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Extracorporeal shockwave therapy shows regeneration in hip necrosis

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Objectives. The effect of shockwave in osteonecrosis of the femoral head (ONFH) is poorly understood. The purpose of this study was to investigate the regeneration effects of shockwave in ONFH.

Methods. This study consisted of 14 femoral heads from 14 patients undergoing total hip arthroplasty for ONFH. Seven patients with seven hips who received shockwave prior to surgery were designated as the study group, whereas, seven patients with seven hips who did not receive shockwave were assigned to the control group. Both groups showed similar demographic characteristics. The femoral heads were investigated with histopathological examination and immunohistochemical analysis with von Willebrand factor (vWF), VEGF, platelet endothelial cell adhesion molecule-1 (PECAM-1) also referred to as (CD 31) and vascular cell adhesion molecule (VCAM) for angiogenesis, and with proliferation cell nuclear antigen (PCNA), Dickkopf-1 (DKK1) and Winless 3a (Wnt 3) for bone remodelling and regeneration.

Results. In histopathological examination, the study group showed significantly more viable bone and less necrotic bone, higher cell concentration and more cell activities including phagocytosis than the control group. In immunohistochemical analysis, the study group showed significant increases in vWF ($P < 0.01$), VEGF ($P = 0.0012$) and CD 31 ($P = 0.0023$), Wnt3 ($P = 0.008$) and PCNA ($P = 0.0011$), and decreases in VCAM ($P = 0.0013$) and DKK1 ($P = 0.0007$) than the control group.

Conclusions. Shockwave treatment significantly promotes angiogenesis and bone remodelling than the control. It appears that application of shockwave results in regeneration effects in hips with ONFH.

Key words: Extracorporeal shockwave, Regeneration, Osteonecrosis, Femoral head.

Introduction

Treatment of osteonecrosis of the femoral head (ONFH) remains controversial [1]. Conservative treatments are generally unsuccessful, and surgery is indicated in symptomatic hips with the type of procedure varying according to the stage of the disease on image studies [2–4]. For early ONFH, femoral head-preserving procedures including core decompression, vascularized or non-vascularized bone graft and osteotomy are recommended [1–4]. The results of femoral head-preserving procedures varied considerably, and most studies reported less satisfactory outcomes [5–13]. For late cases, total hip arthroplasty (THA) is usually performed [14]. In young active patients, the complications of THA are common including thigh pain, polyethylene wear, osteolysis and component loosening [15]. Therefore, an effective and non-invasive method of treatment appears very attractive.

Extracorporeal shockwave therapy (ESWT) was shown to be more effective than core decompression and non-vascularized bone grafting for early ONFH [16]. We hypothesized that ESWT may result in regeneration of the femoral head with the improvement in blood supply. The purpose of this study was to investigate the regeneration effect of shockwave in hips with ONFH.

Materials and methods

The Ethical Committee of the Institutional Review Board on Human Studies of our hospital approved this study and written informed consent was acquired from all subjects according to the Declaration of Helsinki.

Between July 2004 and June 2005, 30 patients with 42 hips were treated for symptomatic ONFH at our hospital. Twenty-three patients with 35 hips with stage I, II or III lesion were treated with ESWT. The source of shockwave was from an OssaTron orthotripter (Sanuwave, Alpharetta, GA, USA). The treatment was performed on the operation table under general anaesthesia. The hip joint was properly positioned by adduction and internal or external rotation of the affected leg. The femoral artery was identified with digital palpation and confirmed with ultrasound Doppler, and was protected from direct shockwave contact. The junctional zone between avascular and normal bones of the femoral head was delineated with C-arm imaging. Four points with 1.0 cm apart within the zone were chosen with a metallic pin under C-arm imaging, and the corresponding locations were marked on the skin in the groin area. The depth of treatment was determined by adjusting the height of the table until the two ring markers of the device synchronized under C-arm imaging. Surgical lubricant was applied to the skin in contact with the shockwave tube. Each of the four locations was treated with 1500 impulses of shockwave at 28 kV (equivalent to 0.62 mJ/mm^2 energy flux density), and a total of 6000 shocks were applied to the femoral head as a single session [16]. After treatment, patients walked with partial weight bearing on the affected leg for 4–6 weeks. Non-narcotic analgesic such as acetaminophen were prescribed for pain. The results showed improvement in 16 patients with 28 hips and un-improved or worsened in seven patients with seven hips. There was no device-related problem. There was no systemic or neurovascular complication. Local complications included ecchymosis in five and local swelling in six, and all spontaneously resolved within a few days.

THA was performed in seven patients with seven hips of the ESWT-treated group due to failure of treatment. The time interval from ESWT to THA ranged from 12 to 24 months. In addition, seven patients with seven hips with advanced stage III or IV lesion were initially treated conservatively with analgesics and protected from weight bearing to the affected leg, and THA was performed when the symptoms became unbearable. The time interval from the initial visit to THA ranged from 4 to 20 months. The patient selection flow diagram is shown in Fig. 1. This study consisted of 14 femoral heads from 14 consecutive patients with 14 hips undergoing THA for symptomatic ONFH. Among them, seven patients with seven hips who received ESWT prior to THA were assigned to the study group, whereas the other seven patients with seven hips who did not receive ESWT prior to THA were assigned to the control group. Both groups showed similar demographic characteristics as shown in Table 1.

The femoral heads were investigated with histopathological examination and immunohistochemical analysis for angiogenesis with von Willebrand factor (vWF), VEGF, platelet endothelial

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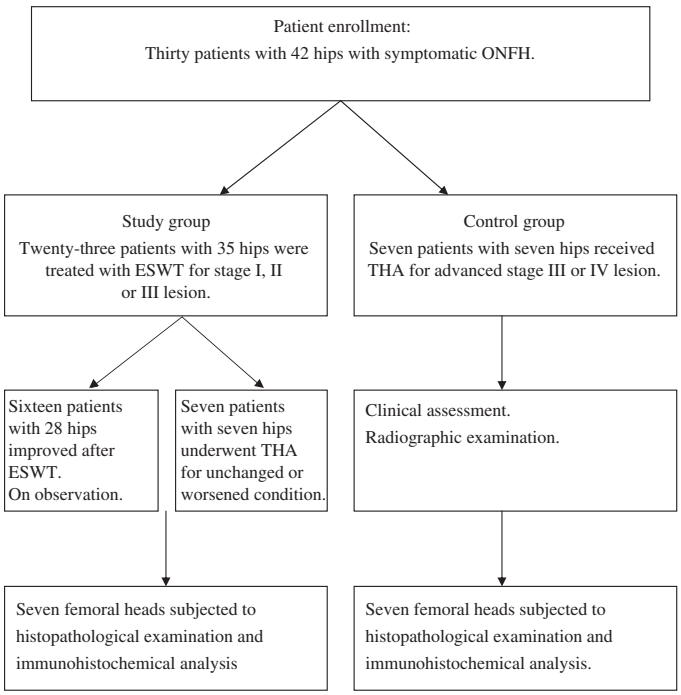

FIG. 1. Patient selection flow diagram.

TABLE 1. Patient demographic characteristics

	Study group	Control group	*P*-value
Number of hips	7	7	1.00
Sex (M/F)	6/1	5/2	0.515
Age (yrs)			
Mean ± S.D. (range)	41.3 ± 11.4 (19–56)	39.9 ± 11.8 (21–57)	0.411
Body weight (kg)			
Mean ± S.D. (range)	67.7 ± 11.4 (59–80)	65.1 ± 15.8 (42–89)	0.36
Body height (cm)			
Mean ± S.D. (range)	164.3 ± 6.1 (155–171)	164.9 ± 7.8 (156–175)	0.44
Duration of disease (months)			
Mean ± S.D. (range)	18.7 ± 9.2 (12–28)	16.3 ± 8.8 (8–30)	0.278
Stage of lesion			
III	5	2	0.063
IV	2	5	0.063
Size of lesion (percentage of total surface)			
Mean ± S.D. (range)	42.0 ± 10.9 (27–53)	48.4 ± 24.1 (20–76)	0.269
Aetiology			
Steroid induced	4	4	1.00
Non-steroid	3	3	1.00

M, male; F, female.

cell adhesion molecule-1 (PECAM-1) also referred to as (CD 31) and vascular cell adhesion molecule (VCAM) and for bone remodelling and regeneration with proliferation cell nuclear antigen (PCNA), Dickkopf-1 (DKK1) and Winless 3a (Wnt 3).

Histopathological examination

The bone specimens were decalcified and embedded in paraffin for section. The microsections were stained with haematoxylin–eosin (HE) stain. The histopathological features were examined by a bone pathologist blinded to the nature of the study. The microscopic features included tissue distributions of viable and necrotic bones, cartilaginous and fibrous tissues, cell concentration and cell activities including phagocytosis.

Immunohistochemical stain

The harvested specimens were fixed in 4% phosphate buffer solution (PBS)-buffered paraformaldehyde for 48 h and decalcified in PBS-buffered 10% ethylenediaminetetraacetic acid (EDTA). Decalcified tissues were embedded in paraffin. The specimens were cut longitudinally into 5-μm thick sections and transferred to polylysine-coated slides. Sections of the specimens were immunostained with specific reagents for vWF, VEGF, CD 31 and VCAM to identify angiogenesis and angiogenesis-related growth and proliferating indicators; and for PCNA, DKK1 and Wnt 3 to examine bone remodelling and regeneration (Santa Cruz Biotechnology Inc., CA, USA). The immunoreactivity in specimens was demonstrated using a horseradish peroxidase (HRP)-3′-,3′-diaminobenzidine (DAB) cell and tissue staining kit (R & D Systems, Inc., MN, USA). The immunoactivities were quantified from five areas in three sections of the same specimen using a Zeiss Axioskop 2 plus microscope (Carl Zeiss, Gottingen, Germany). All the images of each specimen were captured using a Cool CCD camera (SNAP-Pro c.f. Digital kit; Media Cybernetics, MD, USA). Images were analysed using an Image-Pro® Plus image-analysis software (Media Cybernetics). The percentage of positive immunolabelled cells over the total cells in each area was counted. Two pathologists blinded to the treatment regimens performed the measurements on all sections.

Statistical analysis

A power analysis revealed that a sample size of seven is adequate to establish the statistical significance with $\alpha = 0.05$ and power = 0.8 with calculation based on the data provided in this study. The data between the hips with ESWT prior to THA and hips without ESWT are compared statistically using an independent *t*-test with the statistical significance at $P < 0.05$.

Results

The results of histopathological examination are summarized in Table 2. The ESWT group showed significantly more viable bones with live osteocytes and less necrotic bones with empty lacunae and apoptotic cells than the control group. Considerably higher cell concentration and more cell activities including phagocytosis were observed in ESWT group than the control group (Fig. 2).

The results of immunohistochemical analysis are summarized in Table 3. The study group showed significant increases in vWF ($P < 0.01$), VEGF ($P = 0.0012$) and CD 31 ($P = 0.0023$), and a decrease in VCAM ($P = 0.0013$) than the control group. The results suggested that ESWT significantly promotes angiogenesis with new vessel formation and increases the angiogenesis-related growth factors. The study group also showed significant increases in PCNA ($P = 0.0011$) and Wnt 3 ($P = 0.008$) and a decrease in DKK1 ($P = 0.0007$) than the control. The results suggested that ESWT significantly promotes bone remodelling and regeneration. The microscopic features of the immunohistochemical stains for vWF, VEGF, CD 31, VCAM, PCNA, DKK1 and Wnt3 are shown in Figs 3–9, respectively.

Discussion

The aetiologies of ONFH are multi-factorial including corticosteroid, alcohol, smoking, trauma, radiation or caisson disease and genetic [17–23]. The pathophysiology of ONFH is uncertain for most cases with speculation of vascular impairment and changes in cell biology [24, 25]. The natural history of hips with ONFH, either symptomatic or silent, usually resulted in collapse of the femoral head, and surgery became inevitable [26–29]. Core decompression is the most common procedure performed in early ONFH [5, 6, 10]. The results of core decompression varied considerably ranging from 29% to 84% in the reported literatures [1, 5, 6, 16]. The rationale of core decompression is to relieve the intra-osseous pressure of the femoral head and to promote the remodelling and regeneration of the femoral head. [5, 6, 9].

TABLE 2. The results of histopathological examination

	Shockwave (+) ($n=7$)		Shockwave (−) ($n=7$)		
	Mean ± S.D.	95% CI	Mean ± S.D.	95% CI	*P*-value
Viable bone (%) (range)	45 ± 11.9 (30–60)	42.8 ± 11.3 (29–57)	23.3% ± 16.8 (0–60)	22.1 ± 15.9 (0–57)	0.014
Necrotic bone (%) (range)	17.1 ± 7.6 (10–30)	16.3 ± 7.2 (9.5–29)	41.1 ± 19.3 (20–70)	39.1 ± 18.4 (19–67)	0.0047
Cartilage (%) (range)	5.7 ± 10.2 (0–25)	5.4 ± 9.7 (0–24)	3.9 ± 4.9 (0–10)	3.7 ± 4.6 (0–10)	0.4206
Fibrosis (%) (range)	18.6 ± 7.5 (10–30)	17.6 ± 7.1 (10–29)	22.8 ± 9.4 (10–40)	21.6 ± 8.9 (10–38)	0.3523
Phagocytic histiocyte (%) (range)	13.6 ± 10.3 (5–35)	12.9 ± 9.8 (5–33)	7.5 ± 16 (5–15)	6.3 ± 15.2 (4.8–14)	0.2000

TABLE 3. The results of immunohistochemical analysis

	Shockwave (+) ($n=7$)		Shockwave (−) ($n=7$)		
	Mean ± SD	95% CI	Mean ± SD	95% CI	*P*-value
VWF (%) (range)	66 ± 5 (59–70)	63 ± 4.7 (56–67)	31 ± 5.3 (29–39)	29 ± 5.1 (26–37)	<0.01
VEGF (%) (range)	87 ± 5.4 (79–94)	83 ± 5.2 (75–89)	64 ± 9.3 (49–72)	60 ± 8.8 (47–68)	0.0012
CD 31 (%) (range)	62 ± 20 (35–92)	59 ± 19 (33–87)	11 ± 4 (6–16)	10.5 ± 3.6 (6–15)	0.0023
VCAM (%) (range)	12 ± 5 (8–20)	11.6 ± 4. 5 (8–19)	29 ± 7 (20–38)	27.9 ± 6.6 (19–36)	0.0013
PCNA (%) (range)	85 ± 4.5 (78–90)	80 ± 4.3 (74–86)	62 ± 9 (52–73)	59 ± 8.5 (49–69)	0.0011
DKK1 (%) (range)	26 ± 11 (12–36)	25 ± 10 (12–34)	71 ± 11.8 (61–85)	67 ± 11.2 (58–81)	0.0007
Wnt3 (%) (range)	55 ± 1.1 (53–55)	52 ± 1.0 (50–53)	35 ± 8 (25–42)	34 ± 7.6 (24–40)	0.0080

The data are in mean ± S.D. (range).

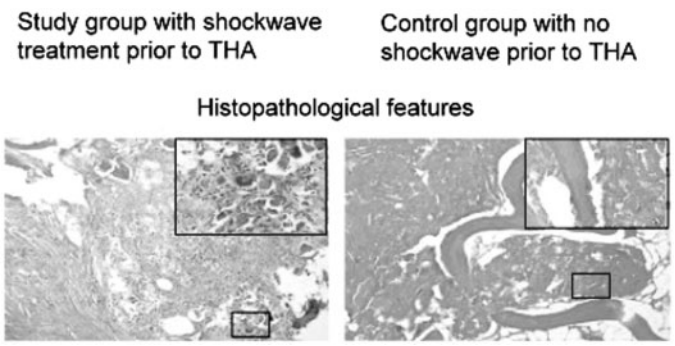

FIG. 2. Microscopic findings with HE stain showed significantly more viable bone and cell concentration and cell activity in study group than the control group.

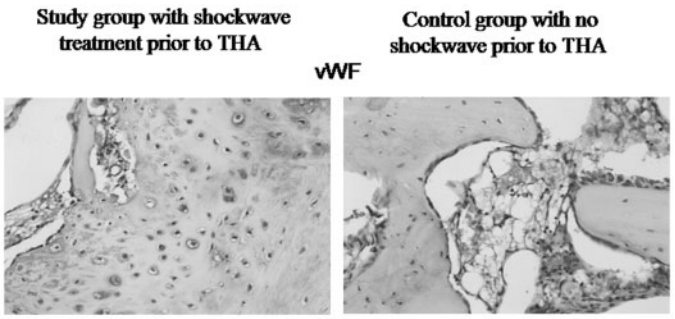

FIG. 3. Microscopic findings with vWF stain showed significantly more new vessels (angiogenesis) in the study group than the control group.

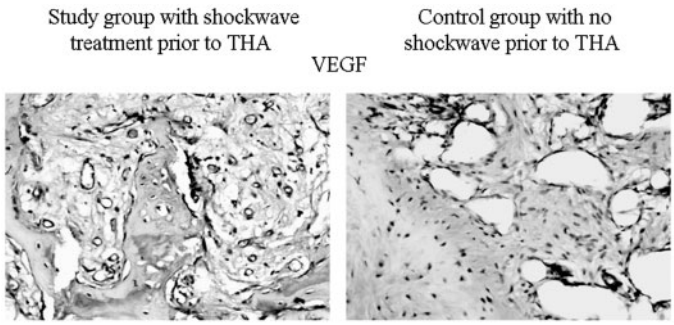

FIG. 4. Microscopic features with immunohistochemical stain showed significantly higher VEGF expressions in the study group than the control group.

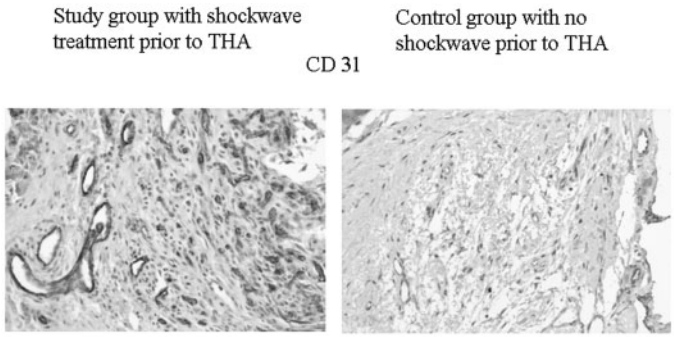

FIG. 5. Microscopic features with immunohistochemical stain showed significantly more CD 31 expressions in the study group than the control group.

Many studies reported the reparative effects of the femoral head with different methods of non-invasive treatment for hips with early ONFH [16, 30–35]. Levin *et al*. [30], in an experiment in rats, reported the reparative process of hyperbaric oxygen therapy with less necrotic bone as compared with the control, and hyper-oxygenation-mediated relief of ischaemia in fibroblastic, angioblastic, osteoblastic and osteoclastic activities of rat's femoral head. Alendronate was shown to be effective in the prevention of early collapse of the femoral head affected by osteonecrosis by inhibiting the osteoclast activities and decreasing the bone turnover [31–34]. Alendronate sodium is characterized pharmacologically by the ability to inhibit bone resorption by binding to bone mineral and subsequently inhibiting the activity of osteclasts [36]. Part of the osteoclast inhibiting action of alendronate is mediated through an action on osteoblasts [37]. Prostacyclin analogue iloprost was reported to be effective in thromboangiitis obliterans (Buerger's disease) with critical ischaemia and the management of bone necrosis-associated and idiopathic bone-marrow oedema [38–40]. However, the value of iloprost in hips with ONFH is unknown.

ESWT was shown to be effective in early ONFH. [16, 35] The results of our previous study showed that ESWT is

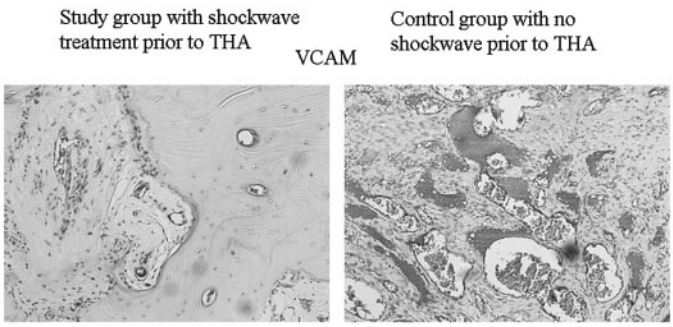

FIG. 6. Microscopic features with immunohistochemical stain showed significantly less VCAM expressions in the study group than the control group.

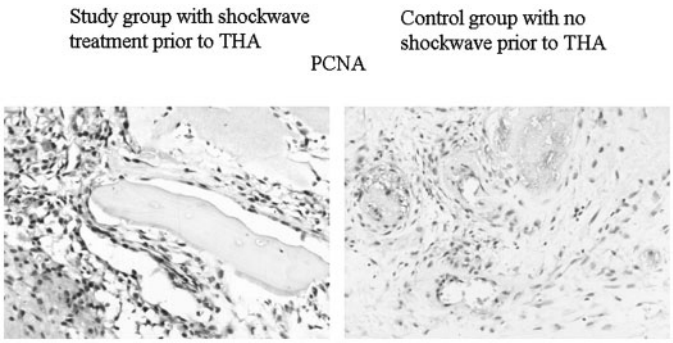

FIG. 7. Microscopic features with immunohistochemical stain showed significantly more PCNA expressions and cell proliferations in the study group than the control group.

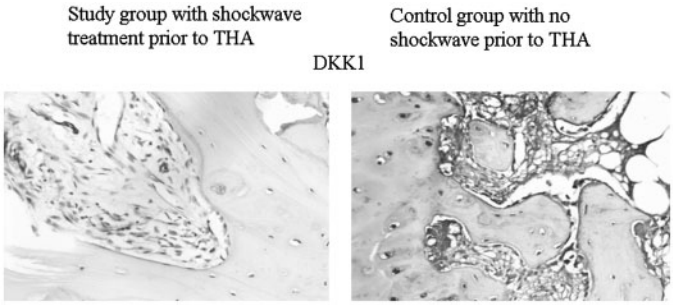

FIG. 8. Microscopic features with immunohistochemical stain showed significantly less DKK1 expressions in the study group than the control group.

effective in early ONFH with 79% clinical improvement and 39% regression of the lesion on MRI [16]. Despite good clinical results, the effect of shockwave in ONFH is poorly understood. The results of the current study demonstrated that ESWT-treated femoral heads showed significant increases in angiogenesis with new vessel formation and cell proliferation, bone remodelling and regeneration than the control. It appears that application of shockwave results in regenerative effects in hips with ONFH. The increased vascularity and bone remodelling do not necessarily assure bone resorption, loss of mechanical integrity and actually predispose to subchondral fracture and failure of the disease. Therefore, shockwave is best applied in hips with early stage ONFH before the crescent sign develops.

The exact mechanism of shockwave remains unknown. The results of our study in animal experiments demonstrated that shockwave treatment induces the ingrowth of neovascularization associated with increased expressions of angiogenic growth factors including endothelial nitric oxide synthase (eNOS), VEGF and

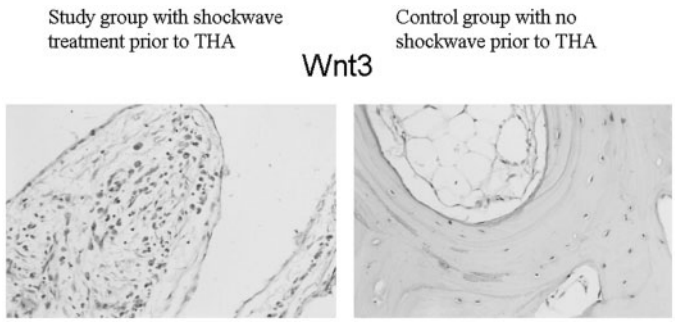

FIG. 9. Microscopic features with immunohistochemical stain showed significantly more Wnt3 expressions in the study group than the control.

PCNA [41, 42] and promotes osteogenesis [43–48]. It is reasonable to believe that neovascularization may play a role in the improvement of blood supply to the femoral head that in turn promotes bone remodelling and regeneration in hips with ONFH.

Conclusions

ESWT-treated hips showed significant increases in angiogenesis with new vessel formation and cell proliferation, and bone remodelling and regeneration than the controls not receiving ESWT. It appears that application of shockwave treatment results in regeneration effects in hips with ONFH.

Rheumatology key message

- Application of extracorporeal shockwave results in regeneration effects in femoral head necrosis.

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References

1 Mont MA, Jones LC, Hungerford DS. Nontraumatic osteonecrosis of the femoral head: ten years later. J Bone Joint Surg 2006;88A:1117–32.
2 Ficat RF. Idiopathic bone necrosis of the femoral head: early diagnosis and treatment. J Bone Joint Surg 1985;67B:3–9.
3 Gardeniers JWM. ARCO (Association Research Circulation Osseous) international classification of osteonecrosis. ARCO Committee on Terminology and Staging. Report on the committee meeting at Santiago de Compostella. ARCO Newsletter 1993;5:79–82.
4 Steinberg ME, Hayken GD, Steinberg DR. A quantitative system for staging avascular necrosis. J Bone Joint Surg 1995;77B:34–41.
5 Hungerford DS. Role of core decompression as treatment method for ischemic femur head necrosis. Orthopäde 1990;19:219–23.
6 Iorio R, Healy WL, Abramowitz AJ, Pfeifer BA. Clinical outcome and survivorship analysis of core decompression for early osteonecrosis of the femoral head. J Arthroplasty 1998;13:34–41.
7 Ishizaka M, Sofue M, Dohmae Y, Endo N, Takahashi HE. Vascularized iliac bone graft for avascular necrosis of the femoral head. Clin Orthop 1997;337:140–8.
8 Kim SY, Kim YG, Kim PT, Ihn JC, Cho BC, Koo KH. Vascularized compared with nonvascularized fibular grafts for large osteonecrotic lesions of the femoral head. J Bone Joint Surg 2005;87A:2012–8.

9 Leung PC. Femoral head reconstruction and revascularization: treatment for ischemic necrosis. Clin Orthop 1996;323:139–45.
10 Mont MA, Carbone JJ, Fairbank AC. Core decompression versus non-operative management for osteonecrosis of the hip. Clin Orthop 1996;324:169–78.
11 Scully SP, Aaron RK, Urbaniak JR. Survival analysis of hips treated with core decompression or vascularized fibular grafting because of avascular necrosis. J Bone Joint Surg 1998;80A:1270–5.
12 Belal MA, Reichelt A. Clinical results of rotational osteotomy for treatment of avascular necrosis of the femoral head. Arch Orthop Trauma Surg 1996;115:80–4.
13 Langlais F, Fourastier J. Rotation osteotomies for osteonecrosis of the femoral head. Clin Orthop 1997;343:110–23.
14 Dudkiewicz I, Covo A, Salai M, Israeli A, Amit Y, Chechik A. Total hip arthroplasty after avascular necrosis of the femoral head: does etiology affect the results? Achives Orthop Trauma Surg 2004;124:82–5.
15 Cabanela ME. Bipolar versus total hip arthroplasty for avascular necrosis of the femoral head. A comparison. Clin Orthop 1990;261:59–62.
16 Wang CJ, Wang FS, Huang CC, Yang KD, Weng LH, Huang HY. Treatment of osteonecrosis of the femoral head – comparison of extracorporeal shockwave and core decompression and bone grafting. J Bone Joint Surg 2005;87A:2380–7.
17 Aldridge JM, Urbaniak JR. Avascualr necrosis of the femoral head: etiology, pathophysiology, classification, and current treatment guidelines. Am J Orthop 2004;33:327–32.
18 Beltran J, Herman LJ, Burk JM *et al.* Femoral head avascular necrosis: MR imaging with clinical-pathologic and radionuclide correction. Radiology 1988;166:215–20.
19 Inoue A, Ono K, Takaoka K, Yoshioka T, Hosoya T. A comparative study of histology in Perthes' disease and idiopathic avascular necrosis of the femoral head in adults (IANF). Intern Orthop 1980;4:39–46.
20 Chao YC, Wang SJ, Chu HC, Chang WK, Hsieh TY. Investigation of alcohol metabolizing enzyme genes in Chinese alcoholics with avascular necrosis of hip joint, pancreatitis and cirrhosis of the liver. Alcohol Alcoholism 2003;38:431–6.
21 Koo KH, Kim R, Kim YS *et al.* Risk period for developing osteonecrosis of the femoral head in patients on steroid treatment. Clin Rheumatol 2002;21:299–303.
22 Wang GJ, Gui Q, Balian G. The pathogenesis and prevention of steroid-induced osteonecrosis. Clin Orthop 2000;370:295–310.
23 Wang GJ, Gui Q. The pathogenesis of steroid-induced osteonecrosis and the effect of lipid-clearing agents on this mechanism. In: Urbaniak JR, Jones JP, eds. Osteonecrosis: etiology, diagnosis, and treatment. Rosemont, IL: American Academy of Orthopedic Surgeons, 1997;159–66.
24 Ohzono K, Takaoka K, Saito S, Saito M, Matsui M, Ono K. Intraosseous arterial architecture in nontraumatic avascular necrosis of the femoral head. Microangiographic and histologic study. Clin Orthop 1992;277:79–88.
25 Zhou Q, Li Q, Yang L, Liu F. Changes of blood vessels in glucocorticoid-induced avascular necrosis of the femoral head in rabbits. Chung-Hua Wai Ko Tsa Chih [Chinese Journal of Surgery] 2000;38:212–5.
26 Bradway JK, Morrey BF. The natural history of the silent hip in bilateral atraumatic osteonecrosis. J Arthroplasty 1993;8:383–7.
27 Merle D'Aubigne R, Postel M, Mazab A, Massias P, Gueguen J, France P. Idiopathic necrosis of the femoral head in adults. J Bone Joint Surg 1965;47B:612–33.
28 Ohzono K, Saito M, Takaoka K, Saito S, Nishina T, Kadowaki T. Natural history of nontraumatic avascular necrosis of the femoral head. J Bone Joint Surg 1991;73B:68–72.
29 Takatori Y, Kokubo T, Ninomiya S, Nakamura S, Morimoto S, Kusaba I. Avascular necrosis of the femoral head. Natural history and magnetic resonance imaging. J Bone Joint Surg 1993;75B:217–21.
30 Levin D, Norman D, Zinman C *et al.* Treatment of experimental avascular necrosis of the femoral head with hyperbaric oxygen in rats: histological evaluation of the femoral heads during the early phase of the reparative process. Exper Mol Pathol 1999;67:99–108.
31 Agarwala S, Sule A, Pai BU, Joshi VR. Alendronate in the treatment of avascular necrosis of the hip. Rheumatology 2002;41:346–7.
32 Agarwala S, Jain D, Joshi VR, Sule A. Efficacy alendronate, a bisphosphate, in the treatment of AVN of the hip. A prospective open-label study. Rheumatology 2005;44:352–9.
33 Desai MM, Sonone S, Bhasme V. Efficacy of alendronate in the treatment of avascular necrosis of the hip. Rheumatology 2005;44:1331–2.
34 Lai KA, Shen WJ, Yang CY, Shao CJ, Hsu JT, Lin RM. The use of alendronate to prevent early collapse of the femoral head in patients with nontraumatic osteonecrosis. A randomized clinical study. J Bone Joint Surg 2005;87A:2155–9.
35 Ludwig J, Lauber S, Lauber HJ, Dreisilker U, Raedel R, Hotzinger H. High-energy shock wave treatment of femoral head necrosis in adults. Clin Orthop 2001;387:119–26.
36 Heaney RP, Yates AJ, Santora AC II. Bisphosphonate effects and the bone remodeling transient. J Bone Miner Res 1997;12:1143–51.
37 Sahni M, Guenther HL, Fleisch H, Collin P, Martin TJ. Bisphosphonates act on rat bone resorption through the mediation of osteoblasts. J Clin Invest 1993;91:2004–11.
38 Puéchal X, Fiessinger JN. Thromboangiitis obliterans or Buerger's disease: challenges for the rheumatologist. Rheumatology 2007;46:192–9.
39 Disch AC, Matziolis G, Perka C. The management of necrosis-associated and idiopathic bone-marrow oedema of the proximal femur by intravenous iloprost. J Bone Joint Surg Br 2005;87B:560–4.
40 Meizer R, Radda C, Stolz G *et al.* MRI-controlled analysis of 104 patients with painful bone marrow edema in different joint localizations treated with the prostacyclin analogue iloprost. Wien Klin Wochenschr 2005;117:278–86.
41 Wang CJ, Hung HY, Pai CH. Shock wave-enhanced neovascularization at the tendon-bone junction: an experiment in dogs. J Foot Ankle Surg 2002;41:16–22.
42 Wang CJ, Wang FS, Yang KD, Huang CS, Hsu CC. Shock wave therapy induces neovascularization at the tendon-bone junction. A study in rabbits. J Orthop Res 2003;21:984–9.
43 McCormack D, Lane H, McElwain J. The osteogenic potential of extracorporeal shock wave therapy: An in-vivo study. Ir J Med Sci 1996;165:20–2.
44 Wang CJ, Huang HY, Chen HH, Pai CH, Yang KD. Effect of shock wave therapy on acute fractures of the tibia. Clin Orthop 2001;387:112–8.
45 Wang CJ, Yang KD, Wang FS, Chen HS, Chen HH, Hsu CC. Shock wave therapy enhances bone mass and bone strength after fracture of the femur. A study in rabbits. Bone 2004;34:225–30.
46 Wang FS, Wang CJ, Huang HJ, Chung H, Chen RF, Yang KD. Physical shock wave mediates membrane hyperpolarization and Ras activation for osteogenesis in human bone marrow stromal cells. Biochem Biophys Res Commun 2001;287:648–55.
47 Wang FS, Yang KD, Chen RF, Wang CJ, Sheen-Chen SM. Extracorporeal shock wave promotes bone marrow stromal cell growth and differentiation toward osteoprogenitors associated with TGF-b 1 induction. J Bone Joint Surg 2002;84B:457–61.
48 Wang FS, Wang CJ, Sheen-Chen SM, Kuo YR, Chen RF, Yang KD. Superoxide mediates shock wave induction of RRK-dependent osteogenic transcription factor (CBFA 1) and mesenchymal cells differentiation toward osteoprogenitors. J Biol Chem 2002;277:10931–7.