an increased FD was observed with the increased Pfirrmann grade. Finally, intraclass correlation coefficients (ICCs) were used for testing measurement repeatability. Quantitative measurements were highly repeatable. The ICC of the interobserver measurements was 0.943. The ICC of the intraobserver measurements was 0.954 and 0.962, respectively (radiologist 1 and radiologist 2).

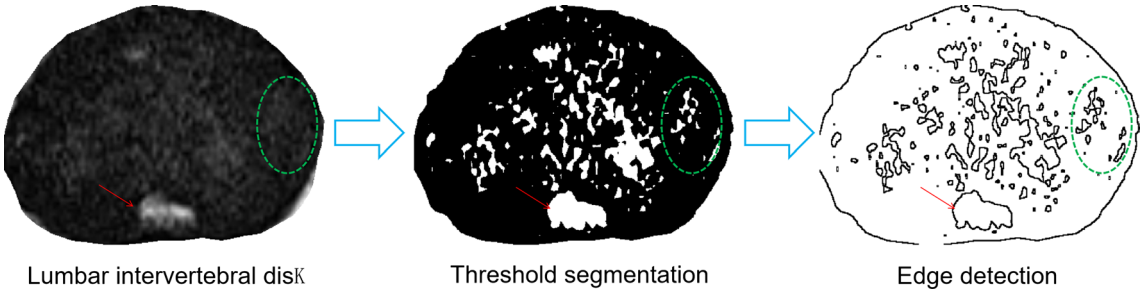


Fig. 3 A 45-year-old patient with low back pain, "island-like" structure appears in the annulus (Red arrow and green circle). The "island-like" structure displayed by the red arrow corresponds to a wide dorsal annular rift, visible as a clear HIZ. In addition, diffuse heterogeneity within the annulus is also manifested as "island-like" structure. These heterogeneities may represent pre-HIZ

Table 2 Fractal dimension values for IVDs of Pfirrmann grade 1–4

	Pfirrmann grade (Pf) and group size (n)			
	Pf = 1, n = 24	Pf = 2, n = 75	Pf = 3, n = 48	Pf = 4, n = 33
Fractal dimension	1.13 ± 0.02	1.30 ± 0.05	1.50 ± 0.05	1.65 ± 0.02

$P = 0.00$* $P = 0.00$* $P = 0.00$
$P = 0.00$
$P = 0.00$
$P = 0.00$

* Indicates significance

Discussion

This study investigated the fractal characteristics of IVDs to find an imaging biomarker for the objective and continuous classification of IVD degradation, suggesting that the decoding of the progressive IVD heterogeneity with a fractal analysis was feasible.

The results presented in this study showed that the FD of IVDs increased significantly with the increase in the Pfirrmann grade. The fractal analysis of IVDs of different Pfirrmann grades generated a continuous range of FD, indicating that the fractal analysis might be a suitable tool for the objective and continuous classification of IVD degeneration.

IVDs undergo age-related degenerative changes earlier in life compared with other tissues. In the early stage of disk degeneration, clefts and tears occur in the inner annulus [11, 12]. These changes may lead to the gradual irregularity of the distinction between NP and AF. FD is a measure of the irregularity of complex shapes [13]. It is speculated that one of the main reasons why the FD increases with degeneration may be the gradual loss of the distinction between NP and AF. As disk degeneration advances, clefts/tears extend into the outer annulus and are filled with granular material [11, 14]. These pathological changes lead to the increase in heterogeneity in annulus fibrosus, which may significantly damage the integrity of the intervertebral disk. Quantitative detection of these pathological changes is of great significance for predicting the fatigue life of the disk or evaluating therapeutic response. This study found diffuse "island-like" structures in the annulus, some of which correspond to the distinct high-intensity zones (HIZs), which was first described in 1992 by Aprill and Bogduk as potential imaging biomarkers related to a symptomatic disk [15], and other diffuse "island-like" structures due to the subvoxel size, which cannot be fully visualized in MRI images. It is speculated that these diffuse "island-like" structures may represent the micro-clefts or tears (may be the pre-HIZ), whether these structures will develop into HIZ requires long-term follow-up confirmation. The pathology of HIZs has not been described clearly to date. Yu et al. [16] thought that HIZs represented the collection of the mucoid fluid within annular fissures. Peng et al. [17] demonstrated that HIZs in patients represented the in-growth of the vascularized granulation tissue into annular fissures. Some studies showed that HIZs were closely related to pain [17–19], while others did not [20]. Waldenberg thought that it might be because the visual interpretation could not find "invisible" fissures [7]. Waldenberg et al. proposed that "invisible" fissures might be identified by histogram analysis. However, different fissure phenotypes might exhibit a vastly different histogram topology due to different signal intensities. For example, the study by Waldenberg found that a wide dorsal annular rift, visible as a clear HIZ, might significantly affect the histogram topology, leading to the reversal of the histogram topology. Hence, classifying the intervertebral disk only by using the histogram feature (Gaussian peak separation, $\Delta\mu$) is not completely reliable, and different fissure phenotypes should be considered additionally. In the present study, edge detection is performed after a single threshold segmentation of the intervertebral disk image. The HIZs and the possible pre-HIZ were split in the same gray scale range. All of these showed an increased complexity of the images and contributed positively to the fractal dimension. Therefore, this method improved the sensitivity of detecting heterogeneity in the disk. It could detect not only the distinct HIZ but also the possible "invisible" fissures. However, single threshold segmentation may not be able to distinguish between symptomatic and asymptomatic disks. Since different fissure phenotypes may exhibit different signal intensities, it is necessary to perform multi-threshold studies on symptomatic disks.

The present study also had a few limitations. First, as only patients with chronic LBP were studied, whether the FD between an asymptomatic group and a symptomatic group would differ remains unknown. Studies comparing FD values of asymptomatic and symptomatic individuals are warranted. Second, this study did not involve detection after treatment, whether the proposed method can detect small changes after treatment needs further exploration. Third, the samples used in this study were small. Although meaningful results were obtained, large-sample studies are still needed to further verify the accuracy of the results. Fourth, this study relied on the Pfirrmann classification as a reference standard for degradation, which is a coarse and, to some extent, a subjective marker of degeneration because it is based on visual interpretation. In addition, the height of IVDs in this study was not included in the evaluation. The height of IVDs is also an important indicator of degeneration.

In conclusion, the FD associated well with IVD degeneration, determined with Pfirrmann grading, suggesting that the IVD fractal analysis was a suitable detection tool for the objective and continuous classification of IVD degeneration.

Acknowledgements This research supported by the Subject Innovation Team of Shaanxi University of Chinese Medicine (#2019-QN09).

Compliance with ethical standards

Conflict of interest The authors declare that they have no competing interests.

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