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Age-related changes in the hemodynamics of the femoral head as evaluated by early phase of bone scintigraphy

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Objective: The femoral head is reported to be in a markedly hypoemic state as compared with other tissues even under normal conditions, and it is therefore necessary to understand its hemodynamics to investigate the pathogenesis of hip disorders. It is known that aspects of intraosseous hemodynamics including blood flow and blood pool can be evaluated soon after radioisotope administration. In this study, hemodynamic changes in the femoral head according to gender and age were examined by investigating accumulation of radioisotope in the tissue during the early phase of bone scintigraphy. ***Methods:*** The subjects of this study consisted of 58 joints of 31 men and 75 joints of 41 women, whose ages ranged from 15 to 87 years (average age: 67.9 years). Images of bone scintigraphy were obtained for 15 to 20 minutes at 5 minutes and at 3 hours after radioisotope administration. The ratio of accumulation in the femoral head to that in the diaphysis (head-to-diaphysis ratio, HD ratio) was calculated. ***Results:*** HD ratios obtained 15–20 minutes later ranged from 0.01 to 7.35 (1.88 ± 0.91, mean ± SD). HD ratios decreased with age, and a significant inverse correlation was observed between age and HD ratio, demonstrating a correlation coefficient of −0.27 ($p = 0.001$). The HD ratio among men was 0.01–3.57 (1.66 ± 0.71), while that among women was 0.53–7.35 (2.05 ± 1.01), and a significant difference was observed in HD ratio between men and women ($p = 0.02$). There was a significant difference in HD ratios between men and women in their teens to forties ($p = 0.03$), while no significant differences was observed in the other age groups. HD ratios obtained 3 hours later ranged from 0.44 to 6.32 (1.95 ± 0.79, mean ± SD), and no significant correlation was observed between age and HD ratio, demonstrating a correlation coefficient of −0.14. ***Conclusion:*** The present study demonstrated that blood flow and blood pool of the femoral head decrease with aging particularly in women. This hemodynamic deterioration of the femoral head caused by aging may have an effect on the onset and progression of hip disorders by influencing bone metabolism.

Key words: early phase, bone scintigraphy, blood flow, blood pool, femoral head

INTRODUCTION

THE PATHOGENESIS of hip disorders, such as non-traumatic osteonecrosis of the femoral head (ONF), rapidly destructive coxarthrosis (RDC) and subchondral insufficient fracture of the femoral head, is still not fully understood. The femoral head is reported to be in a markedly hypoemic state, compared with other tissues even under normal conditions,[1] and it is therefore necessary to understand its hemodynamics in order to investigate the pathogenesis of these disorders. Epidemiological surveys show that these disorders have different incidences depending on gender and age. ONF, which occurs due to ischemia of the femoral head, is most commonly observed in adolescents and young men,[2] while RDC and subchondral insufficient fracture of the femoral head develop in elderly women.[3,4]

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Consequently, analysis of gender- and age-related changes in hemodynamics of the femoral head could provide clues for understanding the pathogenesis of these disorders. Studies on hemodynamics of the femoral head have been conducted mainly in animals due to the invasiveness of the measurement method, and therefore, hardly conducted in humans.[5–8] Although it has recently become possible to measure intraosseous hemodynamics using positron emission tomography (PET),[1,9–11] the complexity of the measurement procedure makes it difficult to perform it in a large number of cases. On the other hand, bone scintigraphy is a common testing procedure that is performed with a comparatively low degree of invasiveness. In this method, bone turnover can be assessed only within a few hours after administration of radioisotope, and aspects of intraosseous hemodynamics including blood flow and blood pool can also be evaluated soon after radioisotope administration.[12–15] In this study, hemodynamic changes in the femoral head depending on gender and age were investigated by evaluating accumulation of radioisotope in the tissue in the early phase of bone scintigraphy.

SUBJECTS AND METHODS

The subjects of this study consisted of 58 joints of 31 men and 75 joints of 41 women, whose ages ranged from 15 to 87 years (average: 67.9 years). All subjects submitted informed consent according to the Helsinki declaration, and this study was approved by the Ethics Committee, Kohoku General Hospital. These cases were observed to have healthy hip joints when bone scintigraphy was performed for neoplastic lesions and trauma. In addition, they showed no osteoarthritic lesions on simple X-ray examinations of the hip joint. Thirty-six joints were from 18 patients with breast cancer, 24 from 12 with prostate cancer, 12 from 7 with multiple trauma, 12 from 6 with colon cancer, 8 from 4 with gastric cancer, 4 from 4 with femoral neck fracture, 4 from 2 with renal cell carcinoma, 4 from 2 with lung cancer, 3 from 2 with gallbladder cancer, 3 from 2 with osteomyelitis, 2 from 2 with osteonecrosis of the femoral head, 2 from 1 with bladder cancer, 2 from 1 with hepatocellular carcinoma, 2 from 1 with bile duct cancer, 2 from 1 with multiple sclerosis, 2 from 1 with tibial bone tumor, 1 from 1 with coxarthrosis, and 10 joints from 5 healthy subjects. Patients with neoplastic lesions who exhibited bone metastasis or who had undergone hormone therapy were excluded from the study.

GCA901A Gamma Camera (Toshiba, Nasu, Japan) was used to capture images for bone scintigraphy. Images of the radioisotope accumulation in the early phase of bone scintigraphy were gathered for 15 to 20 minutes (5 minutes of acquisition time per frame) using a 128 × 128 matrix following rapid infusion of 740 MBq of ^{99m}Tc-HMDP (Nihon Medi-Physics, Nishinomiya, Japan). Ordinary scintigraphic images were obtained 3 hours later. Images were anteroposterior views of the pelvis including the iliac crest and lesser trochanter. Regions of interest (ROIs) were set bilaterally for the femoral head, diaphysis, and soft tissue of the thigh on the images obtained at 15 to 20 minutes and at 3 hours later according to the method of Kubota et al.[12] In short, we set 5 × 5 pixel ROIs directly beneath the joint surface for the femoral head, in the center of diaphysis at the level of the lesser trochanter for the diaphysis, and at the thigh to the outside of the ilium for the soft tissue (Fig. 1). Soft tissue ROIs were set at the lateral side of the ilium as this site is suitable for relatively large ROIs, and because, within the range of scintigraphy, the ilium is the area least affected by body shape. Subsequently, the average counts per pixel were determined. In order to eliminate the additive effects of

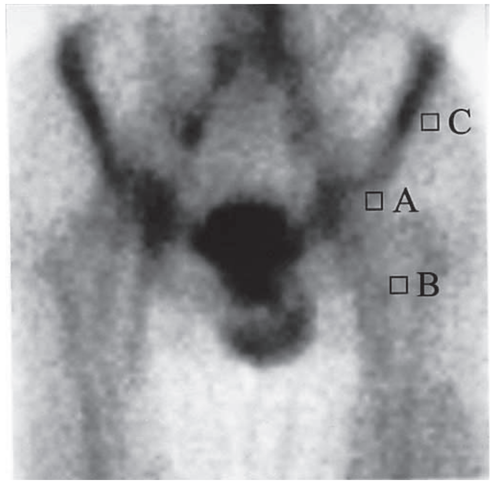

Fig. 1 ROI were set directly beneath the joint surface for the femoral head (A), in the center of diaphysis at the level of the lesser trochanter for the diaphysis (B), and at the thigh to the outside of the ilium for the soft tissue (C).

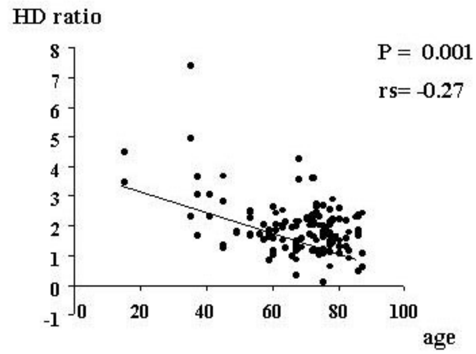

Fig. 2 The relationship between aging and changes in the HD ratio obtained 15–20 minutes later: On the *y*-axis, HD ratio is shown, and on the *x*-axis, age is depicted. There was a negative correlation between HD ratio and age ($r^s = -0.27$, Spearman's rank correlation: p = 0.001).

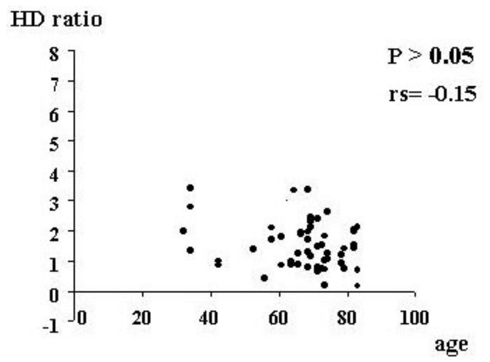

Fig. 3 The relationship between aging and the HD ratio obtained 15–20 minutes later in men: On the *y*-axis, HD ratio is shown, and on the *x*-axis, age is depicted. There was no negative correlation between HD ratio and age in men ($r^s = -0.15$, Spearman's rank correlation: $p > 0.05$).

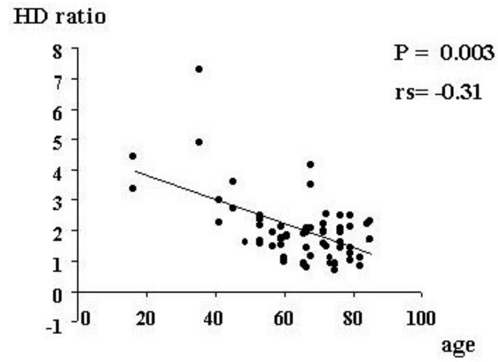

Fig. 4 The relationship between aging and the HD ratio obtained 15–20 minutes later in women: On the *y*-axis, HD ratio is shown, and on the *x*-axis, age is depicted. There was a negative correlation between HD ratio and age in women ($r^s = -0.31$, Spearman's rank correlation: $p = 0.003$).

Table 1 Differences in HD ratio between men and women

Age	HD ratio in men		HD ratio in women		P value
	n	range (mean ± SD)	n	range (mean ± SD)	
10–89	58	0.01–3.57 (1.66 ± 0.71)	75	0.53–7.35 (2.05 ± 1.01)	0.02
10–49	6	1.17–3.57 (2.15 ± 0.97)	10	1.69–7.35 (3.52 ± 1.71)	0.03
50–59	2	0.76–1.66 (1.21 ± 0.64)	11	1.48–2.48 (1.90 ± 0.35)	NS
60–69	10	0.27–2.36 (1.50 ± 0.61)	20	0.80–4.19 (1.88 ± 0.85)	NS
70–79	28	0.01–3.56 (1.70 ± 0.75)	22	0.96–2.56 (1.84 ± 0.43)	NS
80–89	12	0.40–2.38 (1.54 ± 0.54)	12	0.53–2.52 (1.60 ± 0.66)	NS

NS = not statistically significant

radioisotope accumulation in the soft tissue, accumulation in the femoral head was determined by subtracting the average count in the soft tissue from that in the femoral head, and accumulation in the diaphysis by subtracting the average count in the soft tissue from that in the diaphysis. The ratio of accumulation in the femoral head to that in the diaphysis (head-to-diaphysis ratio, HD ratio) was calculated.

The relationship between age and the HD ratio was statistically investigated by using Spearman's rank correlation coefficient. A comparison of HD ratios between men and women was made using the Mann-Whitney U-test. P value of less than 0.05 was considered to be statistically significant.

RESULTS

Images obtained 15 to 20 minutes later

HD ratios ranged from 0.01 to 7.35 (1.88 ± 0.91, mean ± SD). HD ratios decreased with age, and a significant inverse correlation was observed between age and HD ratio, demonstrating a correlation coefficient of −0.27 ($p = 0.001$) (Fig. 2). Concerning gender, in men, a significant correlation was not observed between age and HD ratio, demonstrating a correlation coefficient of −0.15 (Fig. 3). On the other hand, in women, a significant reverse correlation was observed between age and HD ratio, demonstrating a correlation coefficient of −0.31 ($p = 0.003$) (Fig. 4).

The HD ratio in men was 0.01–3.57 (1.66 ± 0.71) and that in women was 0.53–7.35 (2.05 ± 1.01). A significant difference was observed in HD ratio between men and women ($p = 0.02$). Furthermore, among subjects aged 15 to 49 years, the HD ratio was 1.17–3.57 (2.15 ± 0.97) in men and 1.69–7.35 (3.52 ± 1.71) in women. Although a significant difference was observed in HD ratios between men and women aged 15 to 49 years ($p = 0.03$), there were no significant differences in the other age groups (Table 1). A significant difference in the HD ratio was observed between women aged 15 to 49 years and women in the other age groups (Table 2).

Images obtained 3 hours later

HD ratios ranged from 0.44 to 6.32 (1.95 ± 0.79, mean ± SD). No significant correlation was observed between age and HD ratio, demonstrating a correlation coefficient of

Table 2 Differences in HD ratio between age groups

Age		P value in men	P value in women
10–49 vs.	50–59	NS	0.0089
	60–69	NS	0.0059
	70–79	NS	0.0030
	80–89	NS	0.0053

NS = not statistically significant

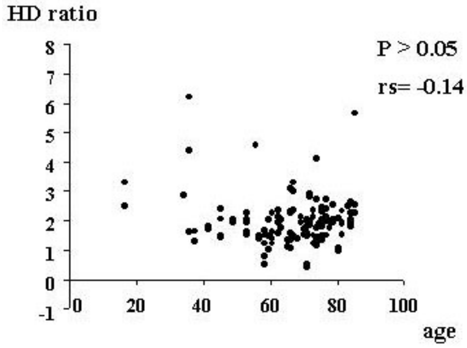

Fig. 5 The relationship between aging and changes in the HD ratio obtained 3 hours later: On the *y*-axis, HD ratio is shown, and on the *x*-axis, age is depicted. There was no negative correlation between HD ratio and age ($r^s = -0.14$, Spearman's rank correlation: $p > 0.05$).

–0.14 (Fig. 5). Concerning gender, no significant correlation was observed between age and HD ratio; correlation coefficient was 0.23 in men and –0.03 in women (Figs. 6, 7).

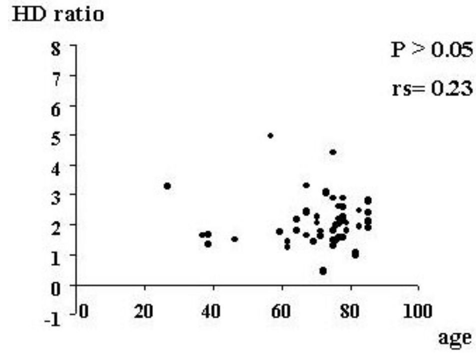

Fig. 6 The relationship between aging and the HD ratio obtained 3 hours later in men: On the *y*-axis, HD ratio is shown, and on the *x*-axis, age is depicted. There was no negative correlation between HD ratio and age in men ($r^s = 0.23$, Spearman's rank correlation: $p > 0.05$).

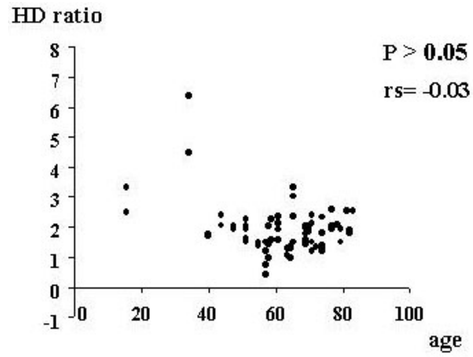

Fig. 7 The relationship between aging and the HD ratio obtained 3 hours later in women: On the *y*-axis, HD ratio is shown, and on the *x*-axis, age is depicted. There was no negative correlation between HD ratio and age in women ($r^s = -0.03$, Spearman's rank correlation: $p > 0.05$).

DISCUSSION

Over the past few decades, a considerable number of studies have been conducted from anatomical aspects of hemodynamics of the femoral head. The main nutrient arteries of the femoral head are the superior retinacular and inferior retinacular arteries that originate in the medial femoral circumflex artery.[16–18] Since both of them are terminal arteries that lack anastomoses, the femoral head is considered to be in a hypoemic state. Kubo et al.[1] report that the blood flow of the femoral head is 1.80 ± 0.74 m*l*/min/100 g based on PET study results. The blood flows in other major organs determined by PET analyses are 50 m*l*/min/100 g in the brain, 70 m*l*/min/100 g in the heart, 25 m*l*/min/100 g in the lungs, 360 m*l*/min/100 g in the kidneys and 95 m*l*/min/100 g in the liver[19]; which clearly indicates that the femoral head is in a markedly hypoemic state compared with other organs. With reference to other osseous tissues, Kahn et al.[11] report that the blood flow in the ilium is 11.1 ± 2.2 m*l*/min/100 g, and demonstrate that the femoral head is hypoemic, even compared with cancellous bone in the form of ilium. Consequently, even slight changes in hemodynamics that would not affect other sites have the potential to cause diseases in the femoral head.

The phosphate compound used in bone scintigraphy is passively transported out of the blood vessels through the capillary endothelium and adheres to the bone mineral matrix.[14] This explains the fact that early phase accumulation following administration of radioisotope in bone scintigraphy reflects local hemodynamic change. Thus, early phase bone scintigraphy can be used to evaluate intraosseous hemodynamics. The use of characteristics of early phase bone scintigraphy (i.e., reflecting local blood flow and blood pooling) is reported to be useful for identifying and diagnosing osteomyelitis and other inflammatory diseases,[20] identifying, diagnosing and assessing the therapeutic effects of localized reflex sympathetic dystrophy (RSD),[21] assessing the therapeutic effects of bone and soft tissue tumors,[22] determining the levels of amputation in cases of arteriosclerosis obliterans,[23] evaluating lower extremity elongation,[24] and evaluating hemodynamics following vascular pedicle bone graft.[25]

Kubota et al.[12] use the accumulation ratio of the femoral head to the diaphysis (head-to-diaphysis ratio, HD ratio) to evaluate hemodynamics of the femoral head after kidney transplantation. An ischemic event in the femoral head has been suggested as a cause of idiopathic femoral head necrosis,[2] and Kubota et al. reported that HD ratio was significantly lower in patients with idiopathic femoral head necrosis than in those without this complication. This suggests that HD ratio is useful for assessing hemodynamics of the femoral head. However, images obtained 15 to 20 minutes after intravenous administration were later than the second-phase images in conventional three-phase bone scintigraphy, and at this time, HD ratio would have been affected by bone metabolism. Therefore, HD ratios were calculated using the images obtained 3 hours after intravenous administration, when the effects of bone metabolism were present. The correlation coefficient between age and HD ratio was examined, but no significant correlation was found. We therefore believe that the effects of bone metabolism on images obtained 15–20 minutes after intravenous administration were not that marked.

Factors related to HD ratio include not only hemodynamics of the femoral head, but also hemodynamics of the femoral shaft. However, blood flow in the shaft exceeds that in the head, and as a result, less individual difference in hemodynamics occurs at the femoral shaft as compared to the femoral head. Hence, HD ratio is mostly affected by hemodynamics of the femoral head. Since a significant inverse correlation was observed between age and the HD ratios, blood flow and blood pool in the femoral head could be confirmed to decrease with age. The only report describing quantitative measurement of changes in hemodynamics in the femoral head caused by aging is by Kubo et al.,[1] who conducted a PET study of 32 joints from 16 men. They reported that blood flow decreased significantly with age, and that blood volume increased significantly in the femoral head in men. On the other hand, in the present study, no significant correlation was observed between age and HD ratio in men. The reason for this difference was that early-phase bone scans in three-phase scintigraphy reflect not only blood pool, but also blood flow and bone metabolism.

With respect to gender differences, the HD ratios tended to decrease with age more markedly in women than in men. On the basis of this finding, blood flow and blood pool in the femoral head were clearly determined to decrease due to aging more in women. A significant difference in the HD ratio was observed between men and women in the relatively young group (15–49 years old), while there were no significant differences between men and women in other age groups. In other words, although the blood flow and blood pool levels of the femoral head were higher in women than in men among young cases, large differences were no longer observed between men and women of old cases (50 years old or above). Thus, abundant blood flow and blood pool of the femoral head in younger women decreased to the similar levels in men due to aging, and a greater age-related decrease in blood flow and blood pool of the femoral head occurs in women than in men. As the present study only examined 16 hip joints from 9 individuals aged 15 to 49 years, further investigations of the same points in a larger subject population are needed.

The findings of this study clearly indicated that blood flow and blood pool of the femoral head decreased with aging particularly in women. On the other hand, hip joint disorders such as rapidly destructive coxarthrosis (RDC) and subchondral insufficient fractures of the femoral head are known to occur with a high frequency in elderly women.[23] Therefore, hemodynamic deterioration of the femoral head caused by aging might have an effect on the onset and progression of these disorders since it influenced bone metabolism.

In this study, the femoral heads in cases of hip joint disorders were excluded in order to assess the changes in hemodynamics of the femoral head in healthy subjects and the differences in hemodynamics of the femoral head between men and women. Since hemodynamic deterioration of the femoral head due to aging implied the possibility of having some effect on the onset and progression of hip joint disorders, evaluation of intraosseous hemodynamics in the cases presenting hip joint disorders might provide an important clue for elucidating the cause of these disorders.

REFERENCES

1. Kubo T, Kimori K, Nakamura F, Inoue S, Fujioka M, Ueshima K, et al. Blood flow and blood volume in the femoral heads of healthy adults according to age: Measurement with positron emission tomography (PET). *Ann Nucl Med* 2001; 15: 231–235.
2. Arlet J. Nontraumatic avascular necrosis of the femoral head. Past, present, and future. *Clin Orthop Relat Res* 1992; 277: 12–21.
3. Postel M, Kerboull M. Total prosthetic replacement in rapidly destructive arthrosis of the hip joint. *Clin Orthop* 1970; 72: 138–144.
4. Yamamoto T, Bullough PG. The role of subchondral insufficiency fracture in rapid destruction of the hip joint: a preliminary report. *Arthritis Rheum* 2000; 43: 2423–2427.
5. McPherson A, Scales JT, Gordon LH. A method of estimating qualitative changes of blood-flow in bone. *J Bone Joint Surg Br* 1961; 43B: 791–799.
6. Kelly PJ, Yipintsoi T, Bassingthwaighte JB. Blood flow in canine tibial diaphysis estimated by iodoantipyrine-^{125}I washout. *J Appl Physiol* 1971; 31 (1): 38–47.
7. Paradis GR, Kelly PJ. Blood flow and mineral deposition in canine tibial fractures. *J Bone Joint Surg Am* 1975; 57 (2): 220–226.
8. Leo AW, Peggy AL, David JS. Measurement of regional

bone and bone marrow blood flow in the rabbit using the hydrogen washout technique. *Clin Orthop* 1977; 122: 340–346.
9. Martiat P, Ferrant A, Cogneau M, Bol A, Michel C, Rodhain J, et al. Assessment of bone marrow blood flow using positron emission tomography: no relationship with bone marrow cellularity. *Br J Haematol* 1987; 66 (3): 307–310.
10. Ashcroft GP, Evans NT, Roeda D, Dodd M, Mallard JR, Porter RW, et al. Measurement of blood flow in tibial fracture patients using positron emission tomography. *J Bone Joint Surg Br* 1992; 74 (5): 673–677.
11. Kahn D, Weiner GJ, Ben-Haim S, Boles Ponto LL, Madsen MT, Bushnell DL, et al. Positron emission tomographic measurement of bone marrow blood flow to the pelvis and lumbar vertebrae in young normal adults. *Blood* 1994; 83: 958–963.
12. Kubota T, Ushijima Y, Okuyama C, Kubo T, Nishimura T. Tracer accumulation in femoral head during early phase of bone scintigraphy after renal transplantation. *J Nucl Med* 2001; 42: 1789–1794.
13. Genant HK, Bautovich GJ, Singh M, Lathrop KA, Harper PV. Bone-seeking radionuclides: an *in vivo* study of factors affecting skeletal uptake. *Radiology* 1974; 113: 373–382.
14. McCarthy ID, Hughes SPF. The role of skeletal blood flow in determining the uptake of ^{99m}Tc-Methylene Diphosphonate. *Calcif Tissue Int* 1983; 35: 508–511.
15. Gaucher A, Bertrand A, Tonnel F, Hocquard C, Adolphe J, Pere P. Bone angioscintigraphy. *Rev Rhum Mal Osteoartic* 1985; 52 (12): 701–705.
16. Tucker FR. Arterial supply to the femoral head and its clinical importance. *J Bone Joint Surg Br* 1949; 31: 82–93.
17. Mussbichler H. Angiography of the hip region. Comparison between different angiographic modifications. *Acta Radiol* 1971; 11: 593–603.
18. Wertheimer LG, Lopes Sde L. Arterial supply of the femoral head. A combined angiographic and histological study. *J Bone Joint Surg Am* 1971; 53 (3): 545–556.
19. Guyton AC. Textbook of medical physiology. Philadelphia; WB Saunderes, 1991: 186.
20. Shafer RB, Edeburn GF. Can the three-phase bone scan differentiate osteomyelitis from metabolic or metastatic bone disease? *Clin Nucl Med* 1984; 9 (7): 373–377.
21. Cuartero PA, Martinez ME, Benito RP, Martinez PS, Sanz MP. Abnormal bone scintigraphy and silent radiography in localized reflex sympathetic dystrophy syndrome. *Eur J Nucl Med* 1992; 19 (5): 330–333.
22. Nishiyama Y, Yamamoto Y, Yokoe K, Kawaguchi Y, Toyama Y, Satoh K, et al. A comparative study of ^{201}Tl scintigraphy and three-phase bone scintigraphy following therapy in patients with bone and soft-tissue tumors. *Ann Nucl Med* 2004; 18 (3): 235–241.
23. Masaoka S. Evaluation of arterial obstructive leg and foot disease by three-phase bone scintigraphy. *Ann Nucl Med* 2001; 15 (3): 281–287.
24. Kawano M, Taki J, Tsuchiya H, Tomita K, Tonami N. Predicting the outcome of distraction osteogenesis by 3-phase bone scintigraphy. *J Nucl Med* 2003; 44 (3): 369–374.
25. Malizos KN, Soucacos PN, Vragalas V, Dailiana ZH, Schina I, Fotopoulos A. Three phase bone scanning and digital arteriograms for monitoring vascularized fibular grafts in femoral head necrosis. *Int Angiol* 1995; 14 (3): 319–326.