35th Annual International Conference of the IEEE EMBS
Osaka, Japan, 3 - 7 July, 2013

Bone Marrow Perfusion of Proximal Femur Varied with BMD—a Longitudinal Study by DCE-MRI*

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Abstract—**This study investigated bone marrow perfusion at proximal femur varying with bone mineral density (BMD) and aging over 4 years. Dynamic contrast enhanced MRI data was extracted pixel-by-pixel and classified into 3 patterns to indicate the perfusion function. Eighty-seven elderly females were involved. A notable reduced perfusion as a whole was observed in osteoporotic subjects. Moreover, perfusion distribution varies as BMD decreases, especially at the area crossing the femoral neck to the shaft. Consistent for all subjects, the perfusion decreases significantly from the lesser trochanter to the greater trochanter. Further, the subjects with good bone marrow perfusion would keep stable BMD after 4 years, while for those with bad perfusion, their BMD consistently decreased over 4 years. The results indicated that the bone marrow perfusion function interacts with bone modeling and could have a long term effect on BMD. A good perfusion function would help to keep the bone health.**

I. Introduction

In recent two decades, more and more evidences showed association between diseases of artery and bone [1,2]. Namely, atherosclerosis and osteoporosis may in part share a common pathogenesis [3,4]. About inner two-thirds of the cortex, the marrow constituents and the trabecular bone are supplied from the nutrient arteries via the marrow cavity. The variation in arteries caused by diseases may change the nutrition supply process in the bone tissue. The term 'perfusion' describes a comprehensive physical process of the fluid with nutrition perfuse into the tissue, which is different from the 'blood flow'. It reflects a more functional process relevant to blood flow, endothelial permeability and interstitial diffusion. Dynamic contrast-enhanced MRI (DCE-MRI) provides a non-invasive approach to measure perfusion process and has been employed in study of bone marrow perfusion [5,6].

The proximal femur is one of the most common sites of osteoporotic fracture and is also an area prone to avascular necrosis and fracture nonunion. Study on the perfusion process will help to deepen understanding of nutrition supply at the proximal femur. Previous DCE-MRI study on proximal femur has shown how perfusion parameters are consistently reduced in osteopenic and osteoporotic bone compared to that with normal bone mineral density (BMD) [7]. However, those parameters derived from region of interest (ROI) are limited in the information regarding the perfusion distribution, which may correspond to BMD distribution and fracture location. Further, if the perfusion function has a long term effect on BMD is unknown yet. Some recent studies have employed pixel-by-pixel analysis on bone perfusion, which revealed detail association between perfusion distribution and bone marrow abnormalities [8].

Therefore, the objectives of this study were to investigate 1) perfusion distribution characteristics at proximal femur in subjects of varying BMD, and 2) its long term effect on BMD changing. Such research will enhance our knowledge of the blood perfusion anomalies occurring at marrow with different perfusion characteristics.

II. Methodology

A. Subjects

In order to avoid gender influence, only female subjects were selected. Subjects were excluded if they had (a) clinical or imaging evidence of renal osteodystrophy or other metabolic bone disease other than osteoporosis or a known malignancy, (b) a history of lumbar spinal surgery or irradiation, or (c) MR imaging evidence of large intravertebral disk herniation, hemangioma, or moderate to severe vertebral fracture of L3. Eighty-seven elderly female subjects (71±4.1 yrs) in total were involved in this study. Among 87 recruited subjects, 79 subjects completed 4-year following up experiments. The whole study was approved by the Ethics committee, Chinese University of Hong Kong with all participating subjects providing written consent.

B. Data acquisition

Dynamic contrast enhancement (DCE-MRI) data were acquired in an oblique coronal plane aligned along the midportion of the proximal femur in the first year. Dynamic MR imaging was performed using a short T1-weighted gradient-echo sequence (2.7/0/95; prepulse inversion time,

*Research supported by the National Natural Science Foundation of China under Grant NSFC 81000647 and Basic Research Foundation (Distinguishing Young Investigator Track) from Shenzhen Science, Industry, Trade & Information Commission under Grant JC201005260124A. Research partially supported by Hong Kong GRC grant SEG_CUHK02

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400 ms; flip angle, 15°). A total of 160 dynamic images were obtained with a temporal resolution of 543 ms, resulting in a total interrogation time of 87 seconds. A bolus of gadoteric acid (Dotarem, Guer-Guerbet, Aulnay, France) at a concentration of 0.15 mmol per kilogram body weight was injected via a power injector (Spectris; Medrad, Indianola, Pa) at a rate of 2.5 mL/s through a 20-gauge antecubitial vein intravenous catheter (Angiocath; Infusion Therapy Systems, Sandy, Utah). Injection was followed by a 20-mL saline flush. Dynamic MR imaging started at the same time as contrast medium injection started ("time zero").

Area bone mineral density (BMD) of proximal femur was measured every two years using the dual-energy X-ray absorptiometry (DXA). Subjects were classified into normal, osteopenia, and osteoporosis according to WHO criteria based on the BMD measurement in the first year.

C. *Data processing*

A pharmacokinetic model [9,10] was employed to analyze DCE-MRI data pixel-by-pixel. Specifically, DCE curve for each pixel was extracted and fitted by the model. According to a previous study [11], normal, osteoponia and osteoporotic subjects could have different patterns of perfusion curves. Fast enhancement followed by a slow enhancement indicated a bad perfusion status, which was most found in osteoporotic patients; fast enhancement followed by a signal plateau was most found in osteopenia subjects; and fast enhancement followed by a quick washout indicated a good perfusion function in bone marrow and was most found in normal subjects. Therefore, in this study, the fitted curves were then classified into 3 patterns, where a threshold (0.0065) was set for the slope of the curve end as the classification criteria (pattern 1: slope> threshold; pattern 3: slope < -threshold; others are pattern 2) (Fig 1). The pixel was colored into red, green and blue corresponding to pattern 1, 2 and 3, as shown in Fig 2. Those uncolored pixel was due to too weak DCE signal. Pattern percentage of ROI (color area / ROI area) were calculated for each pattern as a quantification of perfusion distribution.

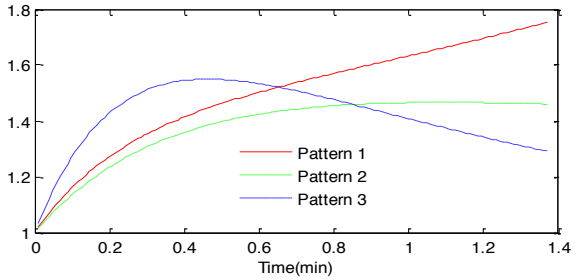

Fig 1. Classification of perfusion curve patterns. Pattern 1 (solid): fast enhancement, followed by a slow enhancement; Pattern 2 (dash-dot): fast enhancement, followed by a signal plateau; Pattern 3 (dash): fast enhancement followed by a quick washout.

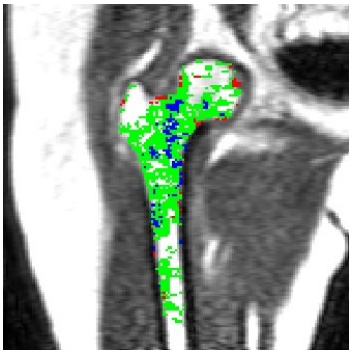

Fig 2. Pixel-by-pixel pattern mapping on the proximal femur

All image processing and curve fitting were conducted in a self-developed software by Matlab platform (ver. 2010a). Analysis of variance method (ANOVA) and *t*-test were employed to evaluate differences in parameters among groups. Statistical analysis was performed using statistical software (SPSS 16.0). A *p* value of less than 0.05 was considered statistically significant.

I. Results

A. *Perfusion vs. BMD*

Figure 3 gives the typical pattern mapping in three BMD groups. The pattern coloring rate showed significant difference among the groups. The area with no color was due to very bad perfusion with too weak DCE signal to be detected.

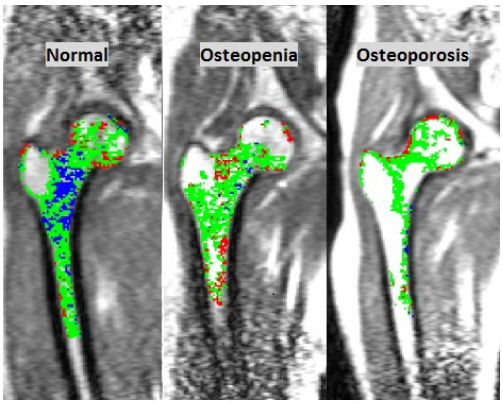

Fig 3. Representative pixel-by-pixel pattern mapping on the proximal femur for the 3 groups with different BMD

TABLE 1
PATTERN PERCENTAGE COMPARISON AMONG BMD GROUPS

Param	Groups	N	Mean	Std	p-value
Age (yrs)	Normal	26	69.73	3.63	0.090
	Osteopenia	44	71.02	4.41	
	Osteoporosis	17	72.59	4.08	
All patterns (%)	Normal	26	56.30	16.34	0.056
	Osteopenia	44	48.68	18.10	
	Osteoporosis	17	43.10	19.78	
Pattern 1 (%)	Normal	26	8.16	5.01	0.716
	Osteopenia	44	8.66	5.88	
	Osteoporosis	17	7.40	4.63	
Pattern 2 (%)	Normal	26	41.70	15.26	0.105
	Osteopenia	44	34.67	14.13	
	Osteoporosis	17	33.14	16.73	
Pattern 3 (%)	Normal	26	6.44	7.40	0.149
	Osteopenia	44	5.36	6.49	
	Osteoporosis	17	2.56	4.06	

ANOVA F-test across the three BMD groups

For the perfusion distribution, ANOVA F-test was employed to investigate the difference across the groups. Table 1 summarizes the comparison results among perfusion pattern percentages.

Overall, normal subjects had a significant higher pattern coloring rate than the other two, especially at the femur head part, which can be observed in Fig.3. This also indicated a better perfusion in normal subjects. Patterns 2 and 3 showed a significant reduction in subjects with lower BMD, while pattern 1 kept stable for the three groups. Furthermore, we observed a blue band (pattern 3: fast enhancement followed by a quick washout) crossing the femur neck to the shaft in most subjects with normal BMD. However, such distribution pattern was rarely observed in osteoporotic patients, while it was sometime observed in osteopenia subjects, as the typical illustration shown in Fig.2. Besides, the age also showed a obvious difference among the groups.

B. Perfusion and BMD over 4 years

For the longitudinal study, subjects were first classified into two groups with BMD decreased and BMD without decrease over the 4 years. There were 42 subjects with decreased BMD and 37 subjects with stable or even increased BMD. Then perfusion pattern distribution in the first year was compared between the two groups. By t-test, color mapping rate and pattern 3 percentage were significant higher in BMD without decrease group, as shown in Table 2. Pattern 1 and pattern 2 showed no significant difference among groups. In other words, subjects with more perfusion pattern 3 would have less bone loss in later 4 years.

TABLE 2
PATTERN PERCENTAGE COMPARISON AMONG PERFUSION GROUPS

Param	Groups	N	Mean	Std	p-value
Age (yrs)	BMD Decrease	42	70.93	4.41	0.942
	BMD NoDecrease	37	71.00	4.24	
	Total	79	70.96	4.30	
All patterns (%)	BMD Decrease	42	45.41	18.12	0.033
	BMD NoDecrease	37	54.01	17.00	
	Total	79	49.44	18.01	
Pattern 1 (%)	BMD Decrease	42	7.70	4.94	0.365
	BMD NoDecrease	37	8.88	5.99	
	Total	79	8.23	5.45	
Pattern 2 (%)	BMD Decrease	42	34.43	15.68	0.333
	BMD NoDecrease	37	37.69	13.80	
	Total	79	35.96	14.82	
Pattern 3 (%)	BMD Decrease	42	3.28	4.67	0.004
	BMD NoDecrease	37	7.49	7.74	
	Total	79	5.25	6.60	

t-test between two groups

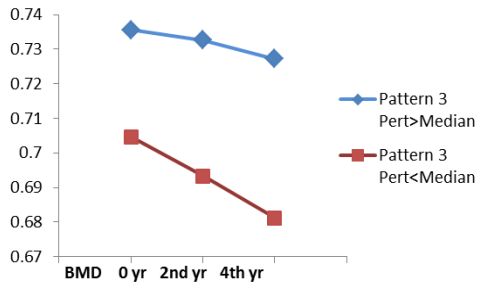

Fig.4 BMD change in 4 years in groups with different perfusion function

Furthermore, as pattern 3 indicated a good perfusion in bone marrow [10], we used pattern 3 percentage as the measure to define good and not good perfusion. 'Good perfusion' was defined as the pattern 3 percentage was above the median value while 'not good perfusion' was the pattern 3 percentage below the median. We found that all the subjects' BMD decreased with aging, while the BMD was reduced more sharply in the group with 'not good perfusion' compared to the other (shown in Fig 4). Therefore, better perfusion function in bone marrow was associated with less bone loss after 4 years.

II. DISCUSSION

This study investigated the interaction between bone marrow perfusion and bone loss. First, a notable reduction in pattern coloring rate in subjects with reduced BMD was observed compared to normal subjects. This implies that the blood perfusion decreased as a whole in the development of osteoporosis. Especially at femoral head and the area crossing the femoral neck to the shaft, perfusion is much weaker in the osteoporotic patients. Further, an interesting finding is that for all 3 groups, alone the intertrochanteric line the perfusion decreases significantly from the lesser trochanter to the greater trochanter. As intertrochanteric fracture is one of the most common fractures at hip, such blood perfusion distribution manner may be one of its underlying mechanism.

Above observations are very intriguing to discover mechanisms of osteoporotic fracture at proximal femur in respect to bone marrow histology and vascular characteristics. The sites which are prone to have fracture, such as the intertrochanteric line, are corresponding to bone marrow with sharply change in perfusion. Such association may imply that fracture may be not only caused by high pressure but also related to the nutrition supply. For different sites, bone fracture may happen at different pressure level. This study shows a great potential of perfusion distribution investigation to contribute in the study of bone metabolism and osteoporotic fracture.

Moreover, we found an interaction between marrow perfusion and BMD in a long term. In our previous study [10], subjects with normal BMD showed an averaged perfusion feature as pattern 3, indicating that pattern 3 implies a better perfusion function for bone marrow health. We therefore supposed that the bone marrow would be healthy when it had high percentage of pattern 3 in bone marrow perfusion. In current study we found that subjects with decreased BMD over 4 years had a significant lower percentage of pattern 3 for bone marrow perfusion at the 0 year. Further, for a four-year period, the subjects' BMD indeed decreased more sharply when they had less bone marrow with perfusion feature as pattern 3. These findings suggested that subjects with bad bone marrow perfusion could consistently loss bone in successive years. This may imply that good bone marrow perfusion would help the bone modeling over years to keep bone health.

A link between vascular disease and osteoporosis has been reported [1,2]. The varied artery function caused by diseases may change the nutrition supply process in the bone tissue. Because perfusion reflects a more functional process relevant to blood flow, endothelial permeability and interstitial diffusion, the vessel variation also can be reflected by the perfusion process. This study provided further evidence that worse perfusion function in bone marrow would lead to faster BMD decrease with aging. In other words, a good bone marrow perfusion function would help to keep the bone health.

However, this study was only carried out for 4 years. Longer time observation would provide more insightful information.

ACKNOWLEDGMENT

This study is supported by the National Natural Science Foundation of China (81000647) and Basic Research Foundation (Outstanding Young Investigator Track) from Shenzhen Science, Industry, Trade & Information Commission (JC201005260124A).

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