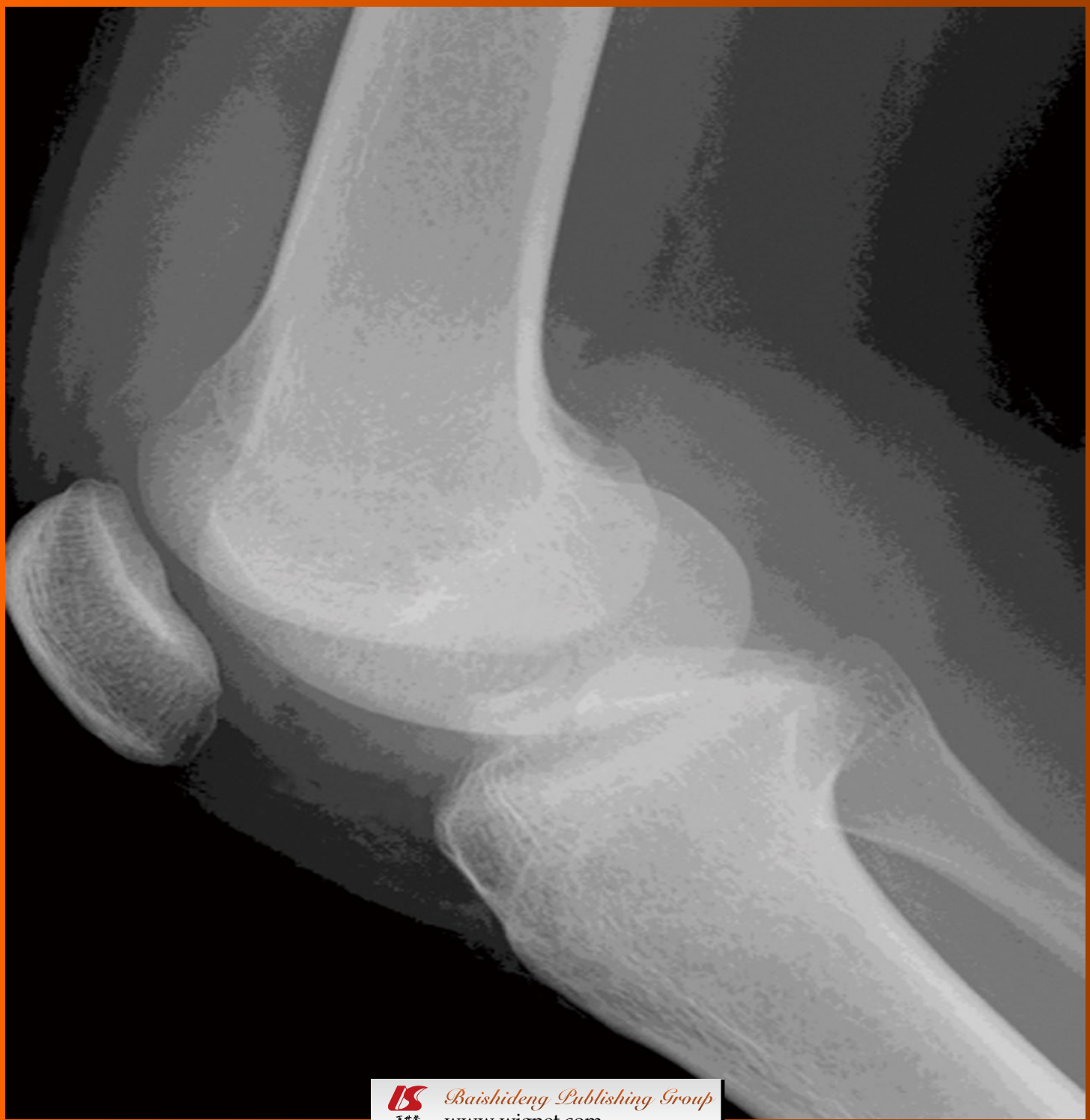
ISSN 2218-5836 (online)

World Journal of *Orthopedics*

World J Orthop 2011 August 18; 2(8): 67-84



Baishideng Publishing Group
www.wjgnet.com

WJO World Journal of Orthopedics

A peer-reviewed, online, open-access journal of orthopedics

Editorial Board

2010-2014

The *World Journal of Orthopedics* Editorial Board consists of 245 members, representing a team of worldwide experts in orthopedics. They are from 30 countries, including Argentina (1), Australia (14), Austria (2), Belgium (1), Brazil (3), Canada (5), China (18), Croatia(2), Denmark (1), Egypt (2), Finland (2), France(2), Germany (10), Greece (5), Hungary (1), India (9), Iran (2), Ireland (1), Israel (5), Italy (19), Japan (14), Morocco (1), Netherlands (10), Norway (2), Portugal (1), Serbia (3), Singapore (3), South Korea (12), Spain (4), Sri Lanka (1), Sweden (3), Switzerland (6), Tunisia (3), Turkey (1), Tunisia (1), United Kingdom (6), and United States (69).

Yrjö T Konttinen, *Helsinki*

France

Federico Canavese, *Clermont-Ferrand*
Yiou Eric, *Orsay Cedex*

Germany

Annegret Mündermann, *Radolfzell*
Beat Knechtle, *Gallen*
Heinz LOHRER, *Frankfurt Am Main*
Olaf Lorbach, *Homburg*
Stefan Grote, *Munich*
Karsten Knobloch, *Hannover*
Philipp Kobbe, *Aachen*
Volker Schöffl, *Bamberg*
Arndt P Schulz, *Lübeck*
Lars V Baron von Engelhardt, *Bochum*

Greece

George C Babis, *Attiki*
Marios Georgios Lykissas, *Ioannina*
Lazaros I Sakkas, *Larissa*
Nikolaos G Papadimitriou, *Thessaloniki*
Konstantinos N Malizos, *Larissa*

Hungary

Andor Sebestyén, *Pécs*

India

Antony Gomes, *Calcutta*
Kunal Sharan, *Lucknow*
Divya Vohora, *New Delhi*
Devdatta Suhas Neogi, *Mumbai*
Mohamed Shafi, *Tamil Nadu State*
Pankaj Kumar, *Andhra Pradesh*
Pramod V Lokhande, *Pune*
Vidyadhara Srinivasa, *Karnataka*
Vaibhav Bagaria, *Ghaziabad*

Iran

Hossein Negahban, *Ahvaz*
Sayed Javad Mousavi, *Tehran*

Ireland

Joseph S Butler, *Dublin*

Israel

Alexander Blankstein, *Ramat Hasharon*
Dror Lakstein, *Haifa*
Itzhak Binderman, *Tel Aviv*
Nahum Rosenberg, *Haifa*
Youssef Maher Masharawi, *Tel Aviv*

Italy

Alessandro Geraci, *Feltre*
Angelo Cacchio, *L'Aquila*
Costantino Errani, *Bologna*
Claudia Mazzà, *Roma*
Donatella Lippi, *Florence*
Giuseppe M Campo, *Messina*
Giuseppe Banfi, *Milano*
Patrizia D'Amelio, *Torino*
Marco Crostelli, *Rome*
Marcello Maggio, *Parma*
Marco Giuseppe Angelo Teli, *Bergamo*
Monica Mattioli-Belmonte, *Ancona*
Marco Monticone, *Lissone*
Pasquale De Negri, *Rionero in Vulture*
Andrea Giusti, *Genova*
Alberto Gobbi, *Milan*
Raoul Saggini, *Chieti*
Saverio Affatato, *Bologna*
Tomaso Villa, *Milano*

Japan

Akio Sakamoto, *Fukuoka*
Jun Iwamoto, *Tokyo*
Kanji Mori, *Otsu*
Makoto Makishima, *Tokyo*
Ryuichi Morishita, *Suita*
Shuichi Kaneyama, *Kobe*
Tadahiko Yotsumoto, *Osaka*
Toru Yamaguchi, *Izumo-shi*
Toshimasa Uemura, *Ibaraki*
Hideki Nagashima, *Yonago*
Hisataka Yasuda, *Nagahama*
Yasuharu Nagano, *Saitama*
Yoichi Aota, *Yokohama*
Yuichi Kasai, *Tsu city*

Morocco

Abdellah El Maghraoui, *Rabat*

Netherlands

Claudine JC Lamoth, *Groningen*
Barend J van Royen, *Amsterdam*
Doug King, *Lower Hutt*
Paul C Jutte, *Groningen*
PE Huijsmans, *Hague*
PM van der Kraan, *Nijmegen*
Michel van den Bekerom, *Amsterdam*
JJ Verlaan, *Utrecht*
Rob GHH Nelissen, *Leiden*
Taco Gosens, *Tilburg*

Norway

Jan Oxholm Gordeladze, *Oslo*
Gunnar Knutsen, *Tromsø*

Portugal

João F Mano, *Guimarães*

Serbia

Radica Dunjic, *Belgrade*
Miroslav Z Milankov, *Novi Sad*
Zoran Vukasinovic, *Belgrade*

Singapore

Anselm Mak, *Singapore*
Dongan Wang, *Singapore*
V Prem Kumar, *Singapore*

South Korea

Dae-Geun Jeon, *Seoul*
Seok Woo Kim, *Gyeonggi*
Sang-Hun Ko, *Ulsan*
Sung-Uk Kuh, *Seoul*
Jaebeom Lee, *Miryang*
Yong Seuk Lee, *Suwon*
Hyun Woo Kim, *Seoul*
Jae Taek Hong, *Suwon*
Jong-Beom Park, *Kyunggi-do*
Kook Jin Chung, *Seoul*
Kyu Hyun Yang, *Seoul*
Sang Ki Lee, *Daejeon*

Spain

Antonio Herrera, *Zaragoza*
Daniel Hernandez Vaquero, *Aviles*
Francisco J Blanco, *A Coruña*
Nuria Vilaboa, *Madrid*

Sri Lanka

Janaka Lenora, *Galle*

Sweden

Jan G Jakobsson, *Stockholm*
Anna Nordström, *Umeå*

Switzerland

Achim Elfering, *Bern*
Benjamin Gantenbein, *Bern*

Nicola A Maffiuletti, *Zurich*
Michael Hirschmann, *Basel*
Elyazid Mouhsine, *Lausanne*
Peter Fennema, *Baar*

Thailand

Boonsin Tangtrakulwanich, *Songkla*
Prachya Kongtawelert, *Chiang Mai*
Sittisak Honsawek, *Bangkok*

Tunisia

Lamia Rezgui-Marhoul, *Tunis*

Turkey

Akmer Mutlu, *Ankara*
Bulent Daglar, *Ankara*
Kemal NAS, *Diyarbakır*
Salih Özgöçmen, *Kayseri*
Serdar Kahraman, *İstanbul*

United Kingdom

Henry DE Atkinson, *London*
Vikas Khanduja, *Cambridge*
Ali Mobasheri, *Sutton Bonington*
Charles Anthony Willis-Owen, *London*
Vikki Wylde, *Bristol*
Tosan Okoro, *Bangor*

United States

Srino Bharam, *New York*
Craig R Bottoni, *Honolulu*
Lavjay Butani, *Sacramento*
Chaoyang Chen, *Detroit*
Ock K Chun, *Storrs*
Christopher J Colloca, *Chandler*
Nabanita S Datta, *Detroit*
Paul E Di Cesare, *Sacramento*
Matthew B Dobbs, *Saint Louis*
Evan F Fkman, *Columbia*
Joel J Gagnier, *Ann Arbor*
Federico P Girardi, *New York*
David L Helfet, *New York*
Johnny Huard, *Pittsburgh*
Stefan Judex, *Stony Brook*
Monroe Laborde, *New Orleans*
Bingyun Li, *Morgantown*
Subburaman Mohan, *Loma Linda*
Arash Momeni, *Palo Alto*
Nader D Nader, *Buffalo*
John Nyland, *Louisville*
Karin Grävare Silbernagel, *Newark*
David H Song, *Chicago*
Nelson F SooHoo, *Los Angeles*
SPA Stawicki, *Columbus*
Ann Marie Swank, *Louisville*
R Shane Tubbs, *Birmingham*
Victoria M Virador, *Bethesda*
Savio LY Woo, *Pittsburgh*
Masayoshi Yamaguchi, *Atlanta*
Feng-Chun Yang, *Indianapolis*
Subhashini Yaturu, *Albany*
Hiroki Yokota, *Troy*
Charalampos Zalavras, *Los Angeles*
Chunfeng Zhao, *Rochester*
Anil Bhave, *Baltimore*
John Elias, *Akron*
Clark Dickin, *Muncie*
John S Early, *Dallas*
James S Harrop, *Philadelphia*
Adam H Hsieh, *Maryland*
Aditya V Maheshwari, *New York*
Zong-Ming Li, *Cleveland*
Richard M Lovering, *Baltimore*
Lyle Joseph Micheli, *Boston*
Ming Pei, *Morgantown*
Juan A Pretell – Mazzini, *Philadelphia*
David M Selkowitz, *Pomona*
Hassan Serhan, *Raynham*
Subhashini Yaturu, *Albany*
Sorin Siegler, *Pennsylvania*
Aaron David Sciascia, *Lexington*
Jeffrey C Wang, *Santa Monica*
David Andrew Spiegel, *Philadelphia*
Inna Belfer, *Pittsburgh*
Angie Botto-van Bemden, *Lauderdale*
Quan-Jun Cui, *Virginia*
Scott D Daffner, *Morgantown*
B Sonny Bal, *Columbia*
Beril Gok, *Baltimore*
Ashraf S Gorgey, *Richmond*
Kee D Kim, *Sacramento*
Brian Michael Haus, *Boston*
Dror Paley, *Pittsburgh*
Bing Wang, *Pittsburgh*
Wen-Bao Wang, *New York*
Li-Qun Zhang, *Chicago*
Nigel Zheng, *Charlotte*

WJO World Journal of Orthopedics

Contents

Monthly Volume 2 Number 8 August 18, 2011

World Journal of Orthopedics
Volume 2 Number 8 August 18, 2011

Contents

NAME OF JOURNAL
World Journal of Orthopedics

LAUNCH DATE
November 18, 2010

SPONSOR
Beijing Baishideng BioMed Scientific Co., Ltd.
Room 903, Building D, Ocean International Center,
No. 62 Dongsihuan Zhonglu, Chaoyang District,
Beijing 100025, China
Telephone: +86-10-8538-1892
Fax: +86-10-8538-1893
E-mail: baishideng@wjgnet.com
http://www.wjgnet.com

EDITING
Editorial Board of *World Journal of Orthopedics*
Room 903, Building D, Ocean International Center,
No. 62 Dongsihuan Zhonglu, Chaoyang District,
Beijing 100025, China
Telephone: +86-10-5908-0036
Fax: +86-10-8538-1893
E-mail: wjo@wjgnet.com
http://www.wjgnet.com

PUBLISHING
Baishideng Publishing Group Co., Limited
Room 1701, 17/F, Henan Building,
No.90 Jaffe Road, Wanchai, Hong Kong, China
Fax: +852-3115-8812
Telephone: +852-5804-2046
E-mail: baishideng@wjgnet.com
http://www.wjgnet.com

SUBSCRIPTION
Beijing Baishideng BioMed Scientific Co., Ltd.
Room 903, Building D, Ocean International Center,
No. 62 Dongsihuan Zhonglu, Chaoyang District,
Beijing 100025, China
Telephone: +86-10-8538-1892
Fax: +86-10-8538-1893
E-mail: baishideng@wjgnet.com
http://www.wjgnet.com

PUBLICATION DATE
August 18, 2011

ISSN
ISSN 2218-5836 (online)

EDITORIAL OFFICE
Xiao-Cui Yang, Assistant Director
World Journal of Orthopedics
Room 903, Building D, Ocean International Center,
No. 62 Dongsihuan Zhonglu, Chaoyang District,
Beijing 100025, China
Telephone: +86-10-8538-1892
Fax: +86-10-8538-1893
E-mail: wjo@wjgnet.com
http://www.wjgnet.com

INSTRUCTIONS TO AUTHORS
Full instructions are available online at http://www.wjgnet.com/2218-5836/g_info_20100722172650.htm.

ONLINE SUBMISSION
http://www.wjgnet.com/2218-5836office

World Journal of Orthopedics

Online Submissions: http://www.wjgnet.com/2218-5836office
wjo@wjgnet.com
doi:10.5312/wjo.v2.i8.67

World J Orthop 2011 August 18; 2(8): 67-74
ISSN 2218-5836 (online)

EDITORIAL

Osteoporotic fracture and parathyroid hormone

Nabanita S Datta

Nabanita S Datta, Department of Internal Medicine, Division Endocrinology, Wayne State University School of Medicine, Detroit, MI 48201, United States
Author contributions: Datta NS solely contributed to this paper.
Supported by The author was partially supported by the grant from The National Institute of Health, NIHDK087848, during writing of this manuscript
Correspondence to: Nabanita S Datta, MS, PhD, Associate Professor of Medicine, Department of Internal Medicine, Division Endocrinology, Wayne State University School of Medicine, Detroit, MI 48201, United States. ndatta@med.wayne.edu
Telephone: +1-313-7454008 Fax: +1-313-5778615
Received: March 4, 2011 Revised: April 19, 2011
Accepted: June 1, 2011
Published online: August 18, 2011

Abstract

Osteoporosis and age-related bone loss is associated with changes in bone remodeling characterized by decreased bone formation relative to bone resorption, resulting in bone fragility and increased risk of fractures. Stimulating the function of bone-forming osteoblasts, is the preferred pharmacological intervention for osteoporosis. Recombinant parathyroid hormone (PTH), PTH(1-34), is an anabolic agent with proven benefits to bone strength and has been characterized as a potential therapy for skeletal repair. In spite of PTH's clinical use, safety is a major consideration for long-term treatment. Studies have demonstrated that intermittent PTH treatment enhances and accelerates the skeletal repair process *via* a number of mechanisms. Recent research into the molecular mechanism of PTH action on bone tissue has led to the development of PTH analogs to control osteoporotic fractures. This review summarizes a number of advances made in the field of PTH and bone fracture to combat these injuries in humans and in animal models. The ultimate goal of providing an alternative to PTH, currently the sole anabolic therapy in clinical use, to promote bone formation and improve bone strength in the aging population is yet to be achieved.

Key words: Osteoporosis; Fracture repair; Parathyroid hormone; Parathyroid hormone-1 receptor; Emerging therapies

Peer reviewer: Prachya Kongtawelert, Associate Professor, Department of Biochemistry, Faculty of Medicine, Chiang Mai University, Chiang Mai 50200, Thailand; Kook Jin Chung, Professor, Department of Orthopaedic Surgery, HallymUniversity, Kangnam Sacred Heart Hospital, 948-1, Daerim 1-dong, Yeongdeungpo-gu, Seoul 150-950, South Korea; Kemal Nas, Professor, Department of Physical Medicine and Rehabilitation, University of Dicle, Medical School, Diyarbakir 21280,Turkey

Datta NS. Osteoporotic fracture and parathyroid hormone. *World J Orthop* 2011; 2(8): 67-74 Available from: URL: http://www.wjgnet.com/2218-5836/full/v2/i8/67.htm DOI: http://dx.doi.org/10.5312/wjo.v2.i8.67

INTRODUCTION

Osteoporosis is a progressive disorder of aging bone in both men and women, and osteoporotic fractures have become a major public health threat in recent years[1,2]. In spite of widespread research, The lack of reliable and effective drugs to cure osteoporosis related fragility fractures remains an important global issue. Long considered a disease of post-menopausal women, osteoporosis is increasingly being recognized among the growing population of elderly men. New treatments and updates are constantly being recognized for treating osteoporosis in women[3,4]. Although only thirty percent of hip fractures occur in men, the mortality rate during initial hospitalization and the first year after fractures twice as high in men as in women. Nevertheless, osteoporosis in men is underdiagnosed and undertreated, and is an increasingly important clinical issue[5,6]. Osteoporosis in men is a heterogeneous clinical entity. While most men experience bone loss with aging, some develop osteoporosis at a relatively young age, often for unexplained reasons (idiopathic

osteoporosis). Declining sex steroid levels and other hormonal changes probably contribute to age-related bone loss, as do impairments in osteoblast number and/or activity[7]. Also, fragility fractures are common in men and are associated with a significant burden in terms of morbidity, mortality and economic cost to the community[7-9].

Intermittent treatment with teriparatide [recombinant human parathyroid hormone (hPTH-(1-34)], the only anabolic hormone, offers the potential to improve skeletal microarchitecture, and is a treatment modality for women with post-menopausal osteoporosis and men at high risk for fractures. Despite its clinical use, PTH has been reported to be associated with incidence of osteosarcoma, and safety is a major consideration for long-term use[10,11]. The molecular mechanisms underlying PTH's action to evoke increased bone mass are not fully understood. Further elucidation is required using more controlled study designs, to develop an understanding the pathophysiology of bone loss, optimize patient care and to yield novel therapeutic strategies for potentiating bone anabolic agents.

OSTEOPOROSIS

"Osteo" means bone, and "porosis" means porous. Osteoporotic bones become more porous with less solid and less dense bone masses. Bone is an active tissue where new bone is being made continuously by osteoblasts, the bone forming cells, and old bone is removed by osteoclasts, the bone resorbing cells, *via* a process known as remodeling. In childhood, more bone is built than removed, and so the bones grow in both mass and size. In older age, osteoporosis results from increased bone resorption and decreased bone formation. The cells that build new bone do not keep up with those that remove bone. The total amount of bone mass then decreases, and osteoporosis may develop as a result. This condition finally makes bone thinner, weaker and more fragile, ultimately leading to loss of their structural and functional protein framework.

The human body also needs enough calcium, phosphorus and hormones, including estrogen in women and testosterone in men, to maintain healthy bone. Sufficient vitamin D is required to allow absorption of calcium from food, which is incorporated into bones to maintain their normal function. Osteoporosis exists in both primary or a secondary forms. Primary osteoporosis is the more common form and is due to the typical age-related loss of bone from skeleton. It is classified as type 1 or postmenopausal osteoporosis. Estrogen deficiency is thought to underlie this form of osteoporosis, rendering the skeleton more sensitive to PTH, and resulting in increased calcium resorption from bone. This in turn decreases PTH secretion, 1,25-dihydroxyvitamin D production, and calcium absorption. This ultimately causes loss of trabecular bone, leading to vertebral crush fractures and Colles' fractures. Primary osteoporosis type 2 or senile osteoporosis occurs in women or men of more than 70 years of age and is usually associated with decreased bone formation along with decreased ability of the kidney to produce $1,25(OH)_2D_3$. Type 3 or secondary osteoporosis results from the presence of other diseases or conditions that predispose to bone loss and occurs equally in men and women and at any age. This type of osteoporosis is associated with a variety of conditions, including hormonal imbalances (e.g. Cushing's syndrome); cancer (notably multiple myeloma); gastrointestinal disorders (especially inflammatory bowel disease which causes mal-absorption); drug use [e.g. corticosteroids, cancer chemotherapy, anticonvulsants, heparin, barbiturates, valporic acid, gonadotropin-releasing hormone, excessive use of aluminum-containing antacids]; chronic renal failure; hyperthyroidism; hypogonadism in men; immobilization; osteogenesis imperfecta and related disorders; inflammatory arthritis (particularly rheumatoid arthritis); and poor nutrition (including malnutrition due to eating disorders)[12-14]. Thus, osteoporosis is classified as a systematic skeletal disease characterized by low bone strength and increased fracture risk[15]. In this disease spine, hip, wrist and other associated bone joints fracture very easily, leading to serious health problems.

OSTEOPOROTIC FRACTURES

Globally more than 30 million people are affected by osteoporosis with about 1.5-2 million osteoporotic fragility fractures happening in every year[16-18]. This includes more than 700 000 vertebral fractures and over 300 000 hip fractures[19]. The mortality rate following a hip fracture in osteoporotic patients is about 10%-20% within the first year, and less than 50% of survivors regain their pre-fracture level of mobility and independence[16]. Furthermore, mortality within 90 d of an osteoporotic fracture in individuals who are older than 65 years is substantially higher than might be expected, and for a subset of these fractures the risk for early lethality increases approximately sevenfold[20]. In the United States alone, osteoporotic fracture cost exceeds US $17 billion per year[21]. The first critical step in reducing the burden of osteoporotic fractures is to identify individuals at high risk of fracture by skeletal health evaluation and to then determine the appropriate pharmacological therapy, applying anabolic or anti-resorptive medication to reduce fracture risk[22,23]. Over the last decade, the prevention of osteoporotic fractures has been limited to the use of anti-resorptive[24] and anabolic drugs, which have proven to be insufficient for decreasing the mortality and morbidity in this patient population.

THERAPEUTIC OPENING FOR FRACTURE REPAIR

The fracture repairing process is biologically controlled and optimized. In approximately 5% to 10% of the 7.9 million fractures sustained annually it is difficult to achieve union[25]. Hence, there is a compelling need to

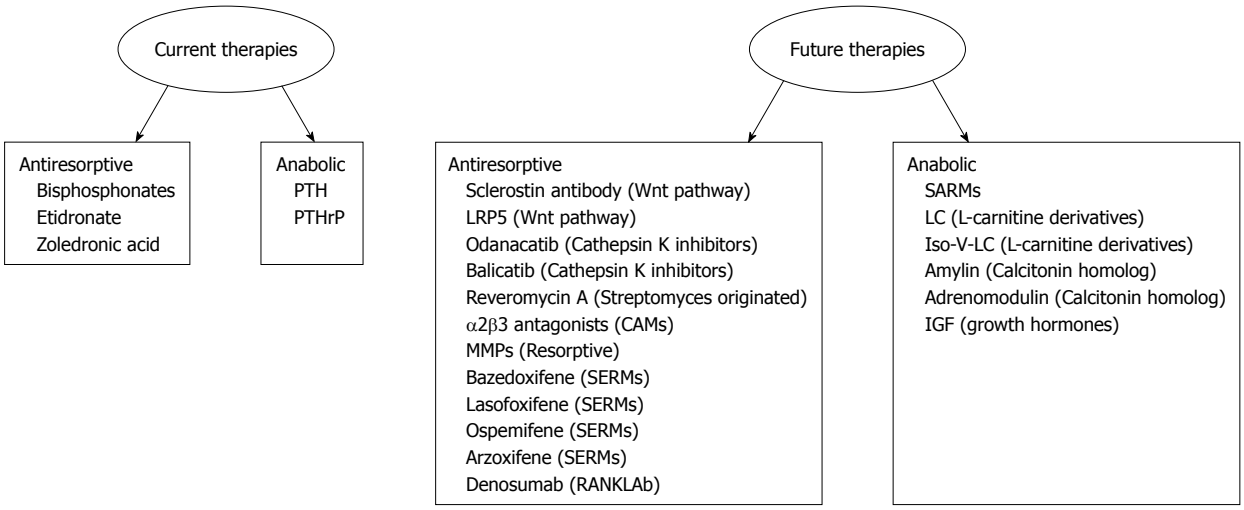


Figure 1 Current and future therapies for osteoporotic fractures[107-109]. SERMs: Selective estrogen receptor modulators; RANKL: Ab-receptor activator of nuclear factor ḰB antibody; Wnt: Wingless signaling pathway; CAM: Cell adhesion molecules; IGF: Insulin growth factor, LC: L-carnitine; Iso-V-LC: Isovaleryl-L-carnitine; MMP: Matrix metalloproteinase; PTH: Parathyroid hormone; LRP: LDL receptor related protein receptor; SARM: Selective androgen receptor modulators.

find novel and effective therapies to enhance fracture repair process. Advances in the understanding of the molecular and cellular signaling pathways of bone biology have led to the development of current and emerging therapeutic agents which are summarized in Figure 1.

The known anabolic effects of PTH on bone formation has led to the development of a human recombinant peptide, teriparatide (1-34 hPTH), corresponding to the first 34 amino acids of PTH. Teriparatide is a drug currently approved for treating patients with osteoporosis who are at high risk for future fracture. Studies have confirmed a striking increase in trabecular bone mass and also showed that an important part of teriparatide's action is to increase cortical bone. A formal trial in postmenopausal women with osteoporosis was conducted by Eli Lilly and Company in the United States. The unexpected occurrence of osteosarcomas in Fisher 344 rats treated long-term with teriparatide provoked an abrupt cessation of this trial. However, ambiguity concerning the relevance of this rat finding to human disease, combined with significant anti-fracture efficacy, led to FDA approval of teriparatide for men and postmenopausal women with osteoporosis "at high risk for fracture" in 2002. Subsequently, teriparatide has been approved also for treatment of patients with glucocorticoid-associated osteoporosis, and papers indicating the utility of this agent for dental and orthopedic applications have begun to appear[26]. In the treatment of osteoporosis, teriparatide works as an anabolic agent stimulating bone formation throughout the skeleton, principally by enhancing osteoblast-derived bone formation relative to osteoclast-derived bone resorption, resulting in a net increase in bone mass. For patients with a fracture, a similar process of increased bone formation is required transiently at the fracture site for repair. Teriparatide has been investigated in animal models and in patients as a potential agent to enhance fracture repair. Interestingly, in conditions with impaired healing such as aging, estrogen withdrawal, and malnutrition fracture repair is expedited by PTH treatment. Subcutaneous injection of PTH once per day led to increased bone mass in patients with osteoporosis[27] and in ovariectomized monkeys[28]. The capability of PTH to augment bone formation is dependent upon the hormone being administered in a way that yields a transient peak blood level[29,30].

It was initially noted that PTH could increase bone mass in rats[31,32]. Using various animal models, several groups have shown that intermittent exposure to PTH stimulates osteoblast differentiation and function *in vivo*[33,34]. Evidence that teriparatide enhances chondrogenesis has generated interest in using the agent for articular cartilage repair. Bukata *et al*[35] and Aleksyniene *et al*[36] found that treatment with PTH during distraction osteogenesis resulted in substantially higher mineralized tissue volume, mineral content, and bending strength. This suggests that treatment with PTH may benefit new bone formation during distraction osteogenesis and could form the basis for clinical application of this therapy in humans.

Knowledge of the effects of intermittent PTH treatment on newly regenerating bone after distraction osteogenesis is very limited. Seebach *et al*[37] reported enhanced mechanical strength and density of new bone after distraction osteogenesis in rats. However, no information is available on the effects of intermittent PTH treatment on distraction osteogenesis in larger animals. Recent experiments with rats have demonstrated that treatment with PTH increases mechanical strength and callus formation in normal healing fractures[38-42]. Furthermore, an increased density of regenerated bone and enhanced fixation of steel implants in rats have been shown after PTH treatment[43,44].

In a recent investigation, to evaluate the potential use as a therapeutic agent for osteoporotic fractures, Kim and Jahng examined the effects of intermittent administration of PTH on fracture healing in ovariectomized rats[45]. At 3 mo post-ovariectomy, bilateral tibial shaft fractures

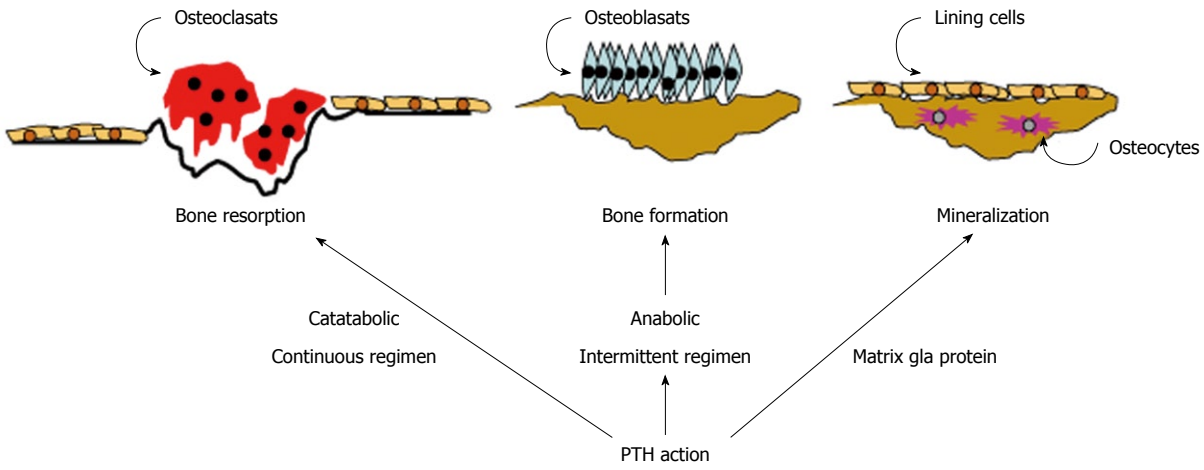


Figure 2 Effect of parathyroid hormone on bone cells.

were induced and stabilized by intramedullary nailing with Kirschner wires. Saline, 17-estradiol, or recombinant human PTH(1-84) was given once a day for 30 consecutive days during fracture healing. Fracture healing was assessed by morphometric and mechanical analysis of fracture callus. Intermittent PTH administration increased the morphometric and mechanical parameters in a dose-dependent manner. 17-estradiol, a bone-resorption inhibiting agent, showed no benefits in terms of fracture healing in ovariectomized rats. Verhaar *et al*[46] reported that exogenous PTH analogs, given as daily subcutaneous injections, stimulate bone formation, increase bone mass and bone strength, and improve calcium balance.

Traditionally PTH was thought to be catabolic to the human skeleton as severe osteoporosis and osteitis fibrosacystica may complicate long standing hyperparathyroidism. In 1932 Selye reported the ability of PTH to stimulate osteogenesis[32]. Subsequently, the anabolic effects of PTH have been examined in greater detail[30,47-52]. PTH was initially developed as a drug to treat postmenopausal osteoporotic women, enhancing bone mineral density[29], cortical thickness and trabecular bone volume[53,54] compared to placebo controls. In addition to its anabolic effects on bone turnover[29,47,55] teriparatide was shown in clinical trials to significantly reduce the risk of vertebral and non-vertebral fractures in osteoporotic women[29,56]. In randomized clinical trials PTH was shown to be useful in preventing fracture in osteoporotic subjects[50,57-59]. It is now well accepted that intermittent administration of PTH and PTH-related peptide (PTHrP) has net anabolic effects on bone[47,52,60,61].

Although it is now well established that PTH is a multifunctional molecule with a unique ability to affect the bone metabolism, the biological complexity of bone repair often makes it difficult to specify what events have failed during the repair process. Currently, several PTH analogs are being developed and are under evaluation. In general, PTH analogs are well tolerated and have an acceptable safety profile. They can be used for the prevention and treatment of fractures in postmenopausal women with severe osteoporosis. Thus PTH analogs reduce the risk of vertebral (PTH 1-34 and PTH 1-84) and non-vertebral fractures (only PTH 1-34). In men and women with glucocorticosteroid-induced osteoporosis, PTH 1-34 has been shown to reduce the risk of vertebral fractures[46]. In recent years β-arrestin-based agonists of PTH-1 receptor (PTH1R) have drawn much attention for promoting bone formation independent of G-protein activation[62,63].

MOLECULAR REGULATION OF PTH AND PTHrP IN BONE

It is well established that PTH, secreted from the parathyroid glands, is involved in calcium homeostasis and is a critical mediator of skeletal development and remodeling[64]. There are several reports of the beneficial use of PTH for treating osteoporosis. However, prolonged use of PTH leads to hypercalciurea, hypercalcemia and osteosarcoma[65], thus limiting the safe use of this peptide hormone. Therefore dissecting the molecular mechanisms of PTH actions is essential as this may uncover novel therapeutic targets for the prevention and reversal of osteoporosis and bone-related diseases and allow minimization of the adverse effects of PTH.

Although a large number of *in-vitro, in-vivo* and human studies have been performed, the mechanisms involved in PTH regulation of osteoblast function is poorly understood and only partly characterized. PTH binds to cells of the osteoblast lineage[66,67] and produces both anabolic and catabolic effects (Figure 2). The fact that PTH has dual effects depending on its administration method raises important questions about its mechanisms of action in bone formation and resorption. It was hypothesized that the anabolic and catabolic effects of PTH and PTHrP on osteoblasts occur through activation of signaling cascades different from PTH1R[64]. The PTH and PTHrP signal *via* PTH1R which is a G protein-coupled receptor with 7 transmembrane spanning domains. The receptor is encoded by a multi-exon gene, characterized in human, rat and mouse, with potential for alternate

splicing and alternate promoter usage[68]. Understanding the physiological roles, molecular and cellular actions of PTH and PTHrP began when PTH1R was first cloned in 1990s[69,70]. PTH1R signaling cascades involve adenylate cyclase/protein kinase A, phospholipase C/protein kinase C, and mitogen activated protein kinases, and lead to various biological effects including both anabolic and catabolic actions in bone[71-75]. Recently, Guo *et al*[76] further established that phospholipase C signaling *via* the PTH receptor is essential for normal bone response to PTH. Other studies suggested that FGF2 is equally important for the anabolic action of PTH on bone[77] and a crosstalk between skeletogenesis and FGF receptor was recently highlighted[78]. Among other mechanisms, PTH anabolic action with or without the involvement of Bcl2 has been described[79,80].

Increased bone formation is largely due to a rise in osteoblast number as a result of increased proliferation and differentiation of osteoblasts *in vitro* and *in vivo*[52,73,74,81-87], decrease in osteoblast apoptosis[88,89], and activation of bone lining cells[48,90]. A mechanism involving cell-cell contact in PTH-induced osteoblast proliferation has also been suggested[91]. Numerous targets of PTH and PTHrP as mediators of bone tissue regeneration have been suggested[71]. These include local cytokines and growth factors[92,93], transcription factors[94-96], and several genes such as MMP-13, a matrix metalloproteinase/collagenase[97,98], IL-6[99], IL-18[100], macrophage-colony stimulating factor[101], ephrinB2[102], and osteoblast cell cycle regulatory proteins[72,74,103,104].

Intermittent PTH 1-34 treatment stimulates bone formation, but the molecular mechanisms mediating this effect have not previously been studied in humans. A very recent study hypothesized that an inhibition of BMP signaling by PTH may, over time, limit the availability of mature osteoblasts on bone surfaces and thereby contribute to the observed decline in the anabolic response to PTH[105]. Several critical steps in the actions of PTH beyond receptor activation have been identified and more are yet to be discovered.

CONCLUSION

Fractures usually repair without incident. When fractures associated with osteoporotic bones do not repair in a timely fashion, the result is painful and detrimental to the patient's quality of life. Treatment, in such cases, is time-consuming and expensive for the health care system [106]. Bone repair after orthopedic fracture is a complicated process. PTH is the first bone anabolic drug approved for the treatment of osteoporosis and associated fractures. Intriguingly, a number of animal studies suggest that PTH could be beneficial in the treatment of fractures and could potentially offer a new treatment option for induction of fracture repair in humans. Furthermore, repair of fractures associated with conditions of impaired healing such as aging, estrogen withdrawal, and malnutrition can be expedited by PTH treatment. Although recent advances in molecular bone research using a variety of *in vivo* and *in vitro* models have increased our understanding of the role of PTH in osteoporotic the fracture repair process, pharmacological intervention using PTH cannot at present be considered a "gold standard". Many future therapies are currently under investigation for the management of fractures associated to osteoporosis.

ACKNOWLEDGMENTS

The author was partially supported by the grants from The National Institute of Health, DK087848, during writing of this manuscript.

REFERENCES

1 **Department of Health and Human Services OotSG**. Bone health and osteoporosis: a report of the surgeon general. Rockville: USDHHS, 2004
2 **Cooper C**, Johnell O, Lips P, Melton LJ, Kanis JA. The global burden of vertebral fractures (abstract). *J Bone Miner Res* 2002; **17** (Suppl 1): S202
3 **Vestergaard P**, Thomsen SV. Treating postmenopausal osteoporosis in women at increased risk of fracture - critical appraisal of bazedoxifene: a review. *Int J Womens Health* 2010; **1**: 97-103
4 **Lindsay R**. Preventing osteoporosis with a tissue selective estrogen complex (TSEC) containing bazedoxifene/conjugated estrogens (BZA/CE). *Osteoporos Int* 2011; **22**: 447-451
5 **Wright VJ**. Osteoporosis in men. *J Am Acad Orthop Surg* 2006; **14**: 347-353
6 **Nuti R**, Merlotti D, Francucci CM, Gennari L. Bone fragility in men: where are we? *J Endocrinol Invest* 2010; **33**: 33-38
7 **Khosla S**, Amin S, Orwoll E. Osteoporosis in men. *Endocr Rev* 2008; **29**: 441-464
8 **Boonen S**, Kaufman JM, Goemaere S, Bouillon R, Vanderschueren D. The diagnosis and treatment of male osteoporosis: Defining, assessing, and preventing skeletal fragility in men. *Eur J Intern Med* 2007; **18**: 6-17
9 **Khosla S**, Westendorf JJ, Oursler MJ. Building bone to reverse osteoporosis and repair fractures. *J Clin Invest* 2008; **118**: 421-428
10 **Sikon A**, Batur P. Profile of teriparatide in the management of postmenopausal osteoporosis. *Int J Womens Health* 2010; **2**: 37-44
11 **Pietrogrande L**. Update on the efficacy, safety, and adherence to treatment of full length parathyroid hormone, PTH (1-84), in the treatment of postmenopausal osteoporosis. *Int J Womens Health* 2010; **1**: 193-203
12 **Alderman CP**, Hill CL. Abnormal bone mineral metabolism after long-term anticonvulsant treatment. *Ann Pharmacother* 1994; **28**: 47-48
13 **Praet JP**, Peretz A, Rozenberg S, Famaey JP, Bourdoux P. Risk of osteoporosis in men with chronic bronchitis. *Osteoporos Int* 1992; **2**: 257-261
14 **Feber J**, Cochat P, Braillon P, Castelo F, Martin X, Glastre C, Chapuis F, David L, Meunier PJ. Bone mineral density after renal transplantation in children. *J Pediatr* 1994; **125**: 870-875
15 **NIH Consensus Development Panel on Osteoporosis Prevention, Diagnosis, and Therapy**. Osteoporosis prevention, diagnosis, and therapy. *JAMA* 2001; **285**: 785-795
16 **Finkelstein JS**. Osteoporosis. In: Cecil RL, Goldman L, Bennett JC, editors. Cecil textbook of medicine. 21st ed. Philadelphia, PA: WB Saunders Co., 2000: 1367-1373
17 **Gardner MJ**, Demetrakopoulos D, Shindle MK, Griffith MH, Lane JM. Osteoporosis and skeletal fractures. *HSS J* 2006; **2**: 62-69

18 **Kaback LA**, Soung do Y, Naik A, Geneau G, Schwarz EM, Rosier RN, O'Keefe RJ, Drissi H. Teriparatide (1-34 human PTH) regulation of osterix during fracture repair. *J Cell Biochem* 2008; **105**: 219-226

19 **Riggs BL**, Melton LJ. The worldwide problem of osteoporosis: insights afforded by epidemiology. *Bone* 1995; **17**: 505S-511S

20 **Heaney RP**. Advances in therapy for osteoporosis. *Clin Med Res* 2003; **1**: 93-99

21 **Burge R**, Dawson-Hughes B, Solomon DH, Wong JB, King A, Tosteson A. Incidence and economic burden of osteoporosis-related fractures in the United States, 2005-2025. *J Bone Miner Res* 2007; **22**: 465-475

22 **van den Bergh JP**, van Geel TA, Lems WF, Geusens PP. Assessment of individual fracture risk: FRAX and beyond. *Curr Osteoporos Rep* 2010; **8**: 131-137

23 **Lewiecki EM**. Fracture risk assessment in clinical practice: T-scores, FRAX, and beyond. *Clin Rev Bone Miner Metab* 2010; **8**: 101-112

24 **Cranney A**, Tugwell P, Zytaruk N, Robinson V, Weaver B, Adachi J, Wells G, Shea B, Guyatt G. Meta-analyses of therapies for postmenopausal osteoporosis. IV. Meta-analysis of raloxifene for the prevention and treatment of postmenopausal osteoporosis. *Endocr Rev* 2002; **23**: 524-528

25 **Marsell R**, Einhorn TA. Emerging bone healing therapies. *J Orthop Trauma* 2010; **24** Suppl 1: S4-S8

26 **Marcus R**. Present at the beginning: a personal reminiscence on the history of teriparatide. *Osteoporos Int* 2011; **22**: 2241-2248

27 **Sone T**, Fukunaga M, Ono S, Nishiyama T. A small dose of human parathyroid hormone(1-34) increased bone mass in the lumbar vertebrae in patients with senile osteoporosis. *Miner Electrolyte Metab* 1995; **21**: 232-235

28 **Brommage R**, Hotchkiss CE, Lees CJ, Stancill MW, Hock JM, Jerome CP. Daily treatment with human recombinant parathyroid hormone-(1-34), LY333334, for 1 year increases bone mass in ovariectomized monkeys. *J Clin Endocrinol Metab* 1999; **84**: 3757-3763

29 **Neer RM**, Arnaud CD, Zanchetta JR, Prince R, Gaich GA, Reginster JY, Hodsman AB, Eriksen EF, Ish-Shalom S, Genant HK, Wang O, Mitlak BH. Effect of parathyroid hormone (1-34) on fractures and bone mineral density in postmenopausal women with osteoporosis. *N Engl J Med* 2001; **344**: 1434-1441

30 **Frolik CA**, Black EC, Cain RL, Satterwhite JH, Brown-Augsburger PL, Sato M, Hock JM. Anabolic and catabolic bone effects of human parathyroid hormone (1-34) are predicted by duration of hormone exposure. *Bone* 2003; **33**: 372-379

31 **Bauer W**, Aub JC, Albright F. Studies of calcium and phosphorus metabolism : V. A study of the bone trabeculae as a readily available reserve supply of calcium. *J Exp Med* 1929; **49**: 145-162

32 **Selye H**. On the stimulation of new bone-formation with parathyroid extract and irradiated ergosterol. *Endocrinology* 1932; **16**: 547-558

33 **Hock JM**, Gera I. Effects of continuous and intermittent administration and inhibition of resorption on the anabolic response of bone to parathyroid hormone. *J Bone Miner Res* 1992; **7**: 65-72

34 **Kulkarni NH**, Wei T, Kumar A, Dow ER, Stewart TR, Shou J, N'cho M, Sterchi DL, Gitter BD, Higgs RE, Halladay DL, Engler TA, Martin TJ, Bryant HU, Ma YL, Onyia JE. Changes in osteoblast, chondrocyte, and adipocyte lineages mediate the bone anabolic actions of PTH and small molecule GSK-3 inhibitor. *J Cell Biochem* 2007; **102**: 1504-1518

35 **Bukata SV**, Puzas JE. Orthopedic uses of teriparatide. *Curr Osteoporos Rep* 2010; **8**: 28-33

36 **Aleksyniene R**, Thomsen JS, Eckardt H, Bundgaard KG, Lind M, Hvid I. Parathyroid hormone PTH(1-34) increases the volume, mineral content, and mechanical properties of regenerated mineralizing tissue after distraction osteogenesis in rabbits. *Acta Orthop* 2009; **80**: 716-723

37 **Seebach C**, Skripitz R, Andreassen TT, Aspenberg P. Intermittent parathyroid hormone (1-34) enhances mechanical strength and density of new bone after distraction osteogenesis in rats. *J Orthop Res* 2004; **22**: 472-478

38 **Holzer G**, Majeska RJ, Lundy MW, Hartke JR, Einhorn TA. Parathyroid hormone enhances fracture healing. A preliminary report. *Clin Orthop Relat Res* 1999; 258-263

39 **Andreassen TT**, Ejersted C, Oxlund H. Intermittent parathyroid hormone (1-34) treatment increases callus formation and mechanical strength of healing rat fractures. *J Bone Miner Res* 1999; **14**: 960-968

40 **Andreassen TT**, Fledelius C, Ejersted C, Oxlund H. Increases in callus formation and mechanical strength of healing fractures in old rats treated with parathyroid hormone. *Acta Orthop Scand* 2001; **72**: 304-307

41 **Alkhiary YM**, Gerstenfeld LC, Krall E, Westmore M, Sato M, Mitlak BH, Einhorn TA. Enhancement of experimental fracture-healing by systemic administration of recombinant human parathyroid hormone (PTH 1-34). *J Bone Joint Surg Am* 2005; **87**: 731-741

42 **Barnes GL**, Kakar S, Vora S, Morgan EF, Gerstenfeld LC, Einhorn TA. Stimulation of fracture-healing with systemic intermittent parathyroid hormone treatment. *J Bone Joint Surg Am* 2008; **90** Suppl 1: 120-127

43 **Skripitz R**, Andreassen TT, Aspenberg P. Strong effect of PTH (1-34) on regenerating bone: a time sequence study in rats. *Acta Orthop Scand* 2000; **71**: 619-624

44 **Skripitz R**, Aspenberg P. Implant fixation enhanced by intermittent treatment with parathyroid hormone. *J Bone Joint Surg Br* 2001; **83**: 437-440

45 **Kim HW**, Jahng JS. Effect of intermittent administration of parathyroid hormone on fracture healing in ovariectomized rats. *Iowa Orthop J* 1999; **19**: 71-77

46 **Verhaar HJ**, Lems WF. PTH analogues and osteoporotic fractures. *Expert Opin Biol Ther* 2010; **10**: 1387-1394

47 **Dempster DW**, Cosman F, Kurland ES, Zhou H, Nieves J, Woelfert L, Shane E, Plavetić K, Müller R, Bilezikian J, Lindsay R. Effects of daily treatment with parathyroid hormone on bone microarchitecture and turnover in patients with osteoporosis: a paired biopsy study. *J Bone Miner Res* 2001; **16**: 1846-1853

48 **Dobnig H**, Turner RT. Evidence that intermittent treatment with parathyroid hormone increases bone formation in adult rats by activation of bone lining cells. *Endocrinology* 1995; **136**: 3632-3638

49 **Cosman F**, Nieves J, Woelfert L, Formica C, Gordon S, Shen V, Lindsay R. Parathyroid hormone added to established hormone therapy: effects on vertebral fracture and maintenance of bone mass after parathyroid hormone withdrawal. *J Bone Miner Res* 2001; **16**: 925-931

50 **Cosman F**, Lindsay R. Therapeutic potential of parathyroid hormone. *Curr Osteoporos Rep* 2004; **2**: 5-11

51 **Frolik CA**, Cain RL, Sato M, Harvey AK, Chandrasekhar S, Black EC, Tashjian AH, Hock JM. Comparison of recombinant human PTH(1-34) (LY333334) with a C-terminally substituted analog of human PTH-related protein(1-34) (RS-66271): In vitro activity and in vivo pharmacological effects in rats. *J Bone Miner Res* 1999; **14**: 163-172

52 **Lindsay R**, Zhou H, Cosman F, Nieves J, Dempster DW, Hodsman AB. Effects of a one-month treatment with PTH(1-34) on bone formation on cancellous, endocortical, and periosteal surfaces of the human ilium. *J Bone Miner Res* 2007; **22**: 495-502

53 **Jiang Y**, Zhao J, Liao EY, Dai RC, Wu XP, Genant HK. Application of micro-CT assessment of 3-D bone microstructure in preclinical and clinical studies. *J Bone Miner Metab* 2005; **23** Suppl: 122-131

54 **Kurland ES**, Cosman F, McMahon DJ, Rosen CJ, Lindsay

R, Bilezikian JP. Parathyroid hormone as a therapy for idiopathic osteoporosis in men: effects on bone mineral density and bone markers. *J Clin Endocrinol Metab* 2000; **85**: 3069-3076
55 **Rodan GA**, Martin TJ. Therapeutic approaches to bone diseases. *Science* 2000; **289**: 1508-1514
56 **Bauer DC**, Garnero P, Bilezikian JP, Greenspan SL, Ensrud KE, Rosen CJ, Palermo L, Black DM. Short-term changes in bone turnover markers and bone mineral density response to parathyroid hormone in postmenopausal women with osteoporosis. *J Clin Endocrinol Metab* 2006; **91**: 1370-1375
57 **Cosman F**, Lindsay R. Is parathyroid hormone a therapeutic option for osteoporosis? A review of the clinical evidence. *Calcif Tissue Int* 1998; **62**: 475-480
58 **Cosman F**, Nieves J, Woelfert L, Gordon S, Shen V, Lindsay R. Parathyroid responsivity in postmenopausal women with osteoporosis during treatment with parathyroid hormone. *J Clin Endocrinol Metab* 1998; **83**: 788-790
59 **Cosman F**, Nieves J, Woelfert L, Shen V, Lindsay R. Alendronate does not block the anabolic effect of PTH in postmenopausal osteoporotic women. *J Bone Miner Res* 1998; **13**: 1051-1055
60 **Misof BM**, Roschger P, Cosman F, Kurland ES, Tesch W, Messmer P, Dempster DW, Nieves J, Shane E, Fratzl P, Klaushofer K, Bilezikian J, Lindsay R. Effects of intermittent parathyroid hormone administration on bone mineralization density in iliac crest biopsies from patients with osteoporosis: a paired study before and after treatment. *J Clin Endocrinol Metab* 2003; **88**: 1150-1156
61 **Zhou H**, Iida-Klein A, Lu SS, Ducayen-Knowles M, Levine LR, Dempster DW, Lindsay R. Anabolic action of parathyroid hormone on cortical and cancellous bone differs between axial and appendicular skeletal sites in mice. *Bone* 2003; **32**: 513-520
62 **Gesty-Palmer D**, Flannery P, Yuan L, Corsino L, Spurney R, Lefkowitz RJ, Luttrell LM. A beta-arrestin-biased agonist of the parathyroid hormone receptor (PTH1R) promotes bone formation independent of G protein activation. *Sci Transl Med* 2009; **1**: 1ra1
63 **Luttrell LM**, Gesty-Palmer D. Beyond desensitization: physiological relevance of arrestin-dependent signaling. *Pharmacol Rev* 2010; **62**: 305-330
64 **Hock JM**, Fitzpatrick LA, Bilezikian JP. Actions of Parathyroid Hormone. In: Bilezikian JP, Raisz LG, Rodan GA, editors. Principles of Bone Biology. 2nd ed. San Diego: Academic Press, 2002: 463-482
65 **Alves de Oliveira EC**, Szejnfeld VL, Pereira da Silva N, Coelho Andrade LE, Heldan de Moura Castro C. Intermittent PTH1-34 causes DNA and chromosome breaks in osteoblastic and nonosteoblastic cells. *Calcif Tissue Int* 2010; **87**: 424-436
66 **Rouleau MF**, Mitchell J, Goltzman D. Characterization of the major parathyroid hormone target cell in the endosteal metaphysis of rat long bones. *J Bone Miner Res* 1990; **5**: 1043-1053
67 **Rouleau MF**, Warshawsky H, Goltzman D. Parathyroid hormone binding in vivo to renal, hepatic, and skeletal tissues of the rat using a radioautographic approach. *Endocrinology* 1986; **118**: 919-931
68 **Kong XF**, Schipani E, Lanske B, Joun H, Karperien M, Defize LH, Jüppner H, Potts JT, Segre GV, Kronenberg HM. The rat, mouse, and human genes encoding the receptor for parathyroid hormone and parathyroid hormone-related peptide are highly homologous. *Biochem Biophys Res Commun* 1994; **201**: 1058
69 **Jüppner H**, Abou-Samra AB, Freeman M, Kong XF, Schipani E, Richards J, Kolakowski LF, Hock J, Potts JT, Kronenberg HM. A G protein-linked receptor for parathyroid hormone and parathyroid hormone-related peptide. *Science* 1991; **254**: 1024-1026
70 **Abou-Samra AB**, Jüppner H, Force T, Freeman MW, Kong XF, Schipani E, Urena P, Richards J, Bonventre JV, Potts JT. Expression cloning of a common receptor for parathyroid hormone and parathyroid hormone-related peptide from rat osteoblast-like cells: a single receptor stimulates intracellular accumulation of both cAMP and inositol trisphosphates and increases intracellular free calcium. *Proc Natl Acad Sci USA* 1992; **89**: 2732-2736
71 **Datta NS**, Abou-Samra AB. PTH and PTHrP signaling in osteoblasts. *Cell Signal* 2009; **21**: 1245-1254
72 **Datta NS**, Chen C, Berry JE, McCauley LK. PTHrP signaling targets cyclin D1 and induces osteoblastic cell growth arrest. *J Bone Miner Res* 2005; **20**: 1051-1064
73 **Datta NS**, Kolailat R, Fite A, Pettway G, Abou-Samra AB. Distinct roles for mitogen-activated protein kinase phosphatase-1 (MKP-1) and ERK-MAPK in PTH1R signaling during osteoblast proliferation and differentiation. *Cell Signal* 2010; **22**: 457-466
74 **Datta NS**, Pettway GJ, Chen C, Koh AJ, McCauley LK. Cyclin D1 as a target for the proliferative effects of PTH and PTHrP in early osteoblastic cells. *J Bone Miner Res* 2007; **22**: 951-964
75 **Datta NS**, Samra TA, Mahalingam CD, Datta T, Abou-Samra AB. Role of PTH1R internalization in osteoblasts and bone mass using a phosphorylation-deficient knock-in mouse model. *J Endocrinol* 2010; **207**: 355-365
76 **Guo J**, Liu M, Yang D, Bouxsein ML, Thomas CC, Schipani E, Bringhurst FR, Kronenberg HM. Phospholipase C signaling via the parathyroid hormone (PTH)/PTH-related peptide receptor is essential for normal bone responses to PTH. *Endocrinology* 2010; **151**: 3502-3513
77 **Sabbieti MG**, Agas D, Xiao L, Marchetti L, Coffin JD, Doetschman T, Hurley MM. Endogenous FGF-2 is critically important in PTH anabolic effects on bone. *J Cell Physiol* 2009; **219**: 143-151
78 **Miraoui H**, Marie PJ. Fibroblast growth factor receptor signaling crosstalk in skeletogenesis. *Sci Signal* 2010; **3**: re9
79 **Jilka RL**. Molecular and cellular mechanisms of the anabolic effect of intermittent PTH. *Bone* 2007; **40**: 1434-1446
80 **Yamashita J**, Datta NS, Chun YH, Yang DY, Carey AA, Kreider JM, Goldstein SA, McCauley LK. Role of Bcl2 in osteoclastogenesis and PTH anabolic actions in bone. *J Bone Miner Res* 2008; **23**: 621-632
81 **Herrmann-Erlee MP**, Heersche JN, Hekkelman JW, Gaillard PJ, Tregear GW, Parsons JA, Potts JT. Effects of bone in vitro of bovine parathyroid hormone and synthetic fragments representing residues 1-34, 2-34 and 3-34. *Endocr Res Commun* 1976; **3**: 21-35
82 **DeBartolo TF**, Pegg LE, Shasserre C, Hahn TJ. Comparison of parathyroid hormone and calcium ionophore A23187 effects on bone resorption and nucleic acid synthesis in cultured fetal rat bone. *Calcif Tissue Int* 1982; **34**: 495-500
83 **MacDonald BR**, Gallagher JA, Russell RG. Parathyroid hormone stimulates the proliferation of cells derived from human bone. *Endocrinology* 1986; **118**: 2445-2449
84 **Canalis E**, Centrella M, Burch W, McCarthy TL. Insulin-like growth factor I mediates selective anabolic effects of parathyroid hormone in bone cultures. *J Clin Invest* 1989; **83**: 60-65
85 **Nishida S**, Yamaguchi A, Tanizawa T, Endo N, Mashiba T, Uchiyama Y, Suda T, Yoshiki S, Takahashi HE. Increased bone formation by intermittent parathyroid hormone administration is due to the stimulation of proliferation and differentiation of osteoprogenitor cells in bone marrow. *Bone* 1994; **15**: 717-723
86 **Partridge NC**, Li X, Qin L. Understanding parathyroid hormone action. *Ann N Y Acad Sci* 2006; **1068**: 187-193
87 **Pettway GJ**, Meganck JA, Koh AJ, Keller ET, Goldstein SA, McCauley LK. Parathyroid hormone mediates bone growth through the regulation of osteoblast proliferation and differentiation. *Bone* 2008; **42**: 806-818
88 **Jilka RL**, Weinstein RS, Bellido T, Roberson P, Parfitt AM,

Manolagas SC. Increased bone formation by prevention of osteoblast apoptosis with parathyroid hormone. *J Clin Invest* 1999; **104**: 439-446
89 **Manolagas SC**. Birth and death of bone cells: basic regulatory mechanisms and implications for the pathogenesis and treatment of osteoporosis. *Endocr Rev* 2000; **21**: 115-137
90 **Leaffer D**, Sweeney M, Kellerman LA, Avnur Z, Krstenansky JL, Vickery BH, Caulfield JP. Modulation of osteogenic cell ultrastructure by RS-23581, an analog of human parathyroid hormone (PTH)-related peptide-(1-34), and bovine PTH-(1-34). *Endocrinology* 1995; **136**: 3624-3631
91 **van der Plas A**, Nijweide PJ. Cell-cell interactions in the osteogenic compartment of bone. *Bone* 1988; **9**: 107-111
92 **Bikle DD**, Sakata T, Leary C, Elalieh H, Ginzinger D, Rosen CJ, Beamer W, Majumdar S, Halloran BP. Insulin-like growth factor I is required for the anabolic actions of parathyroid hormone on mouse bone. *J Bone Miner Res* 2002; **17**: 1570-1578
93 **Sowa H**, Kaji H, Iu MF, Tsukamoto T, Sugimoto T, Chihara K. Parathyroid hormone-Smad3 axis exerts anti-apoptotic action and augments anabolic action of transforming growth factor beta in osteoblasts. *J Biol Chem* 2003; **278**: 52240-52252
94 **Tyson DR**, Swarthout JT, Jefcoat SC, Partridge NC. PTH induction of transcriptional activity of the cAMP response element-binding protein requires the serine 129 site and glycogen synthase kinase-3 activity, but not casein kinase II sites. *Endocrinology* 2002; **143**: 674-682
95 **McCauley LK**, Koh-Paige AJ, Chen H, Chen C, Ontiveros C, Irwin R, McCabe LR. Parathyroid hormone stimulates fra-2 expression in osteoblastic cells in vitro and in vivo. *Endocrinology* 2001; **142**: 1975-1981
96 **Krishnan V**, Moore TL, Ma YL, Helvering LM, Frolik CA, Valasek KM, Ducy P, Geiser AG. Parathyroid hormone bone anabolic action requires Cbfa1/Runx2-dependent signaling. *Mol Endocrinol* 2003; **17**: 423-435
97 **Scott DK**, Brakenhoff KD, Clohisy JC, Quinn CO, Partridge NC. Parathyroid hormone induces transcription of collagenase in rat osteoblastic cells by a mechanism using cyclic adenosine 3′,5′-monophosphate and requiring protein synthesis. *Mol Endocrinol* 1992; **6**: 2153-2159
98 **Chiusaroli R**, Maier A, Knight MC, Byrne M, Calvi LM, Baron R, Krane SM, Schipani E. Collagenase cleavage of type I collagen is essential for both basal and parathyroid hormone (PTH)/PTH-related peptide receptor-induced osteoclast activation and has differential effects on discrete bone compartments. *Endocrinology* 2003; **144**: 4106-4116
99 **Chen C**, Koh AJ, Datta NS, Zhang J, Keller ET, Xiao G, Franceschi RT, D'Silva NJ, McCauley LK. Impact of the mitogen-activated protein kinase pathway on parathyroid hormone-related protein actions in osteoblasts. *J Biol Chem* 2004; **279**: 29121-29129
100 **Raggatt LJ**, Qin L, Tamasi J, Jefcoat SC, Shimizu E, Selvamurugan N, Liew FY, Bevelock L, Feyen JH, Partridge NC. Interleukin-18 is regulated by parathyroid hormone and is required for its bone anabolic actions. *J Biol Chem* 2008; **283**: 6790-6798
101 **Weir EC**, Lowik CW, Paliwal I, Insogna KL. Colony stimulating factor-1 plays a role in osteoclast formation and function in bone resorption induced by parathyroid hormone and parathyroid hormone-related protein. *J Bone Miner Res* 1996; **11**: 1474-1481
102 **Allan EH**, Häusler KD, Wei T, Gooi JH, Quinn JM, Crimeen-Irwin B, Pompolo S, Sims NA, Gillespie MT, Onyia JE, Martin TJ. EphrinB2 regulation by PTH and PTHrP revealed by molecular profiling in differentiating osteoblasts. *J Bone Miner Res* 2008; **23**: 1170-1181
103 **Onishi T**, Zhang W, Cao X, Hruska K. The mitogenic effect of parathyroid hormone is associated with E2F-dependent activation of cyclin-dependent kinase 1 (cdc2) in osteoblast precursors. *J Bone Miner Res* 1997; **12**: 1596-1605
104 **Onyia JE**, Miller B, Hulman J, Liang J, Galvin R, Frolik C, Chandrasekhar S, Harvey AK, Bidwell J, Herring J, Hock JM. Proliferating cells in the primary spongiosa express osteoblastic phenotype in vitro. *Bone* 1997; **20**: 93-100
105 **Drake MT**, Srinivasan B, Mödder UI, Ng AC, Undale AH, Roforth MM, Peterson JM, McCready LK, Riggs BL, Khosla S. Effects of intermittent parathyroid hormone treatment on osteoprogenitor cells in postmenopausal women. *Bone* 2011; **49**: 349-355
106 **Kanakaris NK**, Giannoudis PV. The health economics of the treatment of long-bone non-unions. *Injury* 2007; **38** Suppl 2: S77-S84
107 **Honig S**. Osteoporosis - new treatments and updates. *Bull NYU Hosp Jt Dis* 2010; **68**: 166-170
108 **Silva BC**, Bilezikian JP. New approaches to the treatment of osteoporosis. *Annu Rev Med* 2011; **62**: 307-322
109 **Salari Sharif P**, Abdollahi M, Larijani B. Current, new and future treatments of osteoporosis. *Rheumatol Int* 2011; **31**: 289-300

S- Editor Lv S **L- Editor** Hughes D **E- Editor** Zheng XM

World Journal of Orthopedics

Online Submissions: http://www.wjgnet.com/2218-5836office
wjo@wjgnet.com
doi:10.5312/wjo.v2.i8.75

World J Orthop 2011 August 18; 2(8): 75-84
ISSN 2218-5836 (online)

REVIEW

Imaging of the anterior cruciate ligament

Wing Hung Alex Ng, James Francis Griffith, Esther Hiu Yee Hung, Bhawan Paunipagar, Billy Kan Yip Law, Patrick Shu Hang Yung

Wing Hung Alex Ng, James Francis Griffith, Esther Hiu Yee Hung, Bhawan Paunipagar, Department of Imaging and Interventional Radiology, Prince of Wales Hospital, Chinese University of Hong Kong, Hong Kong, China
Billy Kan Yip Law, Patrick Shu Hang Yung, Department of Orthopedics and Traumatology, Prince of Wales Hospital, Chinese University of Hong Kong, Hong Kong, China
Author contributions: Ng WHA and Griffith JF contributed equally to this work; Ng WHA and Griffith JF designed the research; Ng WHA, Griffith JF, Hung EHY and Paunipagar B collected the images; Ng WHA, Griffith JF, Hung EHY, Paunipagar B, Law BKY and Yung PSH wrote the paper.
Supported by A grant from the Research Grants Council of the Hong Kong Special Administrative Region, China, Project No. SEG_CUHK02
Correspondence to: Wing Hung Alex Ng, MBchB, FRCR, Department of Imaging and Interventional Radiology, Prince of Wales Hospital, Chinese University of Hong Kong, Hong Kong, China. alex@sunghim.com
Telephone: +852-26321248 Fax: +852-26324122
Received: April 20, 2011 Revised: June 5, 2011
Accepted: June 12, 2011
Published online: August 18, 2011

Abstract

The anterior cruciate ligament (ACL) is an important structure in maintaining the normal biomechanics of the knee and is the most commonly injured knee ligament. However, the oblique course of the ACL within the intercondylar fossa limits the visualization and assessment of the pathology of the ligament. This pictorial essay provides a comprehensive and illustrative review of the anatomy and biomechanics as well as updated information on different modalities of radiological investigation of ACL, particularly magnetic resonance imaging.

Key words: Magnetic resonance; Knee; Anterior cruciate ligament; Tear

Peer reviewers: Naiquan Nigel Zheng, Professor, Mechanical Engineering, University of North Carolina, 9201 University City Blvd, Charlotte, NC 28223, United States; John J Elias, PhD, Calhoun Research Laboratory, Akron General Medical Center, 400 Wabash Ave, Akron, OH 44307, United States; Eduardo Magalhães, PT, MD, Eduardo Magalhães Institute, Domingos de M oraes street, n° 2243, room 56, São Paulo 04035-000, Brazil

Ng WHA, Griffith JF, Hung EHY, Paunipagar B, Law KYB, Yung SHP. Imaging of the anterior cruciate ligament. *World J Orthop* 2011; 2(8): 75-84 Available from: URL: http://www.wjgnet.com/2218-5836/full/v2/i8/75.htm DOI: http://dx.doi.org/10.5312/wjo.v2.i8.75

ANATOMY

The anterior cruciate ligament (ACL) runs in an oblique course from the tibia to the lateral femoral condyle. It is an intra-articular extrasynovial ligament composed of fibres running from the anterior intercondylar region of the proximal tibia to the medial aspect of the lateral femoral condyle within the intercondylar groove. The fibres of the ACL are arranged into two bundles known as the anteromedial and posterolateral bundle according to their tibial insertion[1]. The anteromedial bundle inserts at a more medial and superior aspect of the lateral femoral condyle while the posterolateral bundle inserts at a more lateral and distal aspect of the lateral femoral condyle. Occasionally there is an additional intermediate bundle in between these two bundles[2,3]. The whole ACL measures approximately 38 mm in length and 11 mm in width[4]. The anteromedial bundle is 36.9 ± 2.9 mm in length, while the posterolateral bundle is 20.5 ± 2.5 mm in length. Both bundles are similar in size, with an average width of 5.0 ± 0.7 mm and 5.3 ± 0.7 mm in the mid-substance[5].

INJURY MECHANISMS

The ACL resists anterior tibial translation during extension and provides rotational stability[6-8]. The anteromedial bundle is taut when the knee is flexed and the posterolateral bundle is taut when the knee is extended[3]. The anteromedial bundle is longest in flexion and may be the primary component that resists anterior displacement of the tibia in flexion. The posterolateral bundle seems primarily to resist anterior tibial translation in extension and also contributes to rotatory stability of the knee joint[8] being employed in the "screw home" phenomenon i.e. during terminal extension of the knee, the tibia externally rotates relative to the femur serving to "lock" the knee in extension. The anteromedial and posterolateral bundles stabilize the knee joint in response to anterior tibial loads and combined rotatory loads in a synergistic way[9].

ACL tears may be partial or complete. Partial tears can range from a minor tear involving just a few fibres to a high grade near-complete tear involving almost all of the ACL fibres. A partial tear can involve both or only a single bundle to varying degree. Sometimes plastic deformity of the ACL without fibre discontinuity can occur causing ACL insufficiency[10].

The mechanism of the ACL injury includes internal rotation of the tibia relative to the femur. This commonly occurs during falls while skiing, as well as in contact sports such as football. With valgus stress, the medial femorotibial joint compartment is distracted producing medial collateral injury and medial meniscal injury (O' Donoghue's triad). Another mechanism of ACL injury is hyperextension such as occurs during jumping or high kick maneuvers and will lead to contra-coup bone contusion on the anterior tibia and femoral condyle. ACL tears resulting from hyperextension frequently occur without concomitant collateral ligament or meniscal injury[11]. The third mechanism is external rotation of the tibia relative to the femur with varus stress leading to impaction and bone oedema medially and distraction laterally resulting in avulsion of the lateral tibial rim (Segond fracture) and tear of the lateral collateral ligament.

The majority of the ACL injuries can be diagnosed by history and clinical examination. The anterior drawer test, Lachman test and pivot shift test are the most commonly applied clinical tests to diagnose ACL tear though they do rely both on the experience of the clinician and the degree of patient cooperation. In chronic ACL insufficiency, the pivot shift test has reported high sensitivities for detecting the ACL injury ranging from 84% to 98.4%. The test's specificity has been shown to vary more widely, with reported values from as low as 35% in the alert patient to as high as 98.4% in the anesthetized patient[12]. Anterior drawer and Lachman tests have similar sensitivity but lower specificity. However, in acute injury, if the patient is in pain or swelling, the examination may be limited and the sensitivity and specificity of the clinical tests are limited[12]. Association injury such as meniscal tear or chondral injury may also limit a full clinical examination.

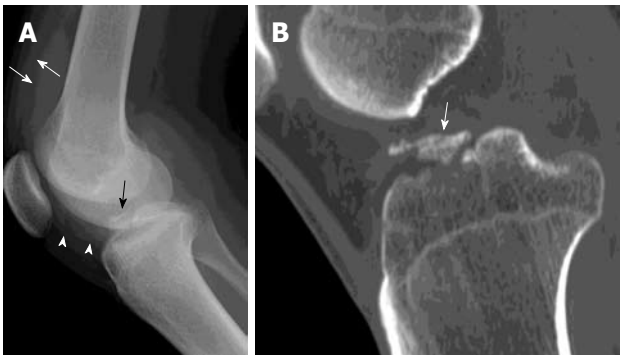


Figure 1 Avulsion fracture of tibial spine. A 20-year-old man suffered knee injury during a football match. A: Lateral radiograph of the knee shows a displaced avulsion fracture of the anterior cruciate ligament (black arrow) at the anterior intercondylar eminence of tibia. The fracture fragment is completely elevated from the native bone. Increased soft tissue opacity in the suprapatellar pouch (white arrows) and infrapatellar pouch (white arrowheads) is in keeping with haemarthrosis; B: Reformatted sagittal computed tomography image of the same patient through the mid tibial plateau shows a displaced avulsion fracture of the tibial intercondylar eminence (white arrow).

As a result, magnetic resonance imaging (MRI) is helpful in the assessment of suspected ACL injury.

Most ACL tears (approximately 80%) are complete, occurring around the middle one-third of the ACL (90%) or less frequently close to the femoral (7%) or tibial (3%) attachments. Less frequently (approximately 20%), ACL tears are incomplete with partial disruption of the ACL fibres[13]. Partial tears may involve only one or both bundles to a varying degree though the anteromedial band does tend to be the more commonly affected. Imaging, and in particular MRI, is very helpful in the assessment of suspected ACL injury.

Radiography

Radiographs have limited value in the diagnosis of acute ACL injury. Findings are indirect and limited to bone abnormalities. On radiography, there are several indirect signs that could raise suspicion of underlying ACL injury. Avulsion fracture of ACL at the tibial insertion or femoral origin can be found on radiographs but is better defined by computed tomography (CT)[14,15] (Figure 1A and B). Avulsion fracture of lateral tibial rim (Segond fracture) (Figure 2) is commonly associated with an ACL tear[16-18] and is classically due to avulsion fracture of the iliotibial band though the term has also been applied when there is avulsion of the fibular collateral ligament or biceps femoris tendon[15,17-19].

Osteochondral impaction fracture may very occasionally be seen in the condylopatellar sulcus of the lateral femoral condyle (lateral femoral notch sign) (Figure 3A). A sulcus deeper than 1.5 mm is a fairly specific though very insensitive indirect radiographic sign of a torn ACL[20] (Figure 3B). Haemarthrosis is very common in ACL tears and is seen as increased opacity in the suprapatellar pouch or even with fat fluid level (lipohemarthrosis) if associated with bone fracture (Figure 1A).

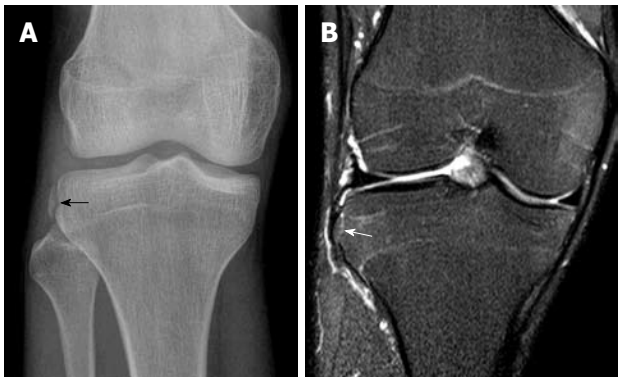


Figure 2 Segond fracture. A 30-year-old man suffered knee injury during a basketball match. A: Frontal radiograph of the right knee shows an avulsion fracture fragment at the lateral tibial rim (black arrow) compatible with Segond fracture. This fracture is frequently associated with a torn anterior cruciate ligament which also happened in this patient (not shown); B: A coronal T2-weighted fat suppression magnetic resonance image of the same patient. Corresponding site reveals a minimally displaced Segond fracture (white arrow) which may be easily missed in this patient with no significant bone bruise or oedema.

Computed tomography

Although the ACL can be visualized on CT, its visibility is impaired in the presence of haemarthrosis and most patients with ACL injury are evaluated by MRI since this is also best for detecting concomitant menisceal, ligamentous or chondral injuries. If ACL avulsion injury is seen by radiography, CT is helpful in determining the size, and comminution of the avulsion bone fragment (Figure 1B) with three-dimensional CT allowing better fracture depiction. CT arthrography can be performed and has a comparable accuracy to MRI in the detection of both cruciate injury as well as menisceal injury[21].

Magnetic resonance imaging

MR sequences applied for optimal visualization of the ACL are 2D fast spin echo sequences either with or without fat suppression. Different planes are used for anatomical correlation. In most centres, the sequences used to visualize ACL include Turbo spin echo (TSE) sagittal intermediate weighted sequence either with fat suppression and non-fat suppression, TSE coronal T2 weighted fat suppression sequence and TSE axial intermediate weighted with fat-suppression sequence. In our centre, the standard knee protocol comprises the following three sequences (Figure 4A-C): (1) Coronal T2 weighted fat suppressed sequence; (2) TSE sagittal intermediate weighted sequence; and (3) TSE axial intermediate weighted with fat-suppression sequence.

Additional sequences comprise oblique views, flexion views, T1-weighted sequences and small FOV or small coil images when necessary. T1-weighted sequences are useful for suspected fracture or characterizing loose bodies within the knee as any osseous fragments may contain a central marrow component. Small field of view sequences with the small coil placed directly over the area of interest are helpful at delineating peripheral pathology around the knee[22]. Oblique views are helpful in determining the presence, severity and location of ACL tears and will be discussed later.

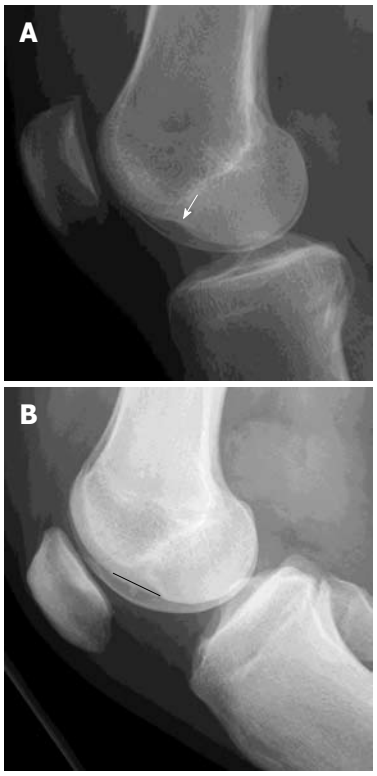


Figure 3 Osteochondral injury lateral femoral condyle. Lateral radiographs of two patients with complete anterior cruciate ligament (ACL) tear. A: Deep notch sign is abnormal deepening of the condylofemoral sulcus larger than 1.5 mm (white arrow); B: Long notch sign is abnormal lengthening of the condylofemoral sulcus (black straight line). These two signs are suggestive of osteochondral fracture of the lateral femoral condyle and highly associated with ACL tear though these are not very common findings.

MR images of the knees in flexion can provide more space around the ACL within the intercondylar area, helping to decrease volume-averaging artifact and thereby allowing better visualization of the femoral end of the ligament[23,24]. Recently 3D fast spin echo imaging with or without suppression has been shown to have the same diagnostic accuracy as 2D sequences. This can decrease volume averaging artifacts and shorten overall MR examination time[25].

The normal ACL should have a taut, low to intermediate signal intensity with continuous fibres in all planes and sequences. It courses parallel or steeper than the intercondylar line. The PL bundle usually has higher signal intensity than the AM bundle.

MRI is highly accurate at diagnosing ACL tears with accuracy, sensitivity and specificity of more than 90%[26-28].

Diagnosis of ACL tear on MR images is usually based on direct signs[26,28,29].

The primary sign of ACL tear is fibre discontinuity (Figure 5A). The oblique sagittal plane is the most helpful in diagnosis supported by coronal and axial imaging. The empty notch sign on coronal imaging is a frequent finding in complete ACL tear[30]. In acute or subacute injury, thickening and oedema of the ACL is found character-

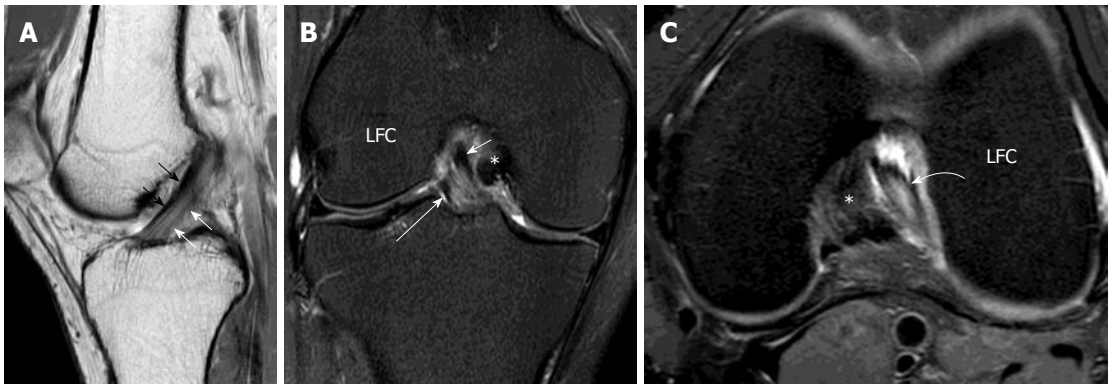


Figure 4 Normal anterior cruciate ligament. Volunteer, 24-year-old man with no history of injury and clinical instability. Sagittal intermediate-weighted magnetic resonance (MR) of the knee. A: Demonstrates a normal anterior cruciate ligament (ACL) which is characterized by a taut, continuous, low signal intensity fibres extending from the tibial plateau anteriorly to the medial aspect of the lateral femoral condyle. The more anterior portion of ACL is the anteromedial (AM) bundle (black arrows) while the more posterior portion is posterolateral (PL) bundle (white arrows). They cannot be well delineated from each other on this sagittal image. The PL bundle shows higher signal intensity than AM bundle. Coronal T2-weighted fat suppression MR knee image; B: The mid and distal ACL in the intercondylar fossa. The fibres are running superiorly and laterally within the intercondylar fossa from tibial attachment to the lateral femoral condyle (LFC). The more medial portion is the AM bundle (white short arrow) while the lateral portion is the PL bundle (white long arrow). Axial intermediate-weighted fat suppression MR image; C: Normal mid substance of ACL (curved white arrow). The ACL is elliptical in appearance because it is running obliquely to the scan plane. The two bundles cannot be differentiated from each other. *: Posterior cruciate ligament.

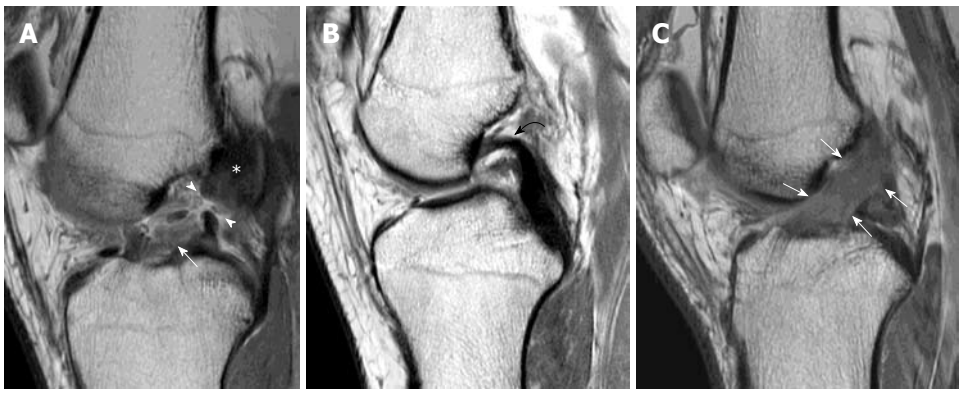


Figure 5 Primary signs of anterior cruciate ligament tear. Sagittal intermediate-weighted images of three different patients showing different patterns of anterior cruciate ligament (ACL) tear. A: Typical appearance of ACL tear at the mid-substance with fibres discontinuity of ACL (arrowheads). Residual stumps on femoral (asterisk) and tibial sides (white arrow) are lax, thickened and increased in signal intensity; B: Chronic ACL tear with absence of normal ACL fibres compatible with complete resorption of fibres. PCL (Curved black arrow); C: Acute high grade intrasubstance tear as characterized by thickening and oedematous change of ACL fibres which show increased signal intensity (white arrows). The fibres are still in continuity suggestive of partial ACL tear.

ized by increased signal intensity on T2 or intermediate-weighted sequences (Figure 5B). In chronic case the fibres can be completely absorbed (Figure 5C) or the residual ACL stump can become adherent to the synovial envelope covering the posterior cruciate ligament[31]. As the orientation of the ACL makes visualization of the entire ACL in one plane difficult, some authors advocate use of oblique planes either parallel or perpendicular to the ACL to increase ligament and tear conspicuity. Oblique coronal and sagittal views parallel to the ACL have been advocated and found to be effective in improving visualization of the ACL[32-34] (Figure 6A and B). We have initiated oblique axial imaging of the ACL and found it to very useful in allowing much clearer delineation of the two ACL bundles, and determining the presence, the location of the normal individual bundle anatomy[34] and possibly individual bundle involvement of partial tears (Figure 7A and B). A clear

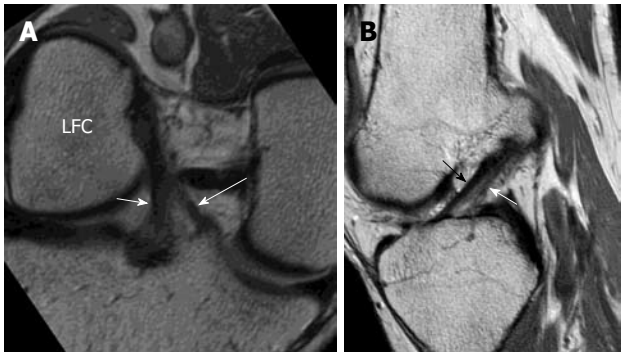


Figure 6 High resolution imaging normal anterior cruciate ligament in oblique coronal and oblique sagittal planes. Volunteer of a 31-year-old man with no history of injury and clinical instability. Note that the AM bundle (white long arrow) and PL bundle (white short arrow) can be well depicted on the oblique coronal image at the tibial attachment but not at the femoral attachment and not by the oblique sagittal image.

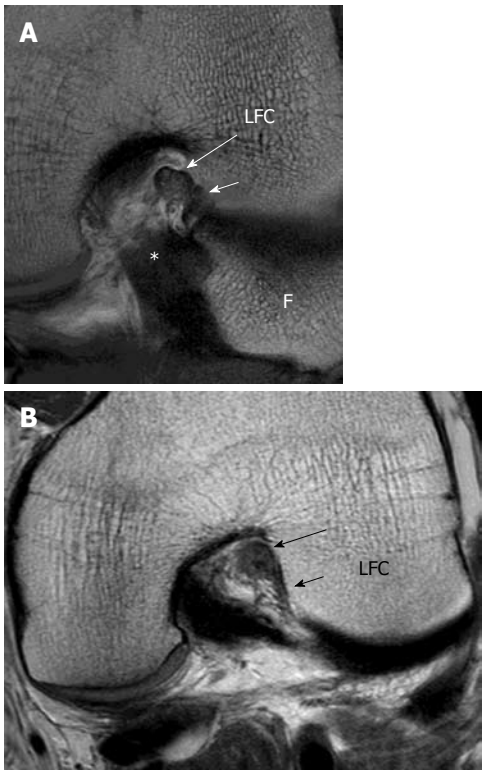


Figure 7 High resolution imaging anterior cruciate ligament in oblique axial plane. A: Oblique axial image can clearly delineate the two bundles and assess each bundle separately; AM bundle (long white arrow) PL bundle (short white arrow). B: Partial tear of the anterior cruciate ligament. Oblique axial image at the femoral side shows thickening and hyperintense signal intensity of the AM bundle (black long arrow) while fibres are absent in the region of the PL bundle (black short arrow). Features are compatible with high grade partial AM bundle tear and complete PL tear which were confirmed in arthroscopy. LFC: Lateral femoral condyle; *: Posterior cruciate ligament; F: Fibular head.

potential benefit of imaging in an oblique axial plane is that it allows the ACL to be visualized on 11-15 contiguous images rather than on 2-3 contiguous images as with oblique sagittal or coronal imaging.

Partial tears of the ACL are more difficult to diagnose than complete ACL tears. Partial tears are characterized by increased signal intensity and fiber laxity with increased concavity (or bowing) of the ACL (Figure 8). Continuous fibres are evident which suggest the tear is not complete. The sensitivity (40% to 75%) and specificity (51% to 89%) of MRI in the diagnosis of partial tears is poor[35,36] though this poor performance may be improved by the higher resolution afforded by 3T imaging. A recent study employing 3T MRI reported a sensitivity of 77% and specificity of 97% in detecting partial tears of the ACL[37]. If more than 50% of the ACL fibres are torn this would be considered a high grade tear, a medium grade tear is 10%-50% of fibres torn, while a low grade tear is less than 10% of fibres torn. The Holy Grail, with respect to imaging of partial ACL tears, would be to have sufficient resolution to determine whether there was a low, medium or high grade tear in each particular ACL bundle.

Potential pitfalls of MR in defining ACL tears are partial volume artifact and reparative fibrosis following an

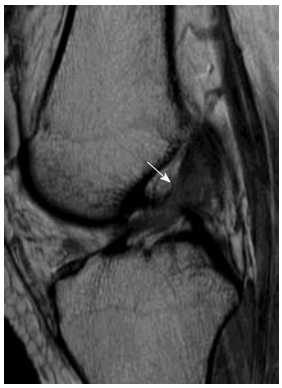


Figure 8 Partial tear of the anterior cruciate ligament. Sagittal intermediate-weighted image of partial anterior cruciate ligament (ACL) tear. The ACL appears lax, concave in appearance (white arrow) and increased in signal intensity. However, the fibres are still in continuity suggestive of partial ACL tear.

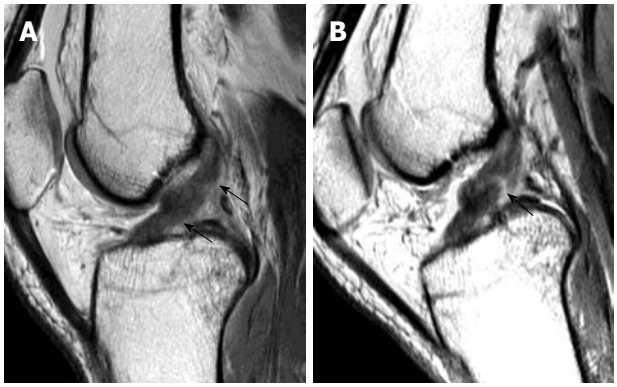


Figure 9 Magnetic resonance knee in partial flexion. Volunteer, 31-year-old man with no history of injury and clinical instability. Sagittal intermediate-weighted magnetic resonance image in full extension. A: And 30 degree of knee flexion; B: Demonstrates the usefulness of knee flexion. When the knee is extended, sagittal image shows features suspicious of an anterior cruciate ligament (ACL) tear. When the knee is flexed, a gap (black arrow) is clearly present confirming the presence of an ACL tear.

ACL injury bridging the residual ACL stump and adjacent structures, such as femoral notch, the posterior cruciate ligament (PCL) or the synovial envelope covering the PCL. This will help retain a near normal alignment of the ACL and may lead to an ACL appearing to be intact in the previous complete or partial tear. It is conceivable however that such a re-attached ACL may still remain functionally sound and this possibility should be consistently reported. Flexion imaging is particularly helpful in this situation as even 20 degrees of flexion helps change the orientation of central structures in the knee joint to such a degree that the ACL stump can be seen to be adherent to the PCL (Figure 9).

Bone bruising is very common in ACL tears. McCauley *et al*[27] suggested that the presence of bone bruising in the posterior aspect of the tibial plateau and posterior displacement of the posterior horn of the lateral meniscus are highly specific for a torn ACL. However, some authors found that secondary signs such as bone bruising do not help significantly in the diagnosis of ACL

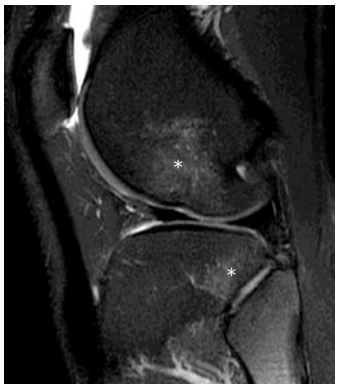


Figure 10 Bone bruises. A 26-year-old man suffered knee injury. Sagittal T2-weighted fat suppression magnetic resonance knee image shows that there are bone rises (asterisks) present in the mid-lateral femoral condyle and postero-lateral tibial plateau which indicate that the mechanism of injury is internal rotation of the tibia in valgus stress injury. This pattern of bone bruise has a high association of anterior cruciate ligament complete tear which is present in this patient (not shown).

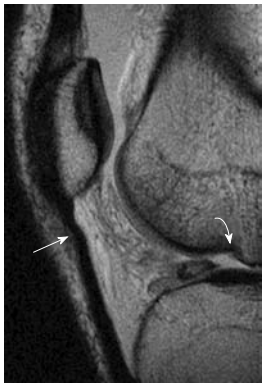


Figure 11 Patellar buckling sign and lateral femoral notch sign. A 37-year-old man who suffered knee injury. Osteochondral injury and patellar buckling sign. Sagittal intermediate-weighted magnetic resonance image demonstrates a deep depression of the middle portion of the lateral femoral condyle (curved white arrow). Normal condylopatellar sulcus should be smaller than 1.5 mm. Notch depth between 1 and 2 mm is suggestive and over 2 mm is diagnostic of anterior cruciate ligament tear. Buckling of proximal patellar tendon (white arrow) also indicates the underlying anterior cruciate ligament tear.

tears[37-39].

A bone bruise is commonly caused by internal rotation in valgus stress injury, where there is impaction of the posterior aspect of the tibial plateau against the mid or anterior portion of the femoral condyle[40] (Figure 10). This abnormal medullary signal intensity is attributed to subcortical microfracture, oedema, or haemorrhage[28,40]. In the case of anteromedial mechanism of injury or direct compression injuries, the bone bruise pattern is different, such as kissing bone oedema lesions or involving the posteromedial tibial plateau.

Bone bruising is a result of impaction at the time of injury. Particularly in young patients who most likely have more elasticity of their ACL fibres, it is distraction and impaction, particularly of the more central rather than posterior aspects of the condyles, that can occur even in the absence of an ACL tear. We would consider bone bruising to be a strong but not absolute indicator of ACL tear.

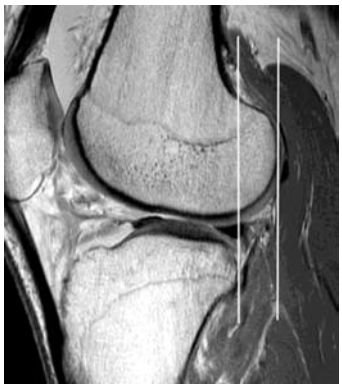


Figure 12 Uncovered posterior horn lateral meniscus and anterior tibial translation. A 32-year-old man who suffered knee injury. Sagittal intermediate-weighted magnetic resonance image of complete anterior cruciate ligament tear patient. The anterior displacement of the tibial translation is measured as the distance between two lines parallel to the picture frame (white lines). At the mid-sagittal plane of lateral femoral condyle, a line is drawn through the most posterior corner of the lateral tibial plateau, and the second line is tangent to the most posterior aspect of the lateral femoral condyle. Anterior tibial translation between 5 and 7 mm is suggestive and over 7 mm is diagnostic of anterior cruciate ligament tear. Note that the lateral meniscus also intersects the tangent to posterior margin of tibia and represents the uncovered posterior horn of lateral meniscus.

The deep lateral femoral notch sign, although uncommon, is quite specific for ACL tear and is due to impaction injury of the lateral femoral condyle onto the tibia[41] (Figure 11). A notch depth of over 2 mm is diagnostic of ACL tear. Segond fracture is due to avulsion fracture of the iliotibial band, fibular collateral ligament and biceps femoris tendon and can be seen on MRI examination (Figure 3B). Bosch-Bock bump relates to a bone excrescence located 2-5 mm below the lateral articular margin of the tibia. This bump indicates a chronic tear of the ACL.

Since the function of the ACL is to prevent anterior tibial translation in extension, ACL tear should increase the degree of anterior tibial translation during knee extension giving rise to "anterior tibial translocation"[41-43] (Figure 12). It is usually apparent on sagittal MR images at the mid-lateral femoral condyle. If there is $\geqslant$ 5 mm anterior translocator of the tibia relative to the femur, this would be indicative of ACL tear (sensitivity 86%, specificity 99%)[44] while an anterior tibial translation > 7 mm is fully diagnostic of ACL tear.

Femorotibial translation and rotation gives rise to a host of other signs which are all moderately suggestive of ACL injury such as buckling of the patellar tendon (Figure 11), buckling of the posterior cruciate ligament[45] (Figure 13), a posterior PCL line[41], uncovered posterior horn of the medial or lateral meniscus[30] (Figure 12) or visibility of the whole posterior cruciate ligament or lateral collateral ligament in one coronal image (Figure 14).

Shearing fat pad injury is also associated with ACL tear[29] and results in fracture of the infrapatellar fat pad (Figure 15).

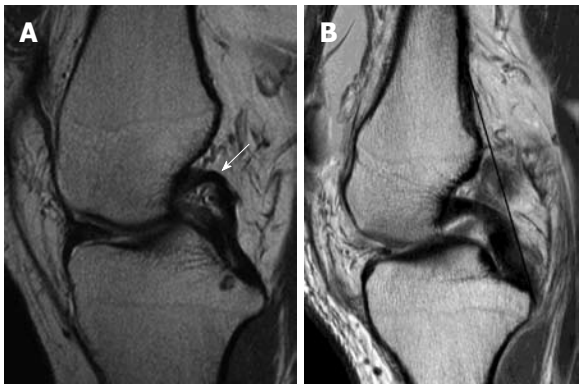


Figure 13 Posterior cruciate ligament buckling and Posterior cruciate ligament line sign. Sagittal intermediate-weighted magnetic resonance knee image of a completely torn anterior cruciate ligament. A: Posterior cruciate ligament (PCL) buckling sign. The PCL is considered to be hyperbuckled if any portion of its posterosuperior border is concave (white arrow); B: The PCL line sign. A line tangential to the posterior margin of the PCL is drawn (black line) and if this tangent does not intersect the posterior cortex of the femur within 5cm of its distal end, the PCL line is considered to be positive.

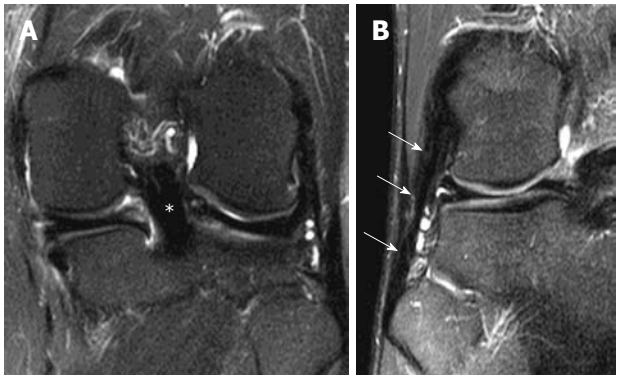


Figure 14 Coronal whole posterior cruciate ligament and lateral collateral ligament sign. Coronal T2-weighted fat suppression magnetic resonance knee images of two different patients with complete anterior cruciate ligament tear show that A: The entire posterior cruciate ligament (*); B: Entire lateral collateral ligament (white arrows) can be seen in a single coronal image.

ASSOCIATED INJURIES

Meniscal injury

Meniscal tear is commonly associated with ACL tear (65%-70%)[46]. Peripheral vertical tear in the posterior horn of lateral meniscus ("posterolateral corner tear") is highly associated with acute ACL tear[47,48] and easily overlooked[49] (Figure 16). Chronic ACL insufficiency or tear increases the incidence of peripheral vertical tear at the posterior horn of medial meniscus most likely related to chronic femorotibial instability[50]. Peripheral posterior horn tears accounted for more than half of meniscal tears seen in patients with acute or chronic ACL injuries[51]. Together with medial collateral ligament tear and ACL tear, these form the classical O'Donoghue's triad (Figure 17).

Posterolateral corner injury

Posterolateral corner injury needs to be addressed because of its contribution to tridimensional instability of the knee

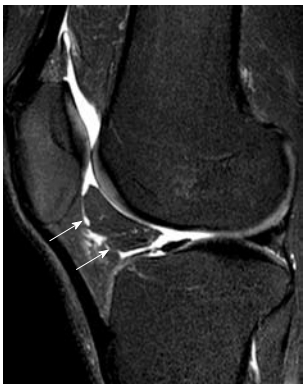


Figure 15 Shearing of fat pad. Sagittal T2-weighted fat suppression magnetic resonance image shows a fracture of Hoffa's fat pad that has isolated a segment of fat (white arrows).

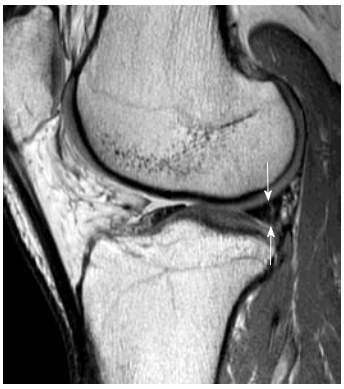


Figure 16 Peripheral vertical tear in a patient with complete anterior cruciate ligament tear. Sagittal intermediate-weighted magnetic resonance image demonstrates a peripheral vertical tear (white arrows) extending of the posterior horn of lateral meniscus. This kind of peripheral vertical tear can be easily missed and is frequently associated with anterior cruciate ligament tear.

(sagittal, frontal and rotational instability). Some of the studies suggest that ACL reconstruction without repair of the posterolateral corner injury increases the likelihood of instability and ACL re-tear[52]. Posterolateral corner injury includes the fibular collateral ligament, the popliteus muscle and tendon, the popliteofibular ligament, the lateral and posterolateral capsule and the biceps femoris tendon (Figure 18). The average length of fibular collateral ligament is 66 mm (59-74 mm) and the average thickness at the mid portion measures 3.4 mm (3-4 mm)[53]. The mean total length of the popliteus tendon was 42.0 mm[54]. The thickness of the popliteomeniscal ligament is variable. Peduto *et al*[55] found that in ten cadaveric knees, half of anteroinferior popliteomeniscal fascicle was $\geqslant$ 2 mm, the other half was smaller than 2 mm.

In general, these normally low-signal-intensity structures are defined as injured or sprained when there is thickening and intermediate signal intensity within the structure on fat-suppressed fast spin-echo T2-weighted images and as torn when the structure is discontinuous with a visible gap[52]. Some researchers support the use of a coronal oblique plane of imaging to improve visualization of some of the finer, obliquely oriented structures

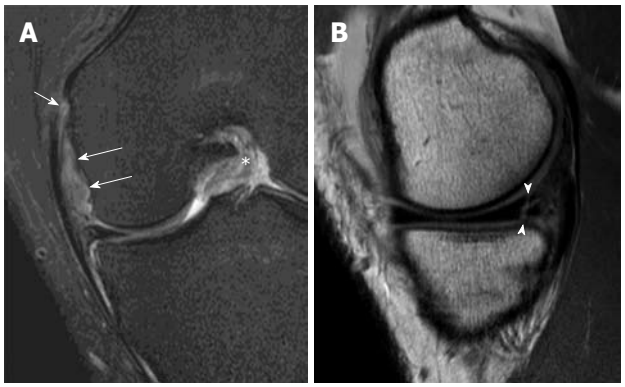


Figure 17 O' Donoghue's triad. Magnetic resonance images of a patient with complete anterior cruciate ligament (ACL) tear showing O' Donoghue's triad. A: Coronal T2-weighted fat suppression magnetic resonance (MR) image demonstrates complete tear of the meniscofemoral ligament (white long arrows) and femoral attachment of the medial collateral ligament (white short arrow). Note that the ACL in the intercondylar fossa has a substantial tear (asterisk); B: Sagittal intermediate-weighted MR image shows an associated vertical and horizontal (complex) peripheral tear at the posterior horn of medial meniscus (arrowheads). These injuries constitute the classical "O Donoghue's triad".

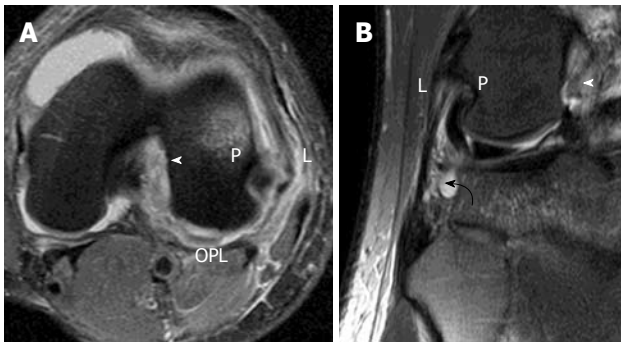


Figure 18 Posterolateral corner injury. A 25-year-old man suffered knee injury during a football match. A: Axial intermediate-weighted; B: Coronal T2-weighted fat suppression images of a patient with acute complete anterior cruciate ligament tear (white arrowhead). Oedema with thickening of the lateral collateral ligament and partial disruption of the fibres are present at the femoral origin (L). The posterior capsule and the oblique popliteal ligament (OPL) also show thickening and oedematous change. There is mild sprain of the femoral insertion of the popliteus tendon (P). The popliteofibular ligament is severely swollen and oedematous suggestive of high grade partial tear (curved black arrow).

of the posterolateral corner, including the popliteofibular, arcuate, and fabellofibular ligaments[56], although this has not become routine.

Ganglion cyst and mucoid degeneration of the ACL

Cystic degeneration of the ACL has been has been attributed to mucinous degeneration of connective tissue[57,58] or considered as intrasubstance ACL tear. On MR imaging, cystic degeneration can manifest as well-defined ganglion cysts arising from the ACL which occur in about 1% of patients[59] (Figure 19) or increased signal intensity of the whole ACL, giving rise to an appearance similar to a stalk of celery[60] (Figure 20). This increase in signal intensity is due to deposition of amorphous mucoid matrix among the ACL fibres, Clinical symptoms include pain,

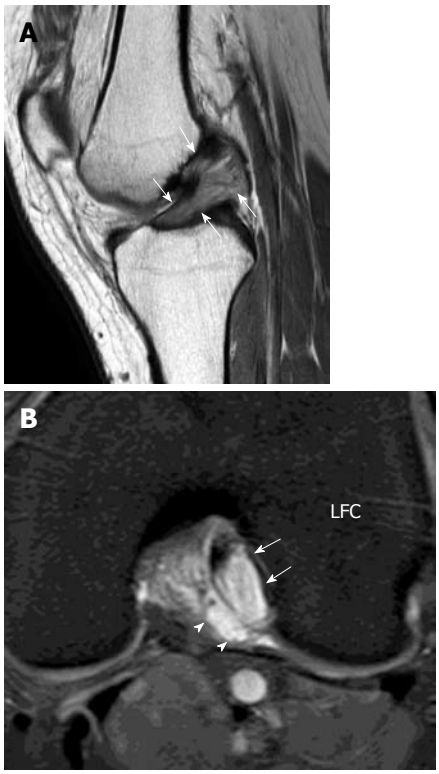


Figure 19 Celery stalk sign (mucoid degeneration). Sagittal intermediate-weighted magnetic resonance (MR) image. A: Enlargement of anterior cruciate ligament (ACL) (white arrows) with increased signal intensity compatible with mucoid degeneration. Low-signal-intensity fibres running parallel to the long axis of high signal ACL i.e. celery stalk sign; B: Axial intermediate-weighted fat suppression MR image shows cystic change within the ACL (white arrows) predominantly in the PL bundle. LFC: Lateral femoral condyle.

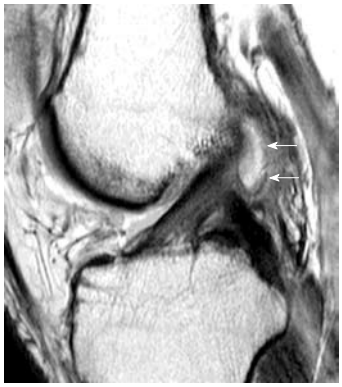


Figure 20 Pericruciate ganglion cyst. Sagittal intermediate-weighted MR image shows a ganglion cyst (white arrows) arising from proximal posterior half of ligament.

swelling symptoms and mechanical locking. ACL ganglion cysts and mucoid degeneration identified on MRI are usually not discernible at arthroscopy[58]. Since the ACL is surrounded by a synovial envelope, masses can arise from this synovium similar to synovium elsewhere. These synovial masses include focal nodular synovitis, pigmented villonodular synovitis, or gouty tophi. Other much less common synovial type masses include synovial vascular malformations[61] and synovial chondromatosis[62].

CONCLUSION

The ACL ligament is a very important ligament structurally and because it is so frequently injured. Imaging, and in particular, MRI has allowed a much more accurate assessment of ACL injuries and other conditions affecting the ACL as well as associated injuries. However, work still needs to be done to improve the accuracy with which partial tears can be diagnosed and located.

REFERENCES

1 **Yasuda K**, van Eck CF, Hoshino Y, Fu FH, Tashman S. Anatomic single- and double-bundle anterior cruciate ligament reconstruction, part 1: basic science. *Am J Sports Med* 2011; **39**: 1789-1799
2 **Norwood LA**, Cross MJ. Anterior cruciate ligament: functional anatomy of its bundles in rotatory instabilities. *Am J Sports Med* 1979; **7**: 23-26
3 **Amis AA**, Dawkins GP. Functional anatomy of the anterior cruciate ligament. Fibre bundle actions related to ligament replacements and injuries. *J Bone Joint Surg Br* 1991; **73**: 260-267
4 **Girgis FG**, Marshall JL, Monajem A. The cruciate ligaments of the knee joint. Anatomical, functional and experimental analysis. *Clin Orthop Relat Res* 1975; 216-231
5 **Cohen SB**, VanBeek C, Starman JS, Armfield D, Irrgang JJ, Fu FH. MRI measurement of the 2 bundles of the normal anterior cruciate ligament. *Orthopedics* 2009; **32**: 687
6 **Takai S**, Woo SL, Livesay GA, Adams DJ, Fu FH. Determination of the in situ loads on the human anterior cruciate ligament. *J Orthop Res* 1993; **11**: 686-695
7 **Sakane M**, Fox RJ, Woo SL, Livesay GA, Li G, Fu FH. In situ forces in the anterior cruciate ligament and its bundles in response to anterior tibial loads. *J Orthop Res* 1997; **15**: 285-293
8 **Gabriel MT**, Wong EK, Woo SL, Yagi M, Debski RE. Distribution of in situ forces in the anterior cruciate ligament in response to rotatory loads. *J Orthop Res* 2004; **22**: 85-89
9 **Zantop T**, Herbort M, Raschke MJ, Fu FH, Petersen W. The role of the anteromedial and posterolateral bundles of the anterior cruciate ligament in anterior tibial translation and internal rotation. *Am J Sports Med* 2007; **35**: 223-227
10 **Larson RL**. Prosthetic replacement of knee ligaments: Overview. In: Feagin JA, editor. The crucial ligaments: Diagnosis and treatment of ligamentous injuries about the knee. New York: Churchill Livingstone, 1988: 495-501
11 **Weber WN**, Neumann CH, Barakos JA, Petersen SA, Steinbach LS, Genant HK. Lateral tibial rim (Segond) fractures: MR imaging characteristics. *Radiology* 1991; **180**: 731-734
12 **Lubowitz JH**, Bernardini BJ, Reid JB. Current concepts review: comprehensive physical examination for instability of the knee. *Am J Sports Med* 2008; **36**: 577-594
13 **Vahey TN**, Broome DR, Kayes KJ, Shelbourne KD. Acute and chronic tears of the anterior cruciate ligament: differential features at MR imaging. *Radiology* 1991; **181**: 251-253
14 **Griffith JF**, Antonio GE, Tong CW, Ming CK. Cruciate ligament avulsion fractures. *Arthroscopy* 2004; **20**: 803-812
15 **Bales CP**, Guettler JH, Moorman CT. Anterior cruciate ligament injuries in children with open physes: evolving strategies of treatment. *Am J Sports Med* 2004; **32**: 1978-1985
16 **Goldman AB**, Pavlov H, Rubenstein D. The Segond fracture of the proximal tibia: a small avulsion that reflects major ligamentous damage. *AJR Am J Roentgenol* 1988; **151**: 1163-1167
17 **Stallenberg B**, Gevenois PA, Sintzoff SA, Matos C, Andrianne Y, Struyven J. Fracture of the posterior aspect of the lateral tibial plateau: radiographic sign of anterior cruciate ligament tear. *Radiology* 1993; **187**: 821-825
18 **Chan KK**, Resnick D, Goodwin D, Seeger LL. Posteromedial tibial plateau injury including avulsion fracture of the semimembranous tendon insertion site: ancillary sign of anterior cruciate ligament tear at MR imaging. *Radiology* 1999; **211**: 754-758
19 **Donald L**. Resnick MD, Heung Sik Kang MD, Michael L. Internal Derangements of Joints (2nd edition). In: Resnick DL, Kang HS, Pretterklieber ML. Chapter 25: knee. Philadelphia : Saunders . P 1823
20 **Pao DG**. The lateral femoral notch sign. *Radiology* 2001; **219**: 800-801
21 **Vande Berg BC**, Lecouvet FE, Poilvache P, Dubuc JE, Maldague B, Malghem J. Anterior cruciate ligament tears and associated meniscal lesions: assessment at dual-detector spiral CT arthrography. *Radiology* 2002; **223**: 403-409
22 **Antonio GE**, Griffith JF, Yeung DK. Small-field-of-view MRI of the knee and ankle. *AJR Am J Roentgenol* 2004; **183**: 24-28
23 **Pereira ER**, Ryu KN, Ahn JM, Kayser F, Bielecki D, Resnick D. Evaluation of the anterior cruciate ligament of the knee: comparison between partial flexion true sagittal and extension sagittal oblique positions during MR imaging. *Clin Radiol* 1998; **53**: 574-578
24 **Niitsu M**, Ikeda K, Fukubayashi T, Anno I, Itai Y. Knee extension and flexion: MR delineation of normal and torn anterior cruciate ligaments. *J Comput Assist Tomogr* 1996; **20**: 322-327
25 **Gene Saragnese.** 3D imaging of the knee takes a step forward. Field strength. 2010; **42**: 16-19
26 **Lee JK**, Yao L, Phelps CT, Wirth CR, Czajka J, Lozman J. Anterior cruciate ligament tears: MR imaging compared with arthroscopy and clinical tests. *Radiology* 1988; **166**: 861-864
27 **McCauley TR**, Moses M, Kier R, Lynch JK, Barton JW, Jokl P. MR diagnosis of tears of anterior cruciate ligament of the knee: importance of ancillary findings. *AJR Am J Roentgenol* 1994; **162**: 115-119
28 **Mink JH**, Levy T, Crues JV. Tears of the anterior cruciate ligament and menisci of the knee: MR imaging evaluation. *Radiology* 1988; **167**: 769-774
29 **Robertson PL**, Schweitzer ME, Bartolozzi AR, Ugoni A. Anterior cruciate ligament tears: evaluation of multiple signs with MR imaging. *Radiology* 1994; **193**: 829-834
30 **Tung GA**, Davis LM, Wiggins ME, Fadale PD. Tears of the anterior cruciate ligament: primary and secondary signs at MR imaging. *Radiology* 1993; **188**: 661-667
31 **Lo IK**, de Maat GH, Valk JW, Frank CB. The gross morphology of torn human anterior cruciate ligaments in unstable knees. *Arthroscopy* 1999; **15**: 301-306
32 **Duc SR**, Zanetti M, Kramer J, Käch KP, Zollikofer CL, Wentz KU. Magnetic resonance imaging of anterior cruciate ligament tears: evaluation of standard orthogonal and tailored paracoronal images. *Acta Radiol* 2005; **46**: 729-733
33 **Hong SH**, Choi JY, Lee GK, Choi JA, Chung HW, Kang HS. Grading of anterior cruciate ligament injury. Diagnostic efficacy of oblique coronal magnetic resonance imaging of the knee. *J Comput Assist Tomogr* 2003; **27**: 814-819
34 **Ng AW**, Griffith JF, Law KY, Ting JW, Tipoe GL, Ahuja AT, Chan KM. Oblique axial MR imaging of the normal anterior cruciate ligament bundles. *Skeletal Radiol* 2011; Epub ahead of print
35 **Umans H**, Wimpfheimer O, Haramati N, Applbaum YH, Adler M, Bosco J. Diagnosis of partial tears of the anterior cruciate ligament of the knee: value of MR imaging. *AJR Am J Roentgenol* 1995; **165**: 893-897
36 **Yao L**, Gentili A, Petrus L, Lee JK. Partial ACL rupture: an MR diagnosis? *Skeletal Radiol* 1995; **24**: 247-251
37 **Van Dyck P**, Vanhoenacker FM, Gielen JL, Dossche L, Van Gestel J, Wouters K, Parizel PM. Three tesla magnetic resonance imaging of the anterior cruciate ligament of the knee: can we differentiate complete from partial tears? *Skeletal Radiol* 2011; **40**: 701-707
38 **Brandser EA**, Riley MA, Berbaum KS, el-Khoury GY, Ben-

nett DL. MR imaging of anterior cruciate ligament injury: independent value of primary and secondary signs. *AJR Am J Roentgenol* 1996; **167**: 121-126
39 **Gentili A**, Seeger LL, Yao L, Do HM. Anterior cruciate ligament tear: indirect signs at MR imaging. *Radiology* 1994; **193**: 835-840
40 **Kaplan PA**, Walker CW, Kilcoyne RF, Brown DE, Tusek D, Dussault RG. Occult fracture patterns of the knee associated with anterior cruciate ligament tears: assessment with MR imaging. *Radiology* 1992; **183**: 835-838
41 **Schweitzer ME**, Cervilla V, Kursunoglu-Brahme S, Resnick D. The PCL line: an indirect sign of anterior cruciate ligament injury. *Clin Imaging* 1992; **16**: 43-48
42 **Vahey TN**, Hunt JE, Shelbourne KD. Anterior translocation of the tibia at MR imaging: a secondary sign of anterior cruciate ligament tear. *Radiology* 1993; **187**: 817-819
43 **Chiu SS**. The anterior tibial translocation sign. *Radiology* 2006; **239**: 914-915
44 **Chan WP**, Peterfy C, Fritz RC, Genant HK. MR diagnosis of complete tears of the anterior cruciate ligament of the knee: importance of anterior subluxation of the tibia. *AJR Am J Roentgenol* 1994; **162**: 355-360
45 **Boeree NR**, Ackroyd CE. Magnetic resonance imaging of anterior cruciate ligament rupture. A new diagnostic sign. *J Bone Joint Surg Br* 1992; **74**: 614-616
46 **Remer EM**, Fitzgerald SW, Friedman H, Rogers LF, Hendrix RW, Schafer MF. Anterior cruciate ligament injury: MR imaging diagnosis and patterns of injury. *Radiographics* 1992; **12**: 901-915
47 **Smith JP**, Barrett GR. Medial and lateral meniscal tear patterns in anterior cruciate ligament-deficient knees. A prospective analysis of 575 tears. *Am J Sports Med* 2001; **29**: 415-419
48 **Vinson EN**, Gage JA, Lacy JN. Association of peripheral vertical meniscal tears with anterior cruciate ligament tears. *Skeletal Radiol* 2008; **37**: 645-651
49 **Laundre BJ**, Collins MS, Bond JR, Dahm DL, Stuart MJ, Mandrekar JN. MRI accuracy for tears of the posterior horn of the lateral meniscus in patients with acute anterior cruciate ligament injury and the clinical relevance of missed tears. *AJR Am J Roentgenol* 2009; **193**: 515-523
50 **Allen CR**, Wong EK, Livesay GA, Sakane M, Fu FH, Woo SL. Importance of the medial meniscus in the anterior cruciate ligament-deficient knee. *J Orthop Res* 2000; **18**: 109-115
51 **Thompson WO**, Fu FH. The meniscus in the cruciate-deficient knee. *Clin Sports Med* 1993; **12**: 771-796
52 **Vinson EN**, Major NM, Helms CA. The posterolateral corner of the knee. *AJR Am J Roentgenol* 2008; **190**: 449-458
53 **Meister BR**, Michael SP, Moyer RA, Kelly JD, Schneck CD. Anatomy and kinematics of the lateral collateral ligament of the knee. *Am J Sports Med* 2000; **28**: 869-878
54 **Fineberg MS**, Duquin TR, Axelrod JR. Arthroscopic visualization of the popliteus tendon. *Arthroscopy* 2008; **24**: 174-177
55 **Peduto AJ**, Nguyen A, Trudell DJ, Resnick DL. Popliteomeniscal fascicles: anatomic considerations using MR arthrography in cadavers. *AJR Am J Roentgenol* 2008; **190**: 442-448
56 **Yu JS**, Salonen DC, Hodler J, Haghighi P, Trudell D, Resnick D. Posterolateral aspect of the knee: improved MR imaging with a coronal oblique technique. *Radiology* 1996; **198**: 199-204
57 **Recht MP**, Applegate G, Kaplan P, Dussault R, Schweitzer M, Dalinka MK, Resnick D. The MR appearance of cruciate ganglion cysts: a report of 16 cases. *Skeletal Radiol* 1994; **23**: 597-600
58 **McIntyre J**, Moelleken S, Tirman P. Mucoid degeneration of the anterior cruciate ligament mistaken for ligamentous tears. *Skeletal Radiol* 2001; **30**: 312-315
59 **Bergin D**, Morrison WB, Carrino JA, Nallamshetty SN, Bartolozzi AR. Anterior cruciate ligament ganglia and mucoid degeneration: coexistence and clinical correlation. *AJR Am J Roentgenol* 2004; **182**: 1283-1287
60 **Papadopoulou P**. The celery stalk sign. *Radiology* 2007; **245**: 916-917
61 **Tzurbakis M**, Mouzopoulos G, Morakis E, Nikolaras G, Georgilas I. Intra-articular knee haemangioma originating from the anterior cruciate ligament: a case report. *J Med Case Reports* 2008; **2**: 254
62 **Majima T**, Kamishima T, Susuda K. Synovial chondromatosis originating from the synovium of the anterior cruciate ligament: a case report. *Sports Med Arthrosc Rehabil Ther Technol* 2009; **1**: 6

S- Editor Lv S **L- Editor** Hughes D **E- Editor** Zheng XM

World Journal of Orthopedics

Online Submissions: http://www.wjgnet.com/2218-5836office
wjo@wjgnet.com
www.wjgnet.com

World J Orthop 2011 August 18; 2(8): I
ISSN 2218-5836 (online)

Acknowledgments to reviewers of *World Journal of Orthopedics*

Many reviewers have contributed their expertise and time to the peer review, a critical process to ensure the quality of *World Journal of Orthopedics*. The editors and authors of the articles submitted to the journal are grateful to the following reviewers for evaluating the articles (including those published in this issue and those rejected for this issue) during the last editing time period.

Kook Jin Chung, Professor, Department of Orthopaedic Surgery, HallymUniversity, Kangnam Sacred Heart Hospital, 948-1, Daerim 1-dong, Yeongdeungpo-gu, Seoul 150-950, South Korea

John J Elias, PhD, Calhoun Research Laboratory, Akron General Medical Center, 400 Wabash Ave, Akron, OH 44307, United States; Eduardo Magalhães, PT, MD, Eduardo Magalhães Institute, Domingos de M oraes street, n° 2243, room 56, São Paulo 04035-000, Brazil

Prachya Kongtawelert, Associate Professor, Department of Biochemistry, Faculty of Medicine, Chiang Mai University, Chiang Mai 50200, Thailand

Kemal Nas, Professor, Department of Physical Medicine and Rehabilitation, University of Dicle, Medical School, Diyarbakir 21280,Turkey

Naiquan Nigel Zheng Professor, Mechanical Engineering, University of North Carolina, 9201 University City Blvd, Charlotte, NC 28223, United States

World Journal of Orthopedics

Online Submissions: http://www.wjgnet.com/2218-5836office
wjo@wjgnet.com
www.wjgnet.com

World J Orthop 2011 August 18; 2(8): I
ISSN 2218-5836 (online)

Events Calendar 2011

January 16-20, 2011
Combined 4th International Conference of the Saudi Orthopaedic Association & SICOT Trainee Day, Abha, Saudi Arabia

January 24-27, 2011
7th Middle East Orthopaedics Conference 2011, Dubai International Convention Centre, Dubai, Saudi Arabia

January 28-30, 2011
National Orthopedic Conference 2011, San Francisco, California, United States

February 15-19, 2011
American Academy of Orthopaedic Surgeons, San Diego, CA, United States

February 16-20, 2011
2011 Annual Meeting of the American Academy of Orthopaedic Surgeons, San Diego, CA, United States

February 19, 2011
Pediatric Orthopaedic Society of North America Specialty Day, San Diego, CA, United States

March 09-11, 2011
Annual London Imperial Spine Course, London, United Kingdom

March 21-25, 2011
31st Caribbean Orthopaedic Meeting, Anse Marcel, Saint Martin

March 28-April 02, 2011
The Association of Children's Prosthetic-Orthotic Clinics 2011 Annual Meeting, Park City, UT, United States

April 01-04, 2011
Ain Shams 2nd Orthopaedic intensive course (Orthopaedics from A to Z), Cairo, Egypt

April 20-22, 2011
IMUKA 2011: Masterclass in Arthroscopy and Related Surgery, Maastricht, Netherlands

May 11-14, 2011
2011 POSNA Annual Meeting, Montreal, Quebec, Canada

May 12-15, 2011
84th Annual Meeting of the Japanese Orthopaedic Association, Yokohama, Japan

May 15-19, 2011
8th Biennial ISAKOS Congress (International Society of Arthroscopy, Knee Surgery and Orthopaedic Sports Medicine), Rio de Janeiro, Brazil

May 25-28, 2011
16th Pan Arab Orthopedic Association Congress & 27th SOTCOT Congress, Tunis, Tunisia

June 01-04, 2011
12th EFORT Congress in cooperation with the Danish Orthopaedic Association (European Federation of National Associations of Orthopaedics and Traumatology), Copenhagen, Denmark

June 08-12, 2011
2011 ABJS Annual Meeting (Association of Bone and Joint Surgeons), Dublin, Ireland

June 15-18, 2011
11th Annual Meeting of the International Society for Computer Assisted Orthopaedic Surgery, London, United Kingdom

July 07-09, 2011
66th Annual Meeting of the Canadian Orthopaedic Association, St. John's, Newfoundland and Labrador, Canada

July 13-16, 2011
18th International Meeting on Advanced Spine Techniques, Copenhagen, Denmark

July 22-24, 2011
Sri Sathya Sai International Orthopaedic Conference- 2011 0n Pelvis And Lower Extremity Trauma", Sri Sathya Sai Institute of Higher Medical Sciences, Prasanthigram, Puttaparthi, Andhra Pradesh, India

July 25-28, 2011
2011 Update in Orthopaedics, Grand Wailea Hotel Resort & Spa,Wailea, Maui, Hawaii, United States

September 06-09, 2011
SICOT 2011 XXV Triennial World Congress, Prague, Czech Republic

September 13-16, 2011
BOA/IOA Combined Meeting(British Orthopaedic Association & Irish Orthopaedic Association), Dublin, Ireland

September 14-17, 2011
23rd SECEC-ESSSE Congress (European Society for Surgery of the Shoulder and the Elbow), Lyon, France

September 14-17, 2011
46th SRS Annual Meeting & Course (Scoliosis Research Society), Louisville, Kentucky, United States

September 15-18, 2011
2011 World Congress on Osteoarthritis, San Diego, California 92167, United States

September 21-23, 2011
HIP IMPROVEMENTS AND PROCEEDINGS, Toulouse, France

October 25-28, 2011
DKOU 2011-Deutscher Kongress für Orthopädie und Unfallchirurgie, Berlin, Germany

November 7-11, 2011
86ème Réunion Annuelle SOFCOT, Paris, France

December 12-15, 2011
EOA 63rd Annual International Conference, Cairo, Egypt

World Journal of Orthopedics

Online Submissions: http://www.wjgnet.com/2218-5836office
wjo@wjgnet.com
www.wjgnet.com

World J Orthop 2011 August 18; 2(8): I-V
ISSN 2218-5836 (online)

INSTRUCTIONS TO AUTHORS

GENERAL INFORMATION

World Journal of Orthopedics (*World J Orthop*, *WJO*, online ISSN 2218-5836, DOI: 10.5312) is a monthly peer-reviewed, online, open-access (OA), journal supported by an editorial board consisting of 122 experts in orthopedics from 30 countries.

The biggest advantage of the OA model is that it provides free, full-text articles in PDF and other formats for experts and the public without registration, which eliminates the obstacle that traditional journals possess and usually delays the speed of the propagation and communication of scientific research results. The open access model has been proven to be a true approach that may achieve the ultimate goal of the journals, i.e. the maximization of the value to the readers, authors and society.

Maximization of personal benefits

The role of academic journals is to exhibit the scientific levels of a country, a university, a center, a department, and even a scientist, and build an important bridge for communication between scientists and the public. As we all know, the significance of the publication of scientific articles lies not only in disseminating and communicating innovative scientific achievements and academic views, as well as promoting the application of scientific achievements, but also in formally recognizing the "priority" and "copyright" of innovative achievements published, as well as evaluating research performance and academic levels. So, to realize these desired attributes of *WJO* and create a well-recognized journal, the following four types of personal benefits should be maximized. The maximization of personal benefits refers to the pursuit of the maximum personal benefits in a well-considered optimal manner without violation of the laws, ethical rules and the benefits of others. (1) Maximization of the benefits of editorial board members: The primary task of editorial board members is to give a peer review of an unpublished scientific article via online office system to evaluate its innovativeness, scientific and practical values and determine whether it should be published or not. During peer review, editorial board members can also obtain cutting-edge information in that field at first hand. As leaders in their field, they have priority to be invited to write articles and publish commentary articles. We will put peer reviewers' names and affiliations along with the article they reviewed in the journal to acknowledge their contribution; (2) Maximization of the benefits of authors: Since *WJO* is an open-access journal, readers around the world can immediately download and read, free of charge, high-quality, peer-reviewed articles from *WJO* official website, thereby realizing the goals and significance of the communication between authors and peers as well as public reading; (3) Maximization of the benefits of readers: Readers can read or use, free of charge, high-quality peer-reviewed articles without any limits, and cite the arguments, viewpoints, concepts, theories, methods, results, conclusion or facts and data of pertinent literature so as to validate the innovativeness, scientific and practical values of their own research achievements, thus ensuring that their articles have novel arguments or viewpoints, solid evidence and correct conclusion; and (4) Maximization of the benefits of employees: It is an iron law that a first-class journal is unable to exist without first-class editors, and only first-class editors can create a first-class academic journal. We insist on strengthening our team cultivation and construction so that every employee, in an open, fair and transparent environment, could contribute their wisdom to edit and publish high-quality articles, thereby realizing the maximization of the personal benefits of editorial board members, authors and readers, and yielding the greatest social and economic benefits.

Aims and scope

The aim of *WJO* is to report rapidly new theories, methods and techniques for prevention, diagnosis, treatment, rehabilitation and nursing in the field of orthopedics. *WJO* covers diagnostic imaging, arthroscopy, evidence-based medicine, epidemiology, nursing, sports medicine, therapy of bone and spinal diseases, bone trauma, osteoarthropathy, bone tumors and osteoporosis, minimally invasive therapy, traditional medicine, and integrated Chinese and Western medicine. The journal also publishes original articles and reviews that report the results of applied and basic research in fields related to orthopedics, such as immunology, physiopathology, cell biology, pharmacology, medical genetics, and pharmacology of Chinese herbs.

Columns

The columns in the issues of *WJO* will include: (1) Editorial: To introduce and comment on major advances and developments in the field; (2) Frontier: To review representative achievements, comment on the state of current research, and propose directions for future research; (3) Topic Highlight: This column consists of three formats, including (A) 10 invited review articles on a hot topic, (B) a commentary on common issues of this hot topic, and (C) a commentary on the 10 individual articles; (4) Observation: To update the development of old and new questions, highlight unsolved problems, and provide strategies on how to solve the questions; (5) Guidelines for Basic Research: To provide Guidelines for basic research; (6) Guidelines for Clinical Practice: To provide guidelines for clinical diagnosis and treatment; (7) Review: To review systemically progress and unresolved problems in the field, comment on the state of current research, and make suggestions for future work; (8) Original Articles: To report innovative and original findings in orthopedics; (9) Brief Articles: To briefly report the novel and innovative findings in orthopedics; (10) Case Report: To report a rare or typical case; (11) Letters to the Editor: To discuss and make reply to the contributions published in *WJO*, or to introduce and comment on a controversial issue of general interest; (12) Book Reviews: To introduce and comment on quality monographs of orthopedics; and (13) Guidelines: To introduce consensuses and guidelines reached by international and national academic authorities worldwide on the research orthopedics.

Name of journal

World Journal of Orthopedics

ISSN

ISSN 2218-5836 (online)

Published by

Baishideng Publishing Group Co., Limited

SPECIAL STATEMENT

All articles published in this journal represent the viewpoints of the authors except where indicated otherwise.

Biostatistical editing

Statisital review is performed after peer review. We invite an expert

in Biomedical Statistics from to evaluate the statistical method used in the paper, including *t*-test (group or paired comparisons), chi-squared test, Ridit, probit, logit, regression (linear, curvilinear, or stepwise), correlation, analysis of variance, analysis of covariance, *etc*. The reviewing points include: (1) Statistical methods should be described when they are used to verify the results; (2) Whether the statistical techniques are suitable or correct; (3) Only homogeneous data can be averaged. Standard deviations are preferred to standard errors. Give the number of observations and subjects (*n*). Losses in observations, such as drop-outs from the study should be reported; (4) Values such as ED50, LD50, IC50 should have their 95% confidence limits calculated and compared by weighted probit analysis (Bliss and Finney); and (5) The word 'significantly' should be replaced by its synonyms (if it indicates extent) or the *P* value (if it indicates statistical significance).

Conflict-of-interest statement

In the interests of transparency and to help reviewers assess any potential bias, *WJO* requires authors of all papers to declare any competing commercial, personal, political, intellectual, or religious interests in relation to the submitted work. Referees are also asked to indicate any potential conflict they might have reviewing a particular paper. Before submitting, authors are suggested to read "Uniform Requirements for Manuscripts Submitted to Biomedical Journals: Ethical Considerations in the Conduct and Reporting of Research: Conflicts of Interest" from International Committee of Medical Journal Editors (ICMJE), which is available at: http://www.icmje.org/ethical_4conflicts.html.

Sample wording: [Name of individual] has received fees for serving as a speaker, a consultant and an advisory board member for [names of organizations], and has received research funding from [names of organization]. [Name of individual] is an employee of [name of organization]. [Name of individual] owns stocks and shares in [name of organization]. [Name of individual] owns patent [patent identification and brief description].

Statement of informed consent

Manuscripts should contain a statement to the effect that all human studies have been reviewed by the appropriate ethics committee or it should be stated clearly in the text that all persons gave their informed consent prior to their inclusion in the study. Details that might disclose the identity of the subjects under study should be omitted. Authors should also draw attention to the Code of Ethics of the World Medical Association (Declaration of Helsinki, 1964, as revised in 2004).

Statement of human and animal rights

When reporting the results from experiments, authors should follow the highest standards and the trial should conform to Good Clinical Practice (for example, US Food and Drug Administration Good Clinical Practice in FDA-Regulated Clinical Trials; UK Medicines Research Council Guidelines for Good Clinical Practice in Clinical Trials) and/or the World Medical Association Declaration of Helsinki. Generally, we suggest authors follow the lead investigator's national standard. If doubt exists whether the research was conducted in accordance with the above standards, the authors must explain the rationale for their approach and demonstrate that the institutional review body explicitly approved the doubtful aspects of the study.

Before submitting, authors should make their study approved by the relevant research ethics committee or institutional review board. If human participants were involved, manuscripts must be accompanied by a statement that the experiments were undertaken with the understanding and appropriate informed consent of each. Any personal item or information will not be published without explicit consents from the involved patients. If experimental animals were used, the materials and methods (experimental procedures) section must clearly indicate that appropriate measures were taken to minimize pain or discomfort, and details of animal care should be provided.

SUBMISSION OF MANUSCRIPTS

Manuscripts should be typed in 1.5 line spacing and 12 pt. Book Antiqua with ample margins. Number all pages consecutively, and start each of the following sections on a new page: Title Page, Abstract, Introduction, Materials and Methods, Results, Discussion, Acknowledgements, References, Tables, Figures, and Figure Legends. Neither the editors nor the publisher are responsible for the opinions expressed by contributors. Manuscripts formally accepted for publication become the permanent property of Baishideng Publishing Group Co., Limited, and may not be reproduced by any means, in whole or in part, without the written permission of both the authors and the publisher. We reserve the right to copy-edit and put onto our website accepted manuscripts. Authors should follow the relevant guidelines for the care and use of laboratory animals of their institution or national animal welfare committee. For the sake of transparency in regard to the performance and reporting of clinical trials, we endorse the policy of the ICMJE to refuse to publish papers on clinical trial results if the trial was not recorded in a publicly-accessible registry at its outset. The only register now available, to our knowledge, is http://www.clinicaltrials.gov sponsored by the United States National Library of Medicine and we encourage all potential contributors to register with it. However, in the case that other registers become available you will be duly notified. A letter of recommendation from each author's organization should be provided with the contributed article to ensure the privacy and secrecy of research is protected.

Authors should retain one copy of the text, tables, photographs and illustrations because rejected manuscripts will not be returned to the author(s) and the editors will not be responsible for loss or damage to photographs and illustrations sustained during mailing.

Online submissions

Manuscripts should be submitted through the Online Submission System at: http://www.wjgnet.com/2218-5836office. Authors are highly recommended to consult the ONLINE INSTRUCTIONS TO AUTHORS (http://www.wjgnet.com/2218-5836/g_info_20100722172650.htm) before attempting to submit online. For assistance, authors encountering problems with the Online Submission System may send an email describing the problem to wjo@wjgnet.com, or by telephone: +86-10-85381892. If you submit your manuscript online, do not make a postal contribution. Repeated online submission for the same manuscript is strictly prohibited.

MANUSCRIPT PREPARATION

All contributions should be written in English. All articles must be submitted using word-processing software. All submissions must be typed in 1.5 line spacing and 12 pt. Book Antiqua with ample margins. Style should conform to our house format. Required information for each of the manuscript sections is as follows:

Title page

Title: Title should be less than 12 words.

Running title: A short running title of less than 6 words should be provided.

Authorship: Authorship credit should be in accordance with the standard proposed by International Committee of Medical Journal Editors, based on (1) substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; (2) drafting the article or revising it critically for important intellectual content; and (3) final approval of the version to be published. Authors should meet conditions 1, 2, and 3.

Institution: Author names should be given first, then the complete name of institution, city, province and postcode. For example, Xu-Chen Zhang, Li-Xin Mei, Department of Pathology,

Chengde Medical College, Chengde 067000, Hebei Province, China. One author may be represented from two institutions, for example, George Sgourakis, Department of General, Visceral, and Transplantation Surgery, Essen 45122, Germany; George Sgourakis, 2nd Surgical Department, Korgialenio-Benakio Red Cross Hospital, Athens 15451, Greece

Author contributions: The format of this section should be: Author contributions: Wang CL and Liang L contributed equally to this work; Wang CL, Liang L, Fu JF, Zou CC, Hong F and Wu XM designed the research; Wang CL, Zou CC, Hong F and Wu XM performed the research; Xue JZ and Lu JR contributed new reagents/analytic tools; Wang CL, Liang L and Fu JF analyzed the data; and Wang CL, Liang L and Fu JF wrote the paper.

Supportive foundations: The complete name and number of supportive foundations should be provided, e.g. Supported by National Natural Science Foundation of China, No. 30224801

Correspondence to: Only one corresponding address should be provided. Author names should be given first, then author title, affiliation, the complete name of institution, city, postcode, province, country, and email. All the letters in the email should be in lower case. A space interval should be inserted between country name and email address. For example, Montgomery Bissell, MD, Professor of Medicine, Chief, Liver Center, Gastroenterology Division, University of California, Box 0538, San Francisco, CA 94143, United States. montgomery.bissell@ucsf.edu

Telephone and fax: Telephone and fax should consist of +, country number, district number and telephone or fax number, e.g. Telephone: +86-10-59080039 Fax: +86-10-85381893

Peer reviewers: All articles received are subject to peer review. Normally, three experts are invited for each article. Decision for acceptance is made only when at least two experts recommend an article for publication. Reviewers for accepted manuscripts are acknowledged in each manuscript, and reviewers of articles which were not accepted will be acknowledged at the end of each issue. To ensure the quality of the articles published in *WJO*, reviewers of accepted manuscripts will be announced by publishing the name, title/position and institution of the reviewer in the footnote accompanying the printed article. For example, reviewers: Professor Jing-Yuan Fang, Shanghai Institute of Digestive Disease, Shanghai, Affiliated Renji Hospital, Medical Faculty, Shanghai Jiaotong University, Shanghai, China; Professor Xin-Wei Han, Department of Radiology, The First Affiliated Hospital, Zhengzhou University, Zhengzhou, Henan Province, China; and Professor Anren Kuang, Department of Nuclear Medicine, Huaxi Hospital, Sichuan University, Chengdu, Sichuan Province, China.

Abstract

There are unstructured abstracts (no more than 256 words) and structured abstracts (no more than 480). The specific requirements for structured abstracts are as follows:

An informative, structured abstracts of no more than 480 words should accompany each manuscript. Abstracts for original contributions should be structured into the following sections. AIM (no more than 20 words): Only the purpose should be included. Please write the aim as the form of "To investigate/study/…"; MATERIALS AND METHODS (no more than 140 words); RESULTS (no more than 294 words): You should present *P* values where appropriate and must provide relevant data to illustrate how they were obtained, e.g. 6.92 ± 3.86 *vs* 3.61 ± 1.67, $P < 0.001$; CONCLUSION (no more than 26 words).

Key words

Please list 5-10 key words, selected mainly from *Index Medicus*, which reflect the content of the study.

Text

For articles of these sections, original articles and brief articles, the main text should be structured into the following sections: INTRODUCTION, MATERIALS AND METHODS, RESULTS and DISCUSSION, and should include appropriate Figures and Tables. Data should be presented in the main text or in Figures and Tables, but not in both. The main text format of these sections, editorial, topic highlight, case report, letters to the editors, can be found at: http://www.wjgnet.com/2218-5836/g_info_list.htm.

Illustrations

Figures should be numbered as 1, 2, 3, *etc.*, and mentioned clearly in the main text. Provide a brief title for each figure on a separate page. Detailed legends should not be provided under the figures. This part should be added into the text where the figures are applicable. Figures should be either Photoshop or Illustrator files (in tiff, eps, jpeg formats) at high-resolution. Examples can be found at: http://www.wjgnet.com/1007-9327/13/4520.pdf; http://www.wjgnet.com/1007-9327/13/4554.pdf; http://www.wjgnet.com/1007-9327/13/4891.pdf; http://www.wjgnet.com/1007-9327/13/4986.pdf; http://www.wjgnet.com/1007-9327/13/4498.pdf. Keeping all elements compiled is necessary in line-art image. Scale bars should be used rather than magnification factors, with the length of the bar defined in the legend rather than on the bar itself. File names should identify the figure and panel. Avoid layering type directly over shaded or textured areas. Please use uniform legends for the same subjects. For example: Figure 1 Pathological changes in atrophic gastritis after treatment. A: ...; B: ...; C: ...; D: ...; E: ...; F: ...; G: …*etc.* It is our principle to publish high resolution-figures for the printed and E-versions.

Tables

Three-line tables should be numbered 1, 2, 3, *etc.*, and mentioned clearly in the main text. Provide a brief title for each table. Detailed legends should not be included under tables, but rather added into the text where applicable. The information should complement, but not duplicate the text. Use one horizontal line under the title, a second under column heads, and a third below the Table, above any footnotes. Vertical and italic lines should be omitted.

Notes in tables and illustrations

Data that are not statistically significant should not be noted. $^{a}P < 0.05$, $^{b}P < 0.01$ should be noted ($P > 0.05$ should not be noted). If there are other series of *P* values, $^{c}P < 0.05$ and $^{d}P < 0.01$ are used. A third series of *P* values can be expressed as $^{e}P < 0.05$ and $^{f}P < 0.01$. Other notes in tables or under illustrations should be expressed as ^{1}F, ^{2}F, ^{3}F; or sometimes as other symbols with a superscript (Arabic numerals) in the upper left corner. In a multicurve illustration, each curve should be labeled with ●, ○, ■, □, ▲, △, *etc.*, in a certain sequence.

Acknowledgments

Brief acknowledgments of persons who have made genuine contributions to the manuscript and who endorse the data and conclusions should be included. Authors are responsible for obtaining written permission to use any copyrighted text and/or illustrations.

REFERENCES

Coding system

The author should number the references in Arabic numerals according to the citation order in the text. Put reference numbers in square brackets in superscript at the end of citation content or after the cited author's name. For citation content which is part of the narration, the coding number and square brackets should be typeset normally. For example, "Crohn's disease (CD) is associated with increased intestinal permeability[1,2]". If references are cited directly in the text, they should be put together within the text, for example, "From references[19,22-24], we know that...".

When the authors write the references, please ensure that the order in text is the same as in the references section, and also ensure the spelling accuracy of the first author's name. Do not list the same citation twice.

PMID and DOI

Pleased provide PubMed citation numbers to the reference list, e.g. PMID and DOI, which can be found at http://www.ncbi.nlm.nih.gov/sites/entrez?db=pubmed and http://www.crossref.org/SimpleTextQuery/, respectively. The numbers will be used in E-version of this journal.

Style for journal references

Authors: the name of the first author should be typed in bold-faced letters. The family name of all authors should be typed with the initial letter capitalized, followed by their abbreviated first and middle initials. (For example, Lian-Sheng Ma is abbreviated as Ma LS, Bo-Rong Pan as Pan BR). The title of the cited article and italicized journal title (journal title should be in its abbreviated form as shown in PubMed), publication date, volume number (in black), start page, and end page [PMID: 11819634 DOI: 10.3748/wjg.13.5396].

Style for book references

Authors: the name of the first author should be typed in bold-faced letters. The surname of all authors should be typed with the initial letter capitalized, followed by their abbreviated middle and first initials. (For example, Lian-Sheng Ma is abbreviated as Ma LS, Bo-Rong Pan as Pan BR) Book title. Publication number. Publication place: Publication press, Year: start page and end page.

Format

Journals

English journal article (list all authors and include the PMID where applicable)

1 **Jung EM**, Clevert DA, Schreyer AG, Schmitt S, Rennert J, Kubale R, Feuerbach S, Jung F. Evaluation of quantitative contrast harmonic imaging to assess malignancy of liver tumors: A prospective controlled two-center study. *World J Gastroenterol* 2007; **13**: 6356-6364 [PMID: 18081224 DOI: 10.3748/wjg.13.6356]

Chinese journal article (list all authors and include the PMID where applicable)

2 **Lin GZ**, Wang XZ, Wang P, Lin J, Yang FD. Immunologic effect of Jianpi Yishen decoction in treatment of Pixu-diarrhoea. *Shijie Huaren Xiaohua Zazhi* 1999; **7**: 285-287

In press

3 **Tian D**, Araki H, Stahl E, Bergelson J, Kreitman M. Signature of balancing selection in Arabidopsis. *Proc Natl Acad Sci USA* 2006; In press

Organization as author

4 **Diabetes Prevention Program Research Group**. Hypertension, insulin, and proinsulin in participants with impaired glucose tolerance. *Hypertension* 2002; **40**: 679-686 [PMID: 12411462 PMCID:2516377 DOI:10.1161/01.HYP.0000035706.28494.09]

Both personal authors and an organization as author

5 **Vallancien G**, Emberton M, Harving N, van Moorselaar RJ; Alf-One Study Group. Sexual dysfunction in 1, 274 European men suffering from lower urinary tract symptoms. *J Urol* 2003; **169**: 2257-2261 [PMID: 12771764 DOI:10.1097/01.ju.0000067940.76090.73]

No author given

6 21st century heart solution may have a sting in the tail. *BMJ* 2002; **325**: 184 [PMID: 12142303 DOI:10.1136/bmj.325.7357.184]

Volume with supplement

7 **Geraud G**, Spierings EL, Keywood C. Tolerability and safety of frovatriptan with short- and long-term use for treatment of migraine and in comparison with sumatriptan. *Headache* 2002; **42** Suppl 2: S93-99 [PMID: 12028325 DOI:10.1046/j.1526-4610.42.s2.7.x]

Issue with no volume

8 **Banit DM**, Kaufer H, Hartford JM. Intraoperative frozen section analysis in revision total joint arthroplasty. *Clin Orthop Relat Res* 2002; (**401**): 230-238 [PMID: 12151900 DOI:10.1097/00003086-200208000-00026]

No volume or issue

9 Outreach: Bringing HIV-positive individuals into care. *HRSA Careaction* 2002; 1-6 [PMID: 12154804]

Books

Personal author(s)

10 **Sherlock S**, Dooley J. Diseases of the liver and billiary system. 9th ed. Oxford: Blackwell Sci Pub, 1993: 258-296

Chapter in a book (list all authors)

11 **Lam SK**. Academic investigator's perspectives of medical treatment for peptic ulcer. In: Swabb EA, Azabo S. Ulcer disease: investigation and basis for therapy. New York: Marcel Dekker, 1991: 431-450

Author(s) and editor(s)

12 **Breedlove GK**, Schorfheide AM. Adolescent pregnancy. 2nd ed. Wieczorek RR, editor. White Plains (NY): March of Dimes Education Services, 2001: 20-34

Conference proceedings

13 **Harnden P**, Joffe JK, Jones WG, editors. Germ cell tumours V. Proceedings of the 5th Germ cell tumours Conference; 2001 Sep 13-15; Leeds, UK. New York: Springer, 2002: 30-56

Conference paper

14 **Christensen S**, Oppacher F. An analysis of Koza's computational effort statistic for genetic programming. In: Foster JA, Lutton E, Miller J, Ryan C, Tettamanzi AG, editors. Genetic programming. EuroGP 2002: Proceedings of the 5th European Conference on Genetic Programming; 2002 Apr 3-5; Kinsdale, Ireland. Berlin: Springer, 2002: 182-191

Electronic journal (list all authors)

15 Morse SS. Factors in the emergence of infectious diseases. Emerg Infect Dis serial online, 1995-01-03, cited 1996-06-05; 1(1): 24 screens. Available from: URL: http://www.cdc.gov/ncidod/eid/index.htm

Patent (list all authors)

16 **Pagedas AC**, inventor; Ancel Surgical R&D Inc., assignee. Flexible endoscopic grasping and cutting device and positioning tool assembly. United States patent US 20020103498. 2002 Aug 1

Statistical data

Write as mean ± SD or mean ± SE.

Statistical expression

Express *t* test as *t* (in italics), *F* test as *F* (in italics), chi square test as χ^2 (in Greek), related coefficient as *r* (in italics), degree of freedom as υ (in Greek), sample number as *n* (in italics), and probability as *P* (in italics).

Units

Use SI units. For example: body mass, m (B) = 78 kg; blood pressure, p (B) = 16.2/12.3 kPa; incubation time, t (incubation) = 96 h, blood glucose concentration, c (glucose) 6.4 ± 2.1 mmol/L; blood CEA mass concentration, p (CEA) = 8.6 24.5 μg/L; CO_2 volume fraction, 50 mL/L CO_2, not 5% CO_2; likewise for 40 g/L formaldehyde, not 10% formalin; and mass fraction, 8 ng/g, *etc.* Arabic numerals such as 23, 243, 641 should be read 23 243 641.

The format for how to accurately write common units and quantums can be found at: http://www.wjgnet.com/2218-5836/g_info_20100724204625.htm.

Abbreviations

Standard abbreviations should be defined in the abstract and on first mention in the text. In general, terms should not be abbreviated unless they are used repeatedly and the abbreviation is helpful to the reader. Permissible abbreviations are listed in Units, Symbols

and Abbreviations: A Guide for Biological and Medical Editors and Authors (Ed. Baron DN, 1988) published by The Royal Society of Medicine, London. Certain commonly used abbreviations, such as DNA, RNA, HIV, LD50, PCR, HBV, ECG, WBC, RBC, CT, ESR, CSF, IgG, ELISA, PBS, ATP, EDTA, mAb, can be used directly without further explanation.

Italics

Quantities: *t* time or temperature, *c* concentration, *A* area, *l* length, *m* mass, *V* volume.
Genotypes: *gyrA*, *arg* 1, *c myc*, *c fos*, *etc.*
Restriction enzymes: *Eco*RI, *Hin*dI, *Bam*HI, *Kbo* I, *Kpn* I, *etc.*
Biology: *H. pylori*, *E coli*, *etc.*

Examples for paper writing

Editorial: http://www.wjgnet.com/2218-5836/g_info_20100723140942.htm

Frontier: http://www.wjgnet.com/2218-5836/g_info_20100723141035.htm

Topic highlight: http://www.wjgnet.com/2218-5836/g_info_20100723141239.htm

Observation: http://www.wjgnet.com/2218-5836/g_info_20100723141532.htm

Guidelines for basic research: http://www.wjgnet.com/2218-5836/g_info_20100723142040.htm

Guidelines for clinical practice: http://www.wjgnet.com/2218-5836/g_info_20100723142248.htm

Review: http://www.wjgnet.com/2218-5836/g_info_20100723145519.htm

Original articles: http://www.wjgnet.com/2218-5836/g_info_20100723145856.htm

Brief articles: http://www.wjgnet.com/2218-5836/g_info_20100723150253.htm

Case report: http://www.wjgnet.com/2218-5836/g_info_20100723150420.htm

Letters to the editor: http://www.wjgnet.com/2218-5836/g_info_20100723150642.htm

Book reviews: http://www.wjgnet.com/2218-5836/g_info_20100723150839.htm

Guidelines: http://www.wjgnet.com/2218-5836/g_info_20100723150924.htm

SUBMISSION OF THE REVISED MANUSCRIPTS AFTER ACCEPTED

Please revise your article according to the revision policies of *WJO*. The revised version including manuscript and high-resolution image figures (if any) should be copied on a floppy or compact disk. The author should send the revised manuscript, along with printed high-resolution color or black and white photos, copyright transfer letter, and responses to the reviewers by courier (such as EMS/DHL).

Editorial Office

World Journal of Orthopedics
Editorial Department: Room 903, Building D,
Ocean International Center,
No. 62 Dongsihuan Zhonglu,
Chaoyang District, Beijing 100025, China
E-mail: wjo@wjgnet.com
http://www.wjgnet.com
Telephone: +86-10-8538-1892
Fax: +86-10-8538-1893

Language evaluation

The language of a manuscript will be graded before it is sent for revision. (1) Grade A: priority publishing; (2) Grade B: minor language polishing; (3) Grade C: a great deal of language polishing needed; and (4) Grade D: rejected. Revised articles should reach Grade A or B.

Copyright assignment form

Please download a Copyright assignment form from http://www.wjgnet.com/2218-5836/g_info_20100724204516.htm.

Responses to reviewers

Please revise your article according to the comments/suggestions provided by the reviewers. The format for responses to the reviewers' comments can be found at: http://www.wjgnet.com/2218-5836/g_info_20100724204306.htm.

Proof of financial support

For paper supported by a foundation, authors should provide a copy of the document and serial number of the foundation.

Links to documents related to the manuscript

WJO will be initiating a platform to promote dynamic interactions between the editors, peer reviewers, readers and authors. After a manuscript is published online, links to the PDF version of the submitted manuscript, the peer-reviewers' report and the revised manuscript will be put on-line. Readers can make comments on the peer reviewer's report, authors' responses to peer reviewers, and the revised manuscript. We hope that authors will benefit from this feedback and be able to revise the manuscript accordingly in a timely manner.

Science news releases

Authors of accepted manuscripts are suggested to write a science news item to promote their articles. The news will be released rapidly at EurekAlert/AAAS (http://www.eurekalert.org). The title for news items should be less than 90 characters; the summary should be less than 75 words; and main body less than 500 words. Science news items should be lawful, ethical, and strictly based on your original content with an attractive title and interesting pictures.

Publication fee

WJO is an international, peer-reviewed, Open-Access, online journal. Articles published by this journal are distributed under the terms of the Creative Commons Attribution Non-commercial License, which permits use, distribution, and reproduction in any medium, provided the original work is properly cited, the use is non commercial and is otherwise in compliance with the license. Authors of accepted articles must pay a publication fee. The related standards are as follows. Publication fee: 1300 USD per article. Editorial, topic highlights, original articles, book reviews and letters to the editor are published free of charge.