Original article

Decrease with aging of the microcirculatory function of the lumbar vertebral marrow preceding the loss of bone material density and the onset of intervertebral discal degeneration: A study about the potential cause

Lin Ou-yang [a],*, Guang-ming Lu [b],*

[a] *Department of Medical Imaging, PLA 175th Hospital, Southeast Hospital, Clinical School of Medical College, Xiamen University, Zhangzhou, Fujian, China*
[b] *Department of Medical Imaging, Nanjing General Hospital, Jinling Hospital, Clinical School of Medical College, Nanjing University, Nanjing, Jiangsu, China*

Abstract

Objective: Using a dynamic computed tomographic perfusion (CTP) imaging method to explore the age-related distribution of the microcirculation perfusion function in the vertebral marrow, the bone material density (BMD), and the intervertebral discal degeneration (IDD). Further, to discuss a possible causation relationship between them.

Methods: One hundred and eighty-six people were randomly enrolled by stratified sampling and grouped by age: ≤15, 16−25, 26−35, 36−45, 46−55, 56−65, 66−75, and ≥76 years old. The average CTP and BMD of the third and fourth lumbar vertebrae marrow were measured and the IDD incidence of the third-fourth vertebrae was assessed. The temporal−spatial distribution patterns of the age-related changes of the CTP, BMD, and IDD were described, and the correlations between them were calculated.

Results: The microcirculatory perfusion function of the vertebral marrow develops to maturity by 25 years and is maintained until age 35, then declines with aging. The BMD grew to a peak from 26 to 45 years old, then decreased yearly. The IDD showed a sudden increase after 45 years of age. The CTP [BF ($r = 0.806$, $P = 0.000$), BV ($r = 0.685$, $P = 0.005$) and PMB ($r = 0.619$, $P = 0.001$)] showed strong positive correlations and CTP [TTP ($r = -0.211$, $P = 0.322$) and MTT ($r = -0.598$, $P = 0.002$)] showed negative correlations with BMD. The CTP [BF ($r = -0.815$, $P = 0.000$), BV ($r = -0.753$, $P = 0.000$) and PMB ($r = -0.690$, $P = 0.000$)] had strong negative correlations, and CTP [TTP ($r = 0.323$, $P = 0.126$) and MTT ($r = 0.628$, $P = 0.001$)] had positive correlations with the incidence of IDD.

* Corresponding authors.
  E-mail address: ddcqzg@126.com (G.-m. Lu).
  Peer review under responsibility of Chinese Medical Association.

ELSEVIER | **Production and Hosting by Elsevier on behalf of KeAi**

Conclusion: The decrease with aging of the microcirculatory perfusion in the lumbar vertebral marrow preceded, and is a potential causative factor for the loss of BMD and the onset of IDD.

Introduction

Currently the therapeutic emphasis in the field of lower back pain associated with lumbar vertebral degeneration is placed on disc surgery[1,2] and lumbar fusion.[3,4] Discal degenerative disease (DDD) and subsequent degenerative spondylosis associated unsteadiness is the downstream problem. Identifying the origin of DDD could be potentially helpful for preventing and/or relieving the disease. It has been suggested in previous studies that reduced blood supply to the vertebrae marrow is correlated with the increased incidence of intervertebral discal degenerative disease (IDD),[5] and loss of vertebral bone material density (BMD).[6] However, these studies achieved a "correlation" rather than proof of a causative relationship. This study aims to investigate the temporal—spatial distribution of the microcirculation of the vertebrae marrow, vertebral BMD and IDD in different age groups by an observational hemodynamics study using the computer tomography perfusion (CTP) technique. We expect to disclose the causation between circulation and pathology.

Materials and methods

Patients

The volunteer subjects enrolled in this study came from the medical examination center of the Southeast Hospital (Clinical School of the Medical College, Xiamen University) from January, 2011 to December, 2013. The exclusion criteria included: body height/weight ratio is more than 20% or less than 10% of normal reference standard, spinal development malformation, any history of spinal surgeries, any history of traumatic spinal fracture, and any disease (for e.g., metabolic disease, renal inadequacy, cardiac insufficiency, connective tissue disorder) or tumor that could potentially affect the spinal homogeneity and influence the results.

All subjects were enrolled by stratified sampling, and were divided into eight subgroups by age: ≤15, 16—25, 26—35, 36—45, 46—55, 56—65, 66—75, and ≥76 years old. Each group was to be a set of 24 randomly selected subjects with an equal number of men and women. In actuality, the subgroup ≤15 years old did not enlisted volunteers from 1 to 9 years of age and was composed of only 18 subjects (9 males and 9 females) from 10 to 15 years old. At the final evaluation there were a total of 186 subjects.

The hospital ethics committee approved the study, and informed consents were obtained from the subjects in the study.

Computed tomographic examinations

Many previous studies had used magnetic resonance tomography perfusion (MRP), mainly due to its being free of X-ray radiation. However, MRP, whether with contrast enhancement or arterial spin label (ASL) methods, has shortcomings. These include unsatisfactory acquisition speed and temporal and spatial resolution, magnetic insensitive to skeleton because of rare hydrogen protein in bone mine material, lower accuracy and reproducibility due to fluctuations of the magnetic field, inflow effect, and nephrogenic systemic fibrosis from Gadolinium-based contrast agents.[7] As opposed to the MRI, the advantages of computed tomography (CT) are its lower cost, excellent availability in the speed of acquisition and the temporal and spatial resolution. In addition, CTP allows the acquisition of successive multiple phases and provides functional information to better analyze bone and soft tissue. The functional analysis is more reproducible than that of MRI. The development of multidetector CT and recent technological advances reduce the radiation dose from examination that the patient is exposed to. The best example is the recent appearance of iterative reconstructions that reduces the dose by half with an equivalent image quality.[8] With these technological innovations and better control of the optimization of the acquisition parameters, it is now possible to obtain CT imaging with a dose almost equal to that of the standard X-ray assessment. In this study an advanced CT dose optimization and reduction scheme were used.[9]

We selected the third and fourth lumbar vertebral bodies as the region of interest (ROI) due to the

vertebrae being situated at the middle lumbar where they are not as susceptible to compression fractures as the first vertebrae and to degeneration as the fifth vertebrae. The CT protocols for measurement consisted of a plain low-dose CT scan and a dynamic enhancement CTP (DE-CTP) scan. All scans were performed using a Somatom Definition AS 4D multi-detector CT scanner (Somatom Definition AS 4D CT; Siemens, Germany). The table position at the level of the marked target lumbar vertebra was recorded, and the scan range was defined by the external laser alignment light. A preliminary plain 5.0 mm thick CT scan of the vertebral region (from the superior border of the third lumbar vertebral body to the inferior border of the forth lumbar vertebral body) was performed to guarantee a panoramic view of the entire anatomical region and thus help with recognition of anatomical landmarks. Specially trained technical personnel conducted the scanning to reduce the chance of human error.

Measurement of structural parameters

The structural parameters, including BMD and intervertebral discal changes, were taken into account because these age-related structural changes are a response to spinal physiological degeneration. The BMD images and data obtained were transferred to an image-processing workstation (syngo MultiModality workplace, series 46531; Siemens). Three slices located at the site of the upper one-third, middle site, and lower one-third of the third vertebral body were selected to measure BMDs, and the averaged value of the three measurements was used as the actual BMD of the vertebral body. Commercially available osteo software licensed by Siemens company was used for the BMD analysis. The selection of the ROI to be measured and calculation of the results were automatically performed by the software. The results are expressed by absolute values in milligrams per milliliter (mg/ml).

The CT indexes of IDD included disc bulge, protrusion, hernia into the endplate, "vacuum sign", ossification, and narrowed intervertebral space.[10] Signs or lesions of discal degeneration were assessed on the combination of CT transection and the reconstructive sagittal plane of the target vertebra segment.

Measurement of hemodynamics

The perfusion scheme was set by manual adjustment in accordance with the principle of CT dose optimization and reduction.[9] The following parameters

were selected for DE-CTP: tube voltage 80 kV, quality reference mAs 50, effective mAs 100 and 203 for subjects younger than 25 years and older than 25 years respectively, pitch 1.5, slice thickness 3.0 mm, gantry rotation time 0.33 s. A bolus injection of 40 ml (weight ≤50 kg) or 50 ml (weight >50 kg) of nonionic iodinated contrast medium (Iopamidol 370mg I/ml; Bracco Sine, Shanghai, China) was given at 5.0 ml/s followed by 50 ml of saline at 2 ml/s via a 20-gauge cannula in the right arm antecubital vein. Contrast material was administered using a dual-head pump injector (Medrad Stellant D, MEDRAD Inc., USA). After administering the contrast material consecutive dynamic CT acquisitions were performed after a 4-s delay from the start of the injection, scanning one time every 5-s period at the same field of view with shallow breathing for 90 s total duration and no delays. A standard reconstruction algorithm with no edge enhancement was used for the dynamic scanning. One set of axial images with a slice thickness of 5 mm for perfusion analysis was reconstructed without overlap using a medium smooth-tissue convolution kernel (B20f smooth). All images were then made anonymous and transferred to an external workstation (Multi-Modality Workplace; Siemens) for further analysis.

Based on our experience with a preliminary test, the total perfusion-monitored duration was set at 90 s because the perfusion period of the lumbar vertebrae marrow is longer. The repeating scanning period was set at 5 s. The timing and intervals were selected to obtain an adequate number of measurements to ensure good perfusion parameter values and to warrant a correct radiation dose. During each of the dynamic perfusion series, the patient received a total local CTDIvol dose of 69mGy for young subjects and 83mGy for old subjects. These doses are within the recommended reference levels of a CTDI(w) of 11 mGy—88 mGy for lumbar vertebrae CT scans.[11,12] According to Ng et al,[13] motion correction is required to obtain optimal CT perfusion imaging with the least variability and the best estimations of CTP. A cradle scanning technique pertaining to Siemens Somatom Definition AS 4D CT was used for to-and-fro dynamic scanning to control motion artifacts.

CTP image data analysis

The CTP images and data obtained were transferred to an image-processing workstation and analyzed by two expert readers (one with 17 years and the other with 11 years of experience in CT diagnosis). Commercially available software (syngoMMWP

version VE36A) was used for the CTP analysis. In one of the series slices, a ROI that was sufficiently small to avoid partial volume effects (two to six pixels) was placed in the aorta to calculate the arterial input, and a ROI was manually drawn along the subcortex margins of the vertebral body (Fig. 1). The software provided automated calculations of the following perfusion parameters in the ROI areas; blood flow (BF), blood volume (BV), mean transit time (MTT), time to peak (TTP), and permeability (PMB). BF was defined as the blood volume flowing across 100 g of tissue per minute $(ml \cdot min^{-1} \cdot 100 \ g^{-1} \ g)$. BV was defined as the total blood volume flowing across 100 g of tissue (ml/100 g). MTT was defined as the mean time taken for blood to flow from the artery to the vein, in seconds (s). TTP was defined as the time for contrast medium to reach the highest enhancement peak of the ROI, in seconds (s). PMB was defined as the product of the capillary endothelial space and the sum of the surface area, which reflects the blood volume flowing from the capillaries to the interstitial space $(ml \cdot min^{-1} \cdot 100 \ g^{-1} \ g)$. Values of the perfusion parameters were averaged across three slices to minimize the variability resulting from the ROI selection. These three ROI slices were selected from the target vertebral body at equal intervals.

Statistical methods

Study had shown that intervertebral disk degeneration is related to reduced marrow perfusion of both the adjacent vertebrae.[5] In this study the BMD and CTP measurements of the third and fourth vertebrae were averaged, and the mean values were the final BMD and CTP used in statistical analysis.

Testing for normality was performed for continuous data with the Shapiro−Wilk test. When the eight age groups had normally distributed data descriptive statistics, including mean and standard deviation (SD) of the CTP parameters (CTPs) and BMD are presented. Multivariate tests of general linear models were used to analyze the differences of CTPs, BMD and the incidence of IDD in the age groups. Their temporal−spatial distribution patterns with age were described as age-related
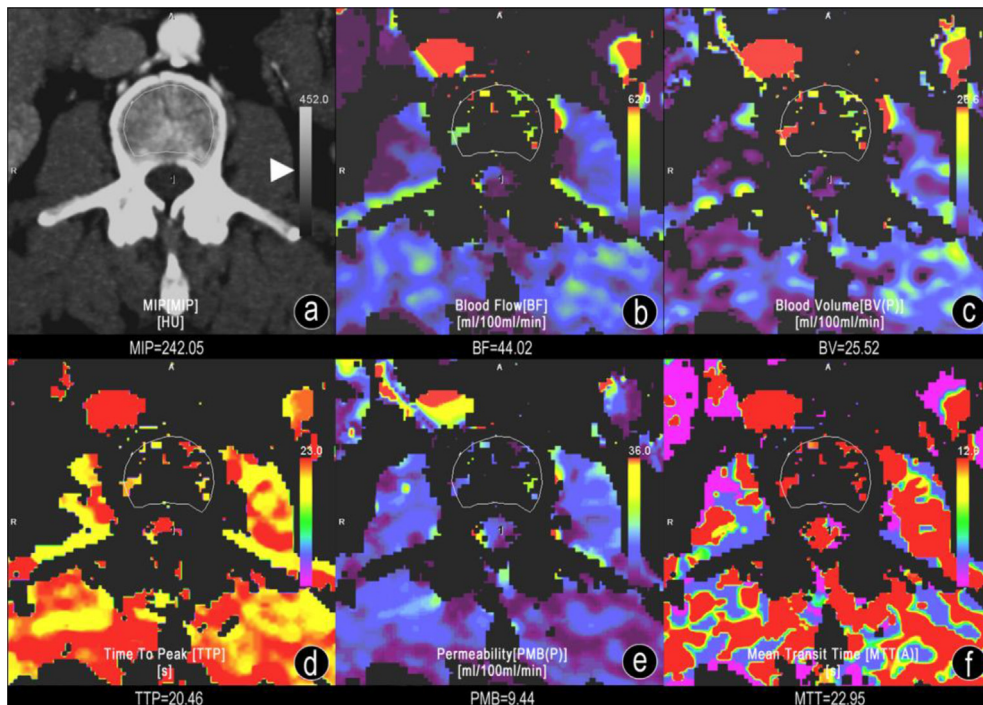

Fig. 1. CTP assessment of the third vertebral body. Images from one of the slices obtained by dynamic perfusion using CT on the third vertebral body of a female with 28 years old. a: a ROI was manually drawn along the subcortical zone of the target vertebral body for calculation of the CTP parameters. b: the blood flow (BF) map of the CTP. c: the blood volume (BV) map. d: the time to peak (TTP) map. e: the permeability (PMB) map. f: the blood flow (BF) map. Three ROIs slices respectively selected from the site of upper one-third, middle and lower one-third of the third vertebral body were assessed. The CTP parameters (CTPs) values were averaged across these three slices and the mean was regarded as the actual CTPs values of the target vertebral body. The colored scales (triangular arrowhead) were designed automatically by software to shows how the perfusion of the ROI were similar to that of the outer tissue.

Table 1
Age-related changes of the averaged CTPs and BMD values of both the third and fourth lumbar vertebral marrow

Parameter	Age groups								Statistical analysis	
	−15 years (I)	−25 years (II)	−35 years (III)	−45 years (IV)	−55 years (V)	−65 years (VI)	−75 years (VII)	−76 years (VIII)	Univariate tests	Pairwise comparisons (Sig.[a])
BMD	177.5 ± 32.1	207.6 ± 35.4	214.3 ± 50.4	212.9 ± 28.4	167.9 ± 39.4	137.2 ± 25.5	118.5 ± 42.2	102.5 ± 55.8	$F = 28.7, P = 0.00$	$P_{V-II,III,IV} = 0.02, 0.00, 0.00, 0.00$ $P_{VI-I,II,III,IV} = 0.00, 0.00, 0.00, 0.00$ $P_{VII-I,II,III,IV,V} = 0.00, 0.00, 0.00, 0.00, 0.00$ $P_{VIII-I,II,III,IV,V} = 0.00, 0.00, 0.00, 0.00, 0.00$
BF	48.0 ± 13.2	52.7 ± 25.7	52.3 ± 20.7	47.0 ± 16.2	40.3 ± 16.9	36.3 ± 11.4	34.0 ± 11.6	31.2 ± 16.0	$F = 5.7, P = 0.00$	$P_{II-VI,VII,VIII} = 0.03, 0.01, 0.00$ $P_{III-VI,VII,VIII} = 0.04, 0.01, 0.00$
BV	14.3 ± 7.5	14.9 ± 9.7	15.0 ± 9.8	12.8 ± 5.1	11.1 ± 7.5	9.0 ± 5.8	8.2 ± 3.6	7.1 ± 6.8	$F = 4.4, P = 0.00$	$P_{II-VII,VIII} = 0.05, 0.01$ $P_{III-VII,VIII} = 0.04, 0.01$
TTP	16.7 ± 2.3	15.4 ± 2.0	15.6 ± 2.4	16.1 ± 2.9	16.7 ± 1.9	18.1 ± 3.8	18.0 ± 3.4	18.4 ± 2.3	$F = 4.7, P = 0.00$	$P_{II-VI,VII,VIII} = 0.04, 0.01, 0.01$ $P_{III-VI,VII,VIII} = 0.05, 0.01, 0.01$
PMB	43.6 ± 13.1	54.5 ± 43.6	55.3 ± 33.7	49.0 ± 18.1	38.7 ± 10.6	35.1 ± 18.5	28.0 ± 10.7	26.7 ± 8.4	$F = 5.6, P = 0.00$	$P_{II-VII,VIII} = 0.00, 0.00$ $P_{III-VII,VIII} = 0.00, 0.00$ $P_{IV-VII,VIII} = 0.05, 0.03$
MTT	11.0 ± 4.4	7.6 ± 4.2	8.0 ± 4.4	10.2 ± 3.3	13.2 ± 4.0	14.0 ± 4.9	15.8 ± 4.6	18.5 ± 5.2	$F = 17.5, P = 0.00$	$P_{I-VII} = 0.02$ $P_{II-V,VI,VII} = 0.00, 0.00, 0.00$ $P_{III-V,VI,VII} = 0.00, 0.00, 0.00$ $P_{IV-VII} = 0.00$ $P_{VIII-I,II,III,IV,V,VI,} = 0.00, 0.00, 0.00, 0.00, 0.00, 0.02.$

[a] Adjustment for multiple comparisons: Bonferroni; CTP:computed tomographic perfusion; BMD: bone material density; BF: blood flow; BV: blood volume; TTP: time to peak; PMB:permeability; MTT: mean transit time
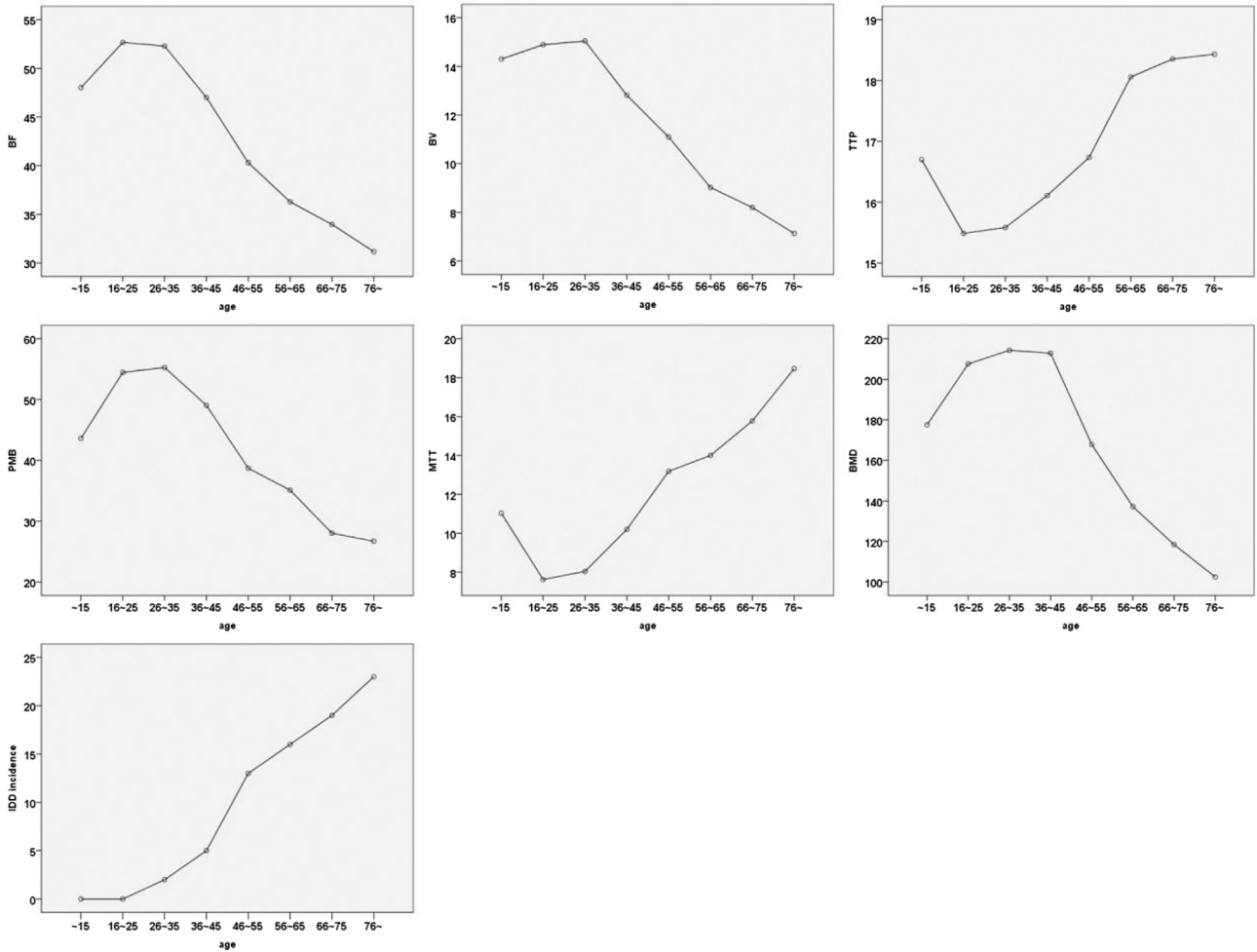
Fig. 2. Age-related temporal—spatial distribution pattern of microcirculatory perfusion function (embodied in CTPs) of both the third and fourth lumbar vertebral marrow and their BMD and IDD incidence.

Table 2
Age-related distribution pattern of the intervertebral disc degeneration (IDD) between the third lumbar and fourth lumbar vertebrae.

IDD signs	Age groups							
	−15 y	−25 y	−35 y	−45 y	−55 y	−65 y	−75 y	−76 y
Bulge	0	0	1	5	7	8	6	9
Protrude	0	0	0	1	4	7	7	9
Hernia	0	0	1	2	1	1	2	4
Ossification	0	0	0	0	0	0	1	2
"Air" sign	0	0	0	0	1	2	4	4
Space-narrowed	0	0	0	3	5	8	14	20
Total cases (incidence)	0 (0)	0 (0)	2 (8%)	5 (21%)	13 (54%)	16 (67%)	18 (75%)	23 (96%)

change curves and correlations between them were calculated by the pearson's correlation coefficient. And a one way ANOVA method was applied to analyze the comparisons of CTPs and BMD with and without IDD subjects for each subgroup. Multiple comparisons were adjusted with the Bonferroni test. The statistical analyses were performed using SPSS 17.0 statistical software (SPSS, Chicago, IL, USA). Statistical significance was assessed at a level of $P < 0.05$.

Results

Temporal−spatial distribution patterns of CTPs, BMD, and DDD with age

The microcirculation perfusion function embodied by the CTPs developed with age, reached a peak by 25 years, remained stable until 35 years and then declined with further aging. BMD had a similar maturing process, but it had a longer stable period from 25 to 45 years of age before it decreased with further aging. Before 45 years of age there was a lower incidence of IDD, much less than 20% for each age group. However, after 45 years there was a sudden increase of IDD with an incidence over 50% (Table 1 and Fig. 2). Moreover, in the subjects over 45 years old the intervertebral disc showed increasing concurrent multiple degenerative signs with aging; including discal bulge, protrusion, hernia, air vacuum, and ossification (Table 2).

Correlation between CTPs and BMD, incidence of IDD

CTP [BF ($r = 0.806$, $p = 0.000$), BV ($r = 0.685$, $p = 0.005$) and PMB ($r = 0.619$, $p = 0.001$)] showed strong positive correlations with BMD, and CTP [TTP ($r = -0.211$, $p = 0.322$) and MTT ($r = -0.598$, $p = 0.002$)] showed negative correlations with BMD. We also found that CTP [BF ($r = -0.815$, $p = 0.000$), BV ($r = -0.753$, $p = 0.000$) and PMB

($r = -0.690$, $p = 0.000$)] had strong negative correlations and CTP [TTP ($r = 0.323$, $p = 0.126$) and MTT ($r = 0.628$, $p = 0.001$)] had positive correlations with the incidence of IDD. In every group older than 45 years the CTPs showed significant differences between subjects with and without IDD. For the groups less than 46 years the differences were not analyzed because the IDD was too small and would cause statistical bias.

Discussion

This study used a CT method called dynamic enhancement scan perfusion imaging to reflect the hemodynamic status of the lumbar vertebral microcirculation. This measurement is potentially helpful for understanding the pathophysiological basis of lumbar vertebral degeneration. The results indicate that the microcirculation of the vertebral marrow changes with age. In people older than 35 years, the perfusion pressure decreases, the velocity of blood flow slows, blood volume decreases, and the capacity of blood diffusion in tissues is lower.

A long-standing goal for most researchers in the field of lower back pain associated with lumbar vertebral degeneration has been to discover its underlying pathogenesis or pathophysiology. Identifying its origin could potentially be helpful for preventing and/or relieving the disease. Mauno K.[14] had discussed in detail the association of impaired blood supply with painful lumbar disc degeneration. They argued that stenosis of the lumbar arteries is significantly associated with decreased diffusion to lumbar discs and may thus play an important role as a mechanism of disc degeneration, that stenosis of lumbar arteries is associated with disc degeneration among sciatica patients, and the grade of occlusion of lumbar arteries and the severity of disc degeneration are significantly higher among sciatica patients compared to asymptomatic subjects. Moreover, we do know that a decreasing BMD in the lumbar vertebral

body is closely correlated with the development and progression of the IDD, and that the decline of microcirculation perfusion of the vertebral bone marrow is highly related to BMD loss.[6,15] However, these studies did not disclose the causation, but only the correlation between these events. Because multiple factors contribute to the IDD within the same temporal–spatial domain, an experimental design that investigated a single in vivo factor was believed to be impossible to carry out. Inspired by a study by Bajwa et al.[16] that found that disk degeneration in lumbar spine precedes osteoarthritic changes in hip and may be a causative factor for hip osteoarthritis. We investigated the temporal–spatial distribution patterns of microcirculation perfusion and BMD of the vertebral bone marrow and IDD to look for causation between them.

These hemodynamic and physiological properties can be measured serially using the functional CTP technique and multiplanar imaging maps.[17] CTP imaging is a developing technique for quantitatively evaluating blood perfusion in tissues.[13] This study demonstrates that the microcirculation perfusion of the vertebral bone marrow developed until 25 years of age and was maintained from 26 to 35 years of age and then declined with aging. BMD showed a similar maturation process to the microcirculation perfusion, with a growth stage until 25 years of age but the stationary phase lasted longer, from 26 to 45 years of age and then decreased with age. However, the IDD-age curve presented no plateau, with 45 years being the dividing line age. After 45 years we see a higher incidence of IDD with age (Fig. 2).

The CTPs had a good correlation with BMD in each age group (all p < 0.05), also the CTPs had a good correlation with the incidence of IDD, and the microcirculation decrease of the lumbar vertebral marrow embodied by CTPs changes preceded BMD loss and IDD increase, as shown in Table 1 and Fig. 2. These results demonstrated that alterations in microcirculation of the lumbar vertebral marrow had an influence on its BMD and the health of the intervertebral disc. Some studies had been done with drugs or cell therapy aimed at prevention and cure of osteoporosis[18] and DDD[19] through maintaining the microcirculatory perfusion to the bone marrow. These successful experimental therapeutics also supported our hypothesis that dysfunction of the microcirculatory perfusion of the vertebral marrow is a cause leading to loss of bone mass and intervertebral disc degeneration. Based on these findings, a view could be established that reduced blood supply to the vertebral marrow leads to

vertebral endplate sclerosis and degeneration of the intervertebral disc because the disc's nutrition depends on the blood supply of the vertebral body passing through the cartilage endplate by diffusion. Intervertebral disc cell injury might be the intermediate step in transferring dysfunction of the microcirculation perfusion to the IDD.[20]

The results of this study showed that the blood flow and blood volume of the lumbar vertebral body, which reflects the blood supply to the lumbar vertebrae marrow, decreased with aging after passing through a mature phase. This phenomenon might be explained by arterial sclerosis, vascular tortuosity, vertebral compression causing vertebral artery stenosis or occlusion, and/or reduced cardiac output and blood volume. CTP of the MTT can be used to reflect the blood recirculation status in the microcirculation. The MTT is considered a marker of perfusion pressure. Any perfusion pressure decrease appears as increased MTT on perfusion CT maps.[21] This study also observed that the MTT was significantly prolonged with aging, which indicated that the microcirculatory blood recirculation slowed with aging. Certain factors might contribute to this pathophysiological change, including the increased diastolic blood pressure that occurs with aging, compression of a vein owing to vertebral body compression, venous thrombosis, a torus on an intervertebral disc oppressing an extra-vertebral vein, or any organized tissue or sterile adhesive drawing, moving, and oppressing an extra-vertebral vein. These factors can lead to increasing venous pressure in the internal vertebral body and subsequently increased interstitial fluid augmentation and pressure, which in turn cause problems for the arterial blood supply. Our results showed that the BF, BV and PMB decreased and TTP and MTT prolonged with aging, which were reflected in the blood flow velocity slowing in the microcirculation of the lumbar vertebral marrow, weakening the perfusion function of dispersed permeability. Subsequently, the metabolism in the vertebral marrow slowed, resulting in BMD decline. Further, in the presence of osteoporosis, which makes bone trabeculae susceptible to distortion (even fracture), vertebral body compression occurs, veins are compressed and become winding or stenotic, blood recirculation is dysfunctional, and venous pressure increases, making the arterial blood supply problematic. These factors form a vicious cycle. Later, the endplate and intervertebral disc are successively implicated. Dysfunction of nutrition in the endplate from the marrow to the disc will bring about intervertebral discal malnutrition degeneration. This

cascade reaction helps to partially explain the observed recessive lumbago that is so difficult to alleviate in elderly patients.

With aging, the loss of microcirculation function and BMD of the vertebral marrow has a significant effect on intervertebral disc degeneration, which is reflected by concurrent multiple degenerative signs of the intervertebral disc; including discal bulge, protrusion, hernia, air vacuum, and ossification. This result also suggested that development of compromised vascular status and osseous structure might have an influence on the initiation and progression of degeneration of the vertebral body and intervertebral discs.

There are some limitations to this study: (1) In the preliminary tests, the blood perfusion time in the vertebral body was delayed by 90 s to reduce radiation exposure during the examination. The study had planned to perform one scan during a 5-s period, so the few sampling points might affect the precise estimation of the CTP. (2) Up to now, no ideal experimental model could alone evaluate any one factor causing intervertebral disc degeneration because multiple factors integrate to contribute to the degeneration within the same temporal—spatial domain. Interestingly, the study disclosed a regular age-related alteration of the microcirculation perfusion function and BMD of the lumbar vertebral marrow and IDD and, with this temporal—spatial distribution pattern, the decline of microcirculation function preceded the decrease of BMD and increase of IDD. Based on our finding and those of previous studies, we hypothesize that dysfunction of the microcirculation is a cause for the loss of BMD and acceleration of IDD. This hypothesis may provide a new therapeutic direction for this hard to cure disease.

References

1. Shahmohammadi M, Asgharzadeh Shirazi H, Karimi A, Navidbakhsh M. Finite element simulation of an artificial intervertebral disk using fiber reinforced laminated composite model. *Tissue Cell*. 2014;46:299—303.
2. Grunert P, Gebhard HH, Bowles RD, et al. Tissue-engineered intervertebral discs: MRI results and histology in the rodent spine. *J Neurosurg Spine*. 2014;20:443—451.
3. Mummaneni PV, Dhall SS, Eck JC, et al. Guideline update for the performance of fusion procedures for degenerative disease of the lumbar spine. Part 11: interbody techniques for lumbar fusion. *J Neurosurg Spine*. 2014;21:67—74.
4. Eck JC, Sharan A, Ghogawala Z, et al. Guideline update for the performance of fusion procedures for degenerative disease of the lumbar spine. Part 7: lumbar fusion for intractable low-back pain without stenosis or spondylolisthesis. *J Neurosurg Spine*. 2014;21:42—47.
5. Liu YJ, Huang GS, Juan CJ, Yao MS, Ho WP, Chan WP. Intervertebral disk degeneration related to reduced vertebral marrow perfusion at dynamic contrast-enhanced MRI. *AJR Am J Roentgenol*. 2009;192:974—979.
6. Griffith JF, Wang YX, Zhou H, et al. Reduced bone perfusion in osteoporosis: likely causes in an ovariectomy rat model. *Radiology*. 2010;254:739—746.
7. Crownover BK, Bepko JL. Appropriate and safe use of diagnostic imaging. *Am Fam Physician*. 2013;87:494—501.
8. Gervaise A, Osemont B, Lecocq S, et al. CT image quality improvement using adaptive iterative dose reduction with wide-volume acquisition on 320-detector CT. *Eur Radiol*. 2012;22:295—301.
9. Gervaise A, Teixeira P, Villani N, Lecocq S, Louis M, Blum A. CT dose optimisation and reduction in osteoarticular disease. *Diagn Interv Imaging*. 2013;94:371—388.
10. Wang YZ, ed. *Musculoskeletal System Volume*. *Chinese Medical Imaging* (Wu EH, ed). Beijing: People's Public Health Publishing Company; 2002:155—165.
11. Pantos I, Thalassinou S, Argentos S, Kelekis NL, Panayiotakis G, Efstathopoulos EP. Adult patient radiation doses from noncardiac CT examinations: a review of published results. *Br J Radiol*. 2011;84:293—303.
12. Biswas D, Bible JE, Bohan M, Simpson AK, Whang PG, Grauer JN. Radiation exposure from musculoskeletal computerized tomographic scans. *J Bone Jt Surg Am*. 2009;91: 1882—1889.
13. Ng CS, Chandler AG, Wei W, et al. Reproducibility of CT perfusion parameters in liver tumors and normal liver. *Radiology*. 2011;260:762—770.
14. Mauno K. Association of impaired blood supply with painful lumbar disc degeneration. *Acta Univ Oul D*. 2003;732.
15. Ma HT, Griffith JF, Zhao X, Lv H, Yeung DK, Leung PC. Relationship between marrow perfusion and bone mineral density: a pharmacokinetic study of DCE-MRI. *Conf Proc IEEE Eng Med Biol Soc*. 2012;2012:377—379.
16. Bajwa NS, Toy JO, Young EY, Cooperman DR, Ahn NU. Disk degeneration in lumbar spine precedes osteoarthritic changes in hip. *Am J Orthop (Belle Mead NJ)*. 2013;42:309—312.
17. Qin HY, Sun HR, Wang XF, Bai RJ, Li YJ, Zhao JK. Correlation between CT perfusion parameters and microvessel density and vascular endothelial growth factor in adrenal tumors. *PLoS One*. 2013;8:e79911.
18. Wang YXJ, Ko CH, Griffith JF, et al. Organic nitrate maintains bone marrow blood perfusion in ovariectomized female rats: a dynamic, contrast-enhanced magnetic resonance imaging (MRI) study. *Pharmaceutics*. 2013;5:23—35.
19. Bendtsen M, Bünger CE, Zou X, Foldager C, Jørgensen HS. Autologous stem cell therapy maintains vertebral blood flow and contrast diffusion through the endplate in experimental intervertebral disc degeneration. *Spine (Phila Pa 1976)*. 2011;36:E373—E379.
20. Seki S, Tsumaki N, Motomura H, et al. Cartilage intermediate layer protein promotes lumbar disc degeneration. *Biochem Biophys Res Commun*. 2014;446:876—881.
21. Kambadakone AR, Sahani DV. Body perfusion CT: technique, clinical applications, and advances. *Radiol Clin North Am*. 2009;47:161—178.

Edited by Wei-Zhu Liu