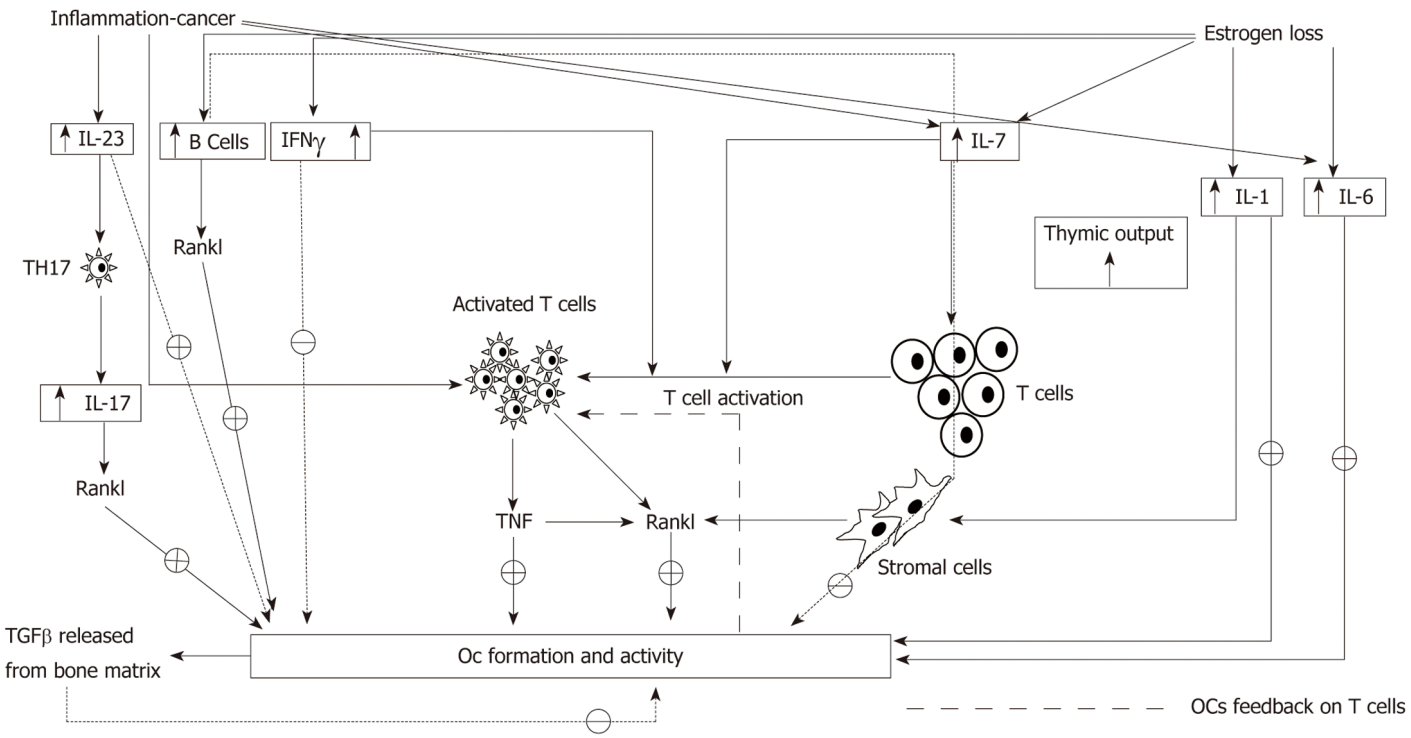
ISSN 2218-5836 (online)

World Journal of *Orthopedics*

World J Orthop 2011 March 18; 2(3): 25-30



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 122 members, representing a team of worldwide experts in orthopedics. They are from 30 countries, including Australia (7), Austria (1), Belgium (1), Brazil (1), Canada (3), China (13), Denmark (1), Finland (2), Germany (6), Greece (1), India (3), Iran (1), Israel (1), Italy (8), Japan (6), Morocco (1), Netherlands (4), Norway (2), Portugal (1), Serbia (2), Singapore (2), South Korea (6), Spain (1), Sri Lanka (1), Sweden (2), Switzerland (2), Tunisia (1), Turkey (1), United Kingdom (3), and United States (38).

WJO World Journal of Orthopedics

Contents

Monthly Volume 2 Number 3 March 18, 2011

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: 0086-10-8538-1892
Fax: 0086-10-8538-1893
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: 0086-10-5908-0036
Fax: 0086-10-8538-1893
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: 00852-3115-8812
Telephone: 00852-5804-2046

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: 0086-10-8538-1892
Fax: 0086-10-8538-1893
E-mail: baishideng@wjgnet.com
http://www.wjgnet.com

ONLINE SUBSCRIPTION
One-Year Price 216.00 USD

PUBLICATION DATE
March 18, 2011

SERIAL PUBLICATION NUMBER
ISSN 2218-5836 (online)

EDITORIAL OFFICE
Hong Sun, Director
World Journal of Orthopedics
Room 903, Building D, Ocean International Center,
No. 62 Dongsihuan Zhonglu, Chaoyang District,
Beijing 100025, China
Telephone: 0086-10-5908-1630
Fax: 0086-10-8538-1893
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. If you do not have web access please contact the editorial office.

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.i3.25

World J Orthop 2011 March 18; 2(3):25-30
ISSN 2218-5836 (online)

EDITORIAL

Interactions between the immune system and bone

Patrizia D'Amelio, Giorgia Fornelli, Ilaria Roato, Giovanni Carlo Isaia

Patrizia D'Amelio, Giorgia Fornelli, Giovanni Carlo Isaia, Department of Surgical and Medical Disciplines, Section of Gerontology, University of Torino, 10126 Torino, Italy
Ilaria Roato, Center for Research and Medical Studies and Polo Oncologico, San Giovanni Battista Hospital, 10126 Torino, Italy
Author contributions: All the authors contributed to the design and writing of this article.
Supported by the University of Torino
Correspondence to: Patrizia D'Amelio, MD, PhD, Department of Surgical and Medical Disciplines, Section of Gerontology, University of Torino, Corso Bramante 88/90, 10126 Torino, Italy. patrizia.damelio@unito.it
Telephone: +39-011-6335533 Fax: +39-011-6636033
Received: December 7, 2010 Revised: January 12, 2011
Accepted: January 19, 2011
Published online: March 18, 2011

Abstract

The relationship between the immune system, estrogen deficiency and bone loss is an intriguing and, as yet, unexplained challenge of the past two decades. Here we summarize the evidence that links immune cells, inflammation, cytokine production and osteoclast formation and activity with particular regard to humans.

Key words: Osteoclast; T cells; Cytokines; Osteoporosis; Immune system; Menopause

Peer reviewer: Dr. Andrea Giusti, Department of Gerontology and MusculoSkeletal Science, Galliera Hospital, via Sapeto 11 a 18, Genora, 16100, Italy

D'Amelio P, Fornelli G, Roato I, Isaia GC. Interactions between immune system and bone. *World J Orthop* 2011; 2(3): 25-30 Available from: URL: http://www.wjgnet.com/2218-5836/full/v2/i3/25.htm DOI: http://dx.doi.org/10.5312/wjo.v2.i3.25

INTRODUCTION

The bone, hematopoietic and immune systems are in deep physical contact and share several common pathways. Inflammatory disease characterized by systemic and local bone loss is an interesting field with which to explore the relationship between activation of the immune system and bone remodelling. In the last few years, investigators have shed light on this topic and T cells have been recognized as key regulators of osteoclast (OC) and osteoblast (OB)[1] formation and activity in different pathological conditions, such as osteoporosis[2], rheumatoid arthritis (RA)[3], bone metastasis[4,5] and periodontitis[6,7].

Estrogen deprivation induces bone loss. At the same time estrogens are well known regulators of the immune system and T cell functions[8,9]. Thus the immune system can be suggested as a key interface between estrogen deprivation and bone metabolism.

The role of the immune system in bone resorption is still controversial: studies on humans are few and the majority of the data have been derived from animal models and cellular cultures. This review aims to summarize the evidences linking immune activation and bone loss with particular attention to humans.

Cytokines and OC formation

The Receptor Activator of NFkB Ligand (RANKL) and Macrophage Colony Stimulating Factor (M-CSF) are produced by bone marrow stromal cells[10], OBs[11] and activated T cells[2,12]. The co-stimulation by RANKL and M-CSF is essential for the differentiation of monocytes into OCs[13-15].

M-CSF induces the proliferation of OC precursors, differentiation and fusion of more mature OCs and increases the survival of mature OCs. RANKL promotes the differentiation of OC precursors into fully mature multinucleated OCs and stimulates the capacity of mature OCs to resorb bone.

RANKL is a member of the TNF superfamily, present both as a transmembrane and in secreted form. It binds to its physiological receptor RANK expressed

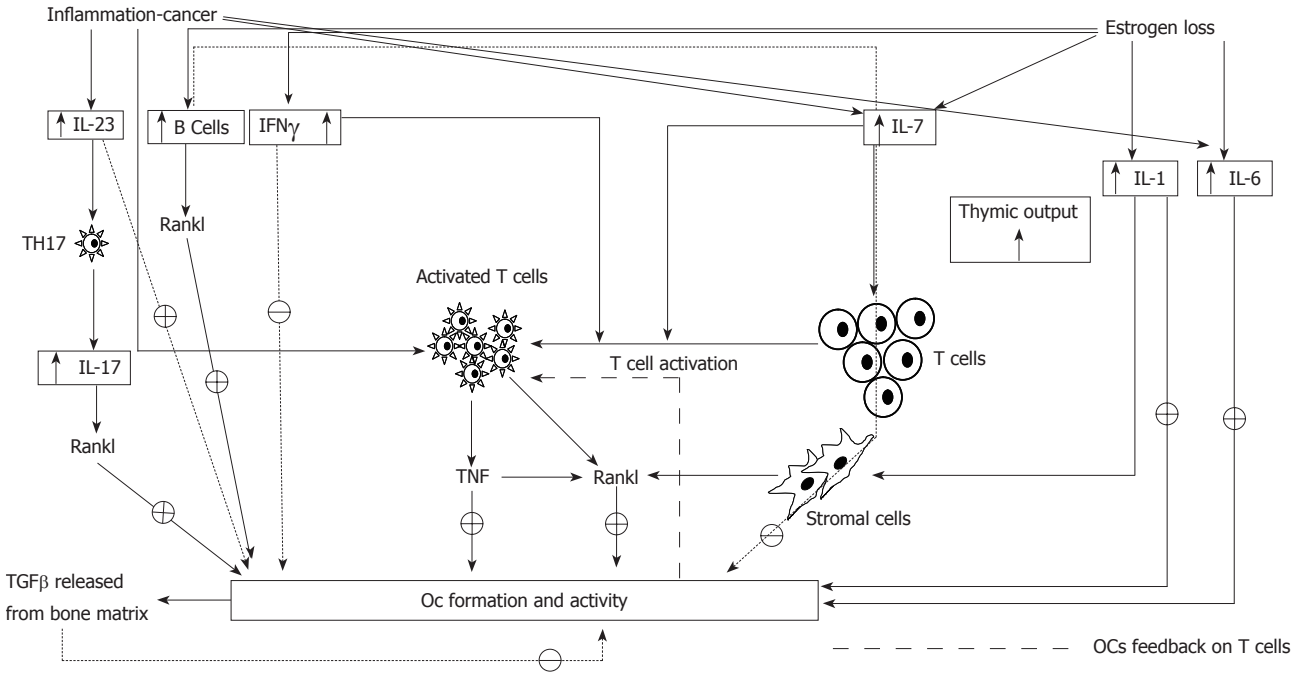


Figure 1 Multiple cytokines have a role in the regulation of OC formation and activity. Their complex interactions are important in explaining bone loss after menopause or in inflammatory diseases.

on the surface of OC lineage cells. Its action is opposed by osteoprotegerin (OPG), a neutralizing soluble decoy receptor, produced by marrow stromal cells and OBs[13]. Estrogen deficiency induces the imbalance between RANKL and OPG; this phenomenon is important in the genesis of post-menopausal bone loss[15,16].

Some studies questioned the central role of RANKL and suggested the hypothesis that activated T cells could induce osteoclastogenesis by an independent mechanism since saturating concentrations of OPG failed to neutralize more than 30% of OC formation induced by activated T cells[17]. Rifas and Weitzmann discovered a novel cytokine called Secreted Osteoclastogenic Factor of Activated T cells (SOFAT) in activated T cell medium. This cytokine induces both osteoblastic IL-6 production and functional OC formation in the absence of OBs or RANKL, insensitive to the effects of OPG.

The demonstration that SOFAT is a potent inducer of IL-6 production by OBs suggests that it could play a significant role in the local inflammatory response and also could exacerbate bone destruction in rheumatoid arthritis indirectly through multiple IL-6-mediated events[18].

Estrogen deficiency induces bone loss through a complex modification of cytokine production balance. Primarily, researchers observed increased TNFα production by T cells both in ovariectomized mice[19] and post-menopausal women[2,20]. TNFα enhances OC formation by up-regulating stromal cell production of RANKL and M-CSF and by increasing the responsiveness of OC precursors to RANKL[5,21]. Besides, other studies showed a key role of T cell-produced TNFα in rheumatoid arthritis[3,22], multiple myeloma[23,6] and bone metastasis[4,5]. The effect of TNFα on osteoclastogenesis is up-regulated by IL-1[24]; this cytokine production increases after menopause[20,25], enhancing RANKL expression by bone marrow stromal cells and directly promoting OC differentiation. In fact, treatment with IL-1 receptor antagonist decreases OC formation and bone resorption in ovariectomized mice[26,27], whereas the blockade of both TNFα and IL-1 reduce bone resorption in post-menopausal osteoporosis[28].

IFNγ role in osteoclastogenesis has been hard to define: this cytokine has an anti osteoclastogenic effect in vitro[29] and in vivo in nude mice models[30,31]. Studies in humans indicate an increased level of IFNγ during estrogen deficiency[32,33], in leprosy and rheumatoid arthritis with bone erosions[34,35]. Moreover, data from randomized controlled trials have shown that IFNγ does not prevent bone loss in patients with RA[36,37] nor the bone wasting effect of cyclosporin A[1]. These data are explained by the finding that IFNγ influences OC formation both via direct and indirect effects[32]. It directly blocks OC formation targeting maturing OC[38] and also induces antigen presentation and thus T cell activation. When IFNγ levels are increased in vivo, activated T cells secrete pro-osteoclastogenic factors and this activity offsets the anti-osteoclastogenic effect of IFNγ[39].

T cells also produce interleukin-7 (IL-7), a cytokine able to enhance B and T cell number and reactivity to antigenic stimulus[40,41]. Some studies have demonstrated that IL-7 promotes osteoclastogenesis by up-regulating T cell-derived osteoclastogenic cytokines including RANKL[42-44] and that the production is up-regulated by estrogen deficiency. In vivo IL-7 blockade is proven to suppress T cell expansion and TNFα and IFNγ production, preventing bone loss due to estrogen deprivation[45,46]. In healthy humans, the expression of IL-7 receptors on T lymphocytes is strictly related to their ability to induce OC formation from peripheral blood

mononuclear cells (PBMC)[47]. A comprehensive summary of these pathways can be found in Figure 1.

Inflammation and bone loss

Both acute and chronic inflammatory diseases in the periosseous tissues are well known to cause bone damage as inflammation increases the OC number and activity. The activation of T cells in autoimmunity or during infection increases RANKL production and promote osteoclastogenesis. The process can be reverted by the administration of OPG in several pathological conditions such as RA and periodontitis[48]. Particularly in autoimmune arthritis, T cell subsets have been examined and Th17 cells, a specialized inflammatory subset, have been identified as responsible for osteoclastogenesis regulation. An inflammatory milieu induces naïve T cells to differentiate into Th17, capable to produce RANKL, TNFα and IL-17, a cytokine that increases RANKL expression by OBs[49].

Researchers recently began to investigate a possible direct role of dendritic cells (DC) in inflammation-related bone damage. DCs are known for their role of antigen presenting cells (APCs) and do not appear to play a role in bone homeostasis in non-pathological conditions, but some data suggest that DC could act as OC precursors in an inflammatory milieu, transforming into DC-derived-OC according to phenotypic and functional characterization studies. Moreover, DCs modulate T cell activity through RANK/RANKL pathway and other cytokines associated with osteoclastogenesis[50-52]. There is a lack of definitive evidence about the physiological relevance of this phenomenon *in vivo* but DCs could act as an osteo-immune interface, contributing to bone loss in inflammatory diseases.

On the other hand investigators have focused on the role of B-lymphocytes in periodontal inflammation. The host immune response is partly responsible for the bone destruction in cases of periodontitis and the RANK/RANK/OPG signalling axis is important both in bone and immune system communication. Data suggest that B-lymphocyte involvement in the adaptive immune response contributes to bone resorption by up-regulating of RANKL expression through Toll-like receptor pathways. These data align with the known ability of T cells to produce RANKL in the presence of immune stimulus and to increase osteoclastogenesis[53].

Other studies focused on psoriatic arthritis, a chronic inflammatory disease characterized by joint erosions mediated by OCs. These OCs seem to derive from CD14+CD16+ circulating monocytes, present at higher level in patients than in healthy controls when exposed to OC-promoting microenvironment (M-CSF and RANKL). OCs do not derive from this population in healthy controls; thus CD16 can be considered a marker of OC precursors in arthritis[54].

OC modulates T cell activity

OC precursors circulate within the mononuclear fraction of peripheral blood[2,4,55-57]. This population acts not only as a reservoir for replenishing the pre-OC pool in the bone marrow but also as a potentially abundant source of pre-OCs that can be recruited into bone or joint tissue in response to reparative or pathological signals. On this basis OCs can be considered as immune cells attracted in bone by stimulatory cytokines, expressed on accessory cells and undergoing specific differentiation.

For a long time, osteoimmunology focused on OC regulation by T cells. Recently investigators have paid attention to the feedback action of OCs on T cells. Kiesel *et al*. observed that OCs are able to present antigenic peptides to T cells and induce FoxP3 expression in CD8+ T cells, thus originating Treg CD8+ cells able to regulate inappropriate activation of the immune response[58].

Senthilkumar *et al*[59] suggest that the cellular responses in cell-to-cell interactions between T cells and OCs are regulated through reciprocal CD137/CD137L and RANK/RANKL interactions. CD137 is a co-stimulatory member of the TNF receptor induced by T cell receptor activation, characterized by the ability to transduce signals in both directions, through the receptor and into the cell that expresses the ligand. Its ligand CD137L is expressed on APCs and OC precursors; *in vitro* CD137L ligation suppresses osteoclastogenesis through the inhibition of multi-nucleation. On the other hand, RANKL expressed on T cells bind to RANK on OCs, producing a reverse signal in T cells able to enhance apoptosis.

Periprosthetic osteolysis is another important research field to understand the reciprocal interactions of OC and T cells. Periprosthetic osteolysis patients show T cell-dependent osteoclastogenesis in PBMC cultures; in fact the process was inhibited by RANK-Fc and T cell depletion[60]. In periprosthetic tissues local CD8+ T cells showed a regulatory phenotype, expressing CD25 and FoxP3, while CD4+ T cells did not express activation markers. These data suggest that in an early stage T cells promote osteoclastogenesis, while subsequently OCs activate FoxP3/CD8+ T cells which inhibit CD4+ effector T cells.

Estrogen loss and immune system

The role of estrogen in the regulation of immune function has been demonstrated in animals and humans: immune cells are more responsive to antigenic stimulus in hormone replacement therapy users than non-users[61].

Our group demonstrated that T cells from postmenopausal women show blunt reaction to immune stimulation in respect to pre-menopausal healthy women. At baseline, T cells are more active than in healthy post- and pre-menopausal controls: this implies their greater ability to produce RANKL and TNFα, thus inducing OC formation and activity[2]. We have also demonstrated that OC formation is abolished in T cell-depleted PBMC cultures and this phenomenon is reversed only by the addition of M-CSF and RANKL in cultures.

Grcevic *et al*[62] suggested a probable role for resting T cells in blunting OC formation; CD4+ and CD8+ T cell-depleted mice have an increased OC formation rate since OPG production is suppressed. T cell-deficient

mice show an increased number of OC in basal conditions and a reduced bone density when compared to controls[42].

Estrogen withdrawal up-regulates TNFα production by T cells through a complex pathway involving the thymus and bone marrow. In the bone marrow, ovariectomy promotes T cell activation by increasing antigen presentation by macrophages and DCs[33,63]. Several studies showed the central role of T cells-produced TNF in bone loss induced by estrogen deficiency; in the murine model ovariectomy increases the number of bone marrow T cell-producing TNF[19,64,65]. In fact, ovariectomy stimulates the expression of the gene encoding Class II TransActivator (CIITA), a transcriptional coactivator acting on the MHCII promoter, with the final effect of up-regulation of expression of MHCII on macrophages[33,66,67]. This process proved essential since data show that ovariectomy induces rapid bone loss in wild type (wt) mice but failed to do so in TNFα-deficient [TNFα (-/-)] mice and in T cell-deficient nude mice. Bone loss was restored by adoptive transfer of wt T cells but not by reconstitution with T cells from TNFα (-/-) mice[19], the bone-wasting effect of TNFα is mediated by the p55 TNFα receptor. In fact, ovariectomy caused bone loss in wt mice and in mice lacking p75 TNFα receptor but failed to do so in mice lacking the p55 TNFα receptor[19].

Moreover, RANKL-expression on lymphocytes and marrow stromal cells is significantly elevated during estrogen deficiency in humans and correlates directly with increases in bone resorption markers and inversely with serum estrogen levels[16].

These data demonstrate the causal relationship between estrogen deprivation, T cell activation with increased production of cytokines, and bone resorption.

Estrogen withdrawal has effects on the B cell compartment as well. In ovariectomized mice B220+ IgM- population expands and can differentiate into OC[68-70]. Activated B cells over-express RANKL, contributing to bone resorption[71].

CONCLUSION

Bone is a dynamic tissue that is constantly formed and resorbed; bone turnover is due to continuous and cyclic bone resorption followed by apposition. These processes are due to the coordinated actions of OC and OB. The action of these two cell types is regulated by paracrine and endocrine factors. In physiological conditions, OB and OC activity is coupled so that the amount of resorption is equal to the amount of formation. However, in pathological conditions or during senescence, resorption is higher than formation, leading to bone loss. OC and OB formation, as well as the coupling between these two cell types, are mediated mainly through cytokines.

Cytokines have pleiotropic functions and regulate several organs and systems. In the last decade several investigators have paid attention to the relationship between estrogen withdrawal, cytokines production, the immune system and skeleton. Today the majority of the data have been obtained in animal models but in recent years, new evidence has been accumulated in humans towards a profound link between estrogen deprivation, immune system deregulation and bone loss. If this relationship is confirmed by future work, postmenopausal osteoporosis should be regarded as an inflammatory disorder sustained by a chronic mild decrease in T cell tolerance.

The relationship between the immune system and bone is complex and depends upon cytokine production and cell to cell contacts. T cells and OCs appear to be the main players in the mechanisms of bone loss. Future studies are needed to fully understand these relationships in humans.

REFERENCES

1 **Mann GN**, Jacobs TW, Buchinsky FJ, Armstrong EC, Li M, Ke HZ, Ma YF, Jee WS, Epstein S. Interferon-gamma causes loss of bone volume in vivo and fails to ameliorate cyclosporin A-induced osteopenia. *Endocrinology* 1994; **135**: 1077-1083

2 **D'Amelio P**, Grimaldi A, Di Bella S, Brianza SZ, Cristofaro MA, Tamone C, Giribaldi G, Ulliers D, Pescarmona GP, Isaia G. Estrogen deficiency increases osteoclastogenesis up-regulating T cells activity: a key mechanism in osteoporosis. *Bone* 2008; **43**: 92-100

3 **Kotake S**, Udagawa N, Hakoda M, Mogi M, Yano K, Tsuda E, Takahashi K, Furuya T, Ishiyama S, Kim KJ, Saito S, Nishikawa T, Takahashi N, Togari A, Tomatsu T, Suda T, Kamatani N. Activated human T cells directly induce osteoclastogenesis from human monocytes: possible role of T cells in bone destruction in rheumatoid arthritis patients. *Arthritis Rheum* 2001; **44**: 1003-1012

4 **Roato I**, Grano M, Brunetti G, Colucci S, Mussa A, Bertetto O, Ferracini R. Mechanisms of spontaneous osteoclastogenesis in cancer with bone involvement. *Faseb J* 2005; **19**: 228-230

5 **Roato I**, Brunetti G, Gorassini E, Grano M, Colucci S, Bonello L, Buffoni L, Manfredi R, Ruffini E, Ottaviani D, Ciuffreda L, Mussa A, Ferracini R. IL-7 up-regulates TNF-alpha-dependent osteoclastogenesis in patients affected by solid tumor. *PLoS One* 2006; **1**: e124

6 **Brunetti G**, Colucci S, Pignataro P, Coricciati M, Mori G, Cirulli N, Zallone A, Grassi FR, Grano M. T cells support osteoclastogenesis in an in vitro model derived from human periodontitis patients. *J Periodontol* 2005; **76**: 1675-1680

7 **Colucci S**, Brunetti G, Cantatore FP, Oranger A, Mori G, Quarta L, Cirulli N, Mancini L, Corrado A, Grassi FR, Grano M. Lymphocytes and synovial fluid fibroblasts support osteoclastogenesis through RANKL, TNFalpha, and IL-7 in an in vitro model derived from human psoriatic arthritis. *J Pathol* 2007; **212**: 47-55

8 **Weitzmann MN**, Pacifici R. T cells: unexpected players in the bone loss induced by estrogen deficiency and in basal bone homeostasis. *Ann N Y Acad Sci* 2007; **1116**: 360-375

9 **Straub RH**. The complex role of estrogens in inflammation. *Endocr Rev* 2007; **28**: 521-574

10 **Khosla S**. Minireview: the OPG/RANKL/RANK system. *Endocrinology* 2001; **142**: 5050-5055

11 **Yasuda H**, Shima N, Nakagawa N, Yamaguchi K, Kinosaki M, Mochizuki S, Tomoyasu A, Yano K, Goto M, Murakami A, Tsuda E, Morinaga T, Higashio K, Udagawa N, Takahashi N, Suda T. Osteoclast differentiation factor is a ligand for osteoprotegerin/osteoclastogenesis-inhibitory factor and is identical to TRANCE/RANKL. *Proc Natl Acad Sci USA* 1998; **95**: 3597-3602

12 **Horwood NJ**, Kartsogiannis V, Quinn JM, Romas E, Martin TJ, Gillespie MT. Activated T lymphocytes support osteo-

clast formation in vitro. *Biochem Biophys Res Commun* 1999; **265**: 144-150
13 **Kong YY**, Yoshida H, Sarosi I, Tan HL, Timms E, Capparelli C, Morony S, Oliveira-dos-Santos AJ, Van G, Itie A, Khoo W, Wakeham A, Dunstan CR, Lacey DL, Mak TW, Boyle WJ, Penninger JM. OPGL is a key regulator of osteoclastogenesis, lymphocyte development and lymph-node organogenesis. *Nature* 1999; **397**: 315-323
14 **Suda T**, Takahashi N, Udagawa N, Jimi E, Gillespie MT, Martin TJ. Modulation of osteoclast differentiation and function by the new members of the tumor necrosis factor receptor and ligand families. *Endocr Rev* 1999; **20**: 345-357
15 **Hofbauer LC**, Khosla S, Dunstan CR, Lacey DL, Boyle WJ, Riggs BL. The roles of osteoprotegerin and osteoprotegerin ligand in the paracrine regulation of bone resorption. *J Bone Miner Res* 2000; **15**: 2-12
16 **Eghbali-Fatourechi G**, Khosla S, Sanyal A, Boyle WJ, Lacey DL, Riggs BL. Role of RANK ligand in mediating increased bone resorption in early postmenopausal women. *J Clin Invest* 2003; **111**: 1221-1230
17 **Weitzmann MN**, Cenci S, Rifas L, Haug J, Dipersio J, Pacifici R. T cell activation induces human osteoclast formation via receptor activator of nuclear factor kappaB ligand-dependent and -independent mechanisms. *J Bone Miner Res* 2001; **16**: 328-337
18 **Rifas L**, Weitzmann MN. A novel T cell cytokine, secreted osteoclastogenic factor of activated T cells, induces osteoclast formation in a RANKL-independent manner. *Arthritis Rheum* 2009; **60**: 3324-3335
19 **Roggia C**, Gao Y, Cenci S, Weitzmann MN, Toraldo G, Isaia G, Pacifici R. Up-regulation of TNF-producing T cells in the bone marrow: a key mechanism by which estrogen deficiency induces bone loss in vivo. *Proc Natl Acad Sci USA* 2001; **98**: 13960-13965
20 **Pacifici R**, Brown C, Puscheck E, Friedrich E, Slatopolsky E, Maggio D, McCracken R, Avioli LV. Effect of surgical menopause and estrogen replacement on cytokine release from human blood mononuclear cells. *Proc Natl Acad Sci USA* 1991; **88**: 5134-5138
21 **Hotokezaka H**, Sakai E, Ohara N, Hotokezaka Y, Gonzales C, Matsuo K, Fujimura Y, Yoshida N, Nakayama K. Molecular analysis of RANKL-independent cell fusion of osteoclast-like cells induced by TNF-alpha, lipopolysaccharide, or peptidoglycan. *J Cell Biochem* 2007; **101**: 122-134
22 **Diarra D**, Stolina M, Polzer K, Zwerina J, Ominsky MS, Dwyer D, Korb A, Smolen J, Hoffmann M, Scheinecker C, van der Heide D, Landewe R, Lacey D, Richards WG, Schett G. Dickkopf-1 is a master regulator of joint remodeling. *Nat Med* 2007; **13**: 156-163
23 **Colucci S**, Brunetti G, Rizzi R, Zonno A, Mori G, Colaianni G, Del Prete D, Faccio R, Liso A, Capalbo S, Liso V, Zallone A, Grano M. T cells support osteoclastogenesis in an in vitro model derived from human multiple myeloma bone disease: the role of the OPG/TRAIL interaction. *Blood* 2004; **104**: 3722-3730
24 **Wei S**, Kitaura H, Zhou P, Ross FP, Teitelbaum SL. IL-1 mediates TNF-induced osteoclastogenesis. *J Clin Invest* 2005; **115**: 282-290
25 **Zheng SX**, Vrindts Y, Lopez M, De Groote D, Zangerle PF, Collette J, Franchimont N, Geenen V, Albert A, Reginster JY. Increase in cytokine production (IL-1 beta, IL-6, TNF-alpha but not IFN-gamma, GM-CSF or LIF) by stimulated whole blood cells in postmenopausal osteoporosis. *Maturitas* 1997; **26**: 63-71
26 **Kitazawa R**, Kimble RB, Vannice JL, Kung VT, Pacifici R. Interleukin-1 receptor antagonist and tumor necrosis factor binding protein decrease osteoclast formation and bone resorption in ovariectomized mice. *J Clin Invest* 1994; **94**: 2397-2406
27 **Kimble RB**, Vannice JL, Bloedow DC, Thompson RC, Hopfer W, Kung VT, Brownfield C, Pacifici R. Interleukin-1 receptor antagonist decreases bone loss and bone resorption in ovariectomized rats. *J Clin Invest* 1994; **93**: 1959-1967
28 **Charatcharoenwitthaya N**, Khosla S, Atkinson EJ, McCready LK, Riggs BL. Effect of blockade of TNF-alpha and interleukin-1 action on bone resorption in early postmenopausal women. *J Bone Miner Res* 2007; **22**: 724-729
29 **Takayanagi H**, Ogasawara K, Hida S, Chiba T, Murata S, Sato K, Takaoka A, Yokochi T, Oda H, Tanaka K, Nakamura K, Taniguchi T. T-cell-mediated regulation of osteoclastogenesis by signalling cross-talk between RANKL and IFN-gamma. *Nature* 2000; **408**: 600-605
30 **Sato K**, Satoh T, Shizume K, Yamakawa Y, Ono Y, Demura H, Akatsu T, Takahashi N, Suda T. Prolonged decrease of serum calcium concentration by murine gamma-interferon in hypercalcemic, human tumor (EC-GI)-bearing nude mice. *Cancer Res* 1992; **52**: 444-449
31 **Tohkin M**, Kakudo S, Kasai H, Arita H. Comparative study of inhibitory effects by murine interferon gamma and a new bisphosphonate (alendronate) in hypercalcemic, nude mice bearing human tumor (LJC-1-JCK). *Cancer Immunol Immunother* 1994; **39**: 155-160
32 **Gao Y**, Grassi F, Ryan MR, Terauchi M, Page K, Yang X, Weitzmann MN, Pacifici R. IFN-gamma stimulates osteoclast formation and bone loss in vivo via antigen-driven T cell activation. *J Clin Invest* 2007; **117**: 122-132
33 **Cenci S**, Toraldo G, Weitzmann MN, Roggia C, Gao Y, Qian WP, Sierra O, Pacifici R. Estrogen deficiency induces bone loss by increasing T cell proliferation and lifespan through IFN-gamma-induced class II transactivator. *Proc Natl Acad Sci USA* 2003; **100**: 10405-10410
34 **Arnoldi J**, Gerdes J, Flad HD. Immunohistologic assessment of cytokine production of infiltrating cells in various forms of leprosy. *Am J Pathol* 1990; **137**: 749-753
35 **Firestein GS**, Alvaro-Gracia JM, Maki R. Quantitative analysis of cytokine gene expression in rheumatoid arthritis. *J Immunol* 1990; **144**: 3347-3353
36 **Cannon GW**, Pincus SH, Emkey RD, Denes A, Cohen SA, Wolfe F, Saway PA, Jaffer AM, Weaver AL, Cogen L. Double-blind trial of recombinant gamma-interferon versus placebo in the treatment of rheumatoid arthritis. *Arthritis Rheum* 1989; **32**: 964-973
37 **Veys EM**, Menkes CJ, Emery P. A randomized, double-blind study comparing twenty-four-week treatment with recombinant interferon-gamma versus placebo in the treatment of rheumatoid arthritis. *Arthritis Rheum* 1997; **40**: 62-68
38 **Takayanagi H**, Kim S, Taniguchi T. Signaling crosstalk between RANKL and interferons in osteoclast differentiation. *Arthritis Res* 2002; **4** Suppl 3: S227-S232
39 **Pacifici R**. Estrogen deficiency, T cells and bone loss. *Cell Immunol* 2008; **252**: 68-80
40 **Komschlies KL**, Back TT, Gregorio TA, Gruys ME, Damia G, Wiltrout RH, Faltynek CR. Effects of rhIL-7 on leukocyte subsets in mice: implications for antitumor activity. *Immunol Ser* 1994; **61**: 95-104
41 **Mackall CL**, Fry TJ, Bare C, Morgan P, Galbraith A, Gress RE. IL-7 increases both thymic-dependent and thymic-independent T-cell regeneration after bone marrow transplantation. *Blood* 2001; **97**: 1491-1497
42 **Toraldo G**, Roggia C, Qian WP, Pacifici R, Weitzmann MN. IL-7 induces bone loss in vivo by induction of receptor activator of nuclear factor kappa B ligand and tumor necrosis factor alpha from T cells. *Proc Natl Acad Sci USA* 2003; **100**: 125-130
43 **Giuliani N**, Colla S, Sala R, Moroni M, Lazzaretti M, La Monica S, Bonomini S, Hojden M, Sammarelli G, Barill□ S, Bataille R, Rizzoli V. Human myeloma cells stimulate the receptor activator of nuclear factor-kappa B ligand (RANKL) in T lymphocytes: a potential role in multiple myeloma bone disease. *Blood* 2002; **100**: 4615-4621
44 **D'Amelio P**, Grimaldi A, Bernabei P, Pescarmona GP, Isaia G. Immune system and bone metabolism: Does thymectomy

influence postmenopausal bone loss in humans? *Bone* 2006; **39**: 658-665
45 **Weitzmann MN**, Roggia C, Toraldo G, Weitzmann L, Pacifici R. Increased production of IL-7 uncouples bone formation from bone resorption during estrogen deficiency. *J Clin Invest* 2002; **110**: 1643-1650
46 **Ryan MR**, Shepherd R, Leavey JK, Gao Y, Grassi F, Schnell FJ, Qian WP, Kersh GJ, Weitzmann MN, Pacifici R. An IL-7-dependent rebound in thymic T cell output contributes to the bone loss induced by estrogen deficiency. *Proc Natl Acad Sci USA* 2005; **102**: 16735-16740
47 **Gendron S**, Boisvert M, Chetoui N, Aoudjit F. Alpha1beta1 integrin and interleukin-7 receptor up-regulate the expression of RANKL in human T cells and enhance their osteoclastogenic function. *Immunology* 2008; **125**: 359-369
48 **Kong YY**, Feige U, Sarosi I, Bolon B, Tafuri A, Morony S, Capparelli C, Li J, Elliott R, McCabe S, Wong T, Campagnuolo G, Moran E, Bogoch ER, Van G, Nguyen LT, Ohashi PS, Lacey DL, Fish E, Boyle WJ, Penninger JM. Activated T cells regulate bone loss and joint destruction in adjuvant arthritis through osteoprotegerin ligand. *Nature* 1999; **402**: 304-309
49 **Sato K**, Suematsu A, Okamoto K, Yamaguchi A, Morishita Y, Kadono Y, Tanaka S, Kodama T, Akira S, Iwakura Y, Cua DJ, Takayanagi H. Th17 functions as an osteoclastogenic helper T cell subset that links T cell activation and bone destruction. *J Exp Med* 2006; **203**: 2673-2682
50 **Cutler CW**, Teng YT. Oral mucosal dendritic cells and periodontitis: many sides of the same coin with new twists. *Periodontol 2000* 2007; **45**: 35-50
51 **Alnaeeli M**, Park J, Mahamed D, Penninger JM, Teng YT. Dendritic cells at the osteo-immune interface: implications for inflammation-induced bone loss. *J Bone Miner Res* 2007; **22**: 775-780
52 **Alnaeeli M**, Teng YT. Dendritic cells: a new player in osteoimmunology. *Curr Mol Med* 2009; **9**: 893-910
53 **Han X**, Lin X, Seliger AR, Eastcott J, Kawai T, Taubman MA. Expression of receptor activator of nuclear factor-kappaB ligand by B cells in response to oral bacteria. *Oral Microbiol Immunol* 2009; **24**: 190-196
54 **Chiu YG**, Shao T, Feng C, Mensah KA, Thullen M, Schwarz EM, Ritchlin CT. CD16 (FcRgammaIII) as a potential marker of osteoclast precursors in psoriatic arthritis. *Arthritis Res Ther* 2010; **12**: R14
55 **Ramnaraine M**, Pan W, Clohisy DR. Osteoclasts direct bystander killing of cancer cells in vitro. *Bone* 2006; **38**: 4-12
56 **Massey HM**, Flanagan AM. Human osteoclasts derive from CD14-positive monocytes. *Br J Haematol* 1999; **106**: 167-170
57 **Shalhoub V**, Elliott G, Chiu L, Manoukian R, Kelley M, Hawkins N, Davy E, Shimamoto G, Beck J, Kaufman SA, Van G, Scully S, Qi M, Grisanti M, Dunstan C, Boyle WJ, Lacey DL. Characterization of osteoclast precursors in human blood. *Br J Haematol* 2000; **111**: 501-512
58 **Kiesel JR**, Buchwald ZS, Aurora R. Cross-presentation by osteoclasts induces FoxP3 in CD8+ T cells. *J Immunol* 2009; **182**: 5477-5487
59 **Senthilkumar R**, Lee HW. CD137L- and RANKL-mediated reverse signals inhibit osteoclastogenesis and T lymphocyte proliferation. *Immunobiology* 2009; **214**: 153-161
60 **Roato I**, Caldo D, D'Amico L, D'Amelio P, Godio L, Patane S, Astore F, Grappiolo G, Boggio M, Scagnelli R, Molfetta L, Ferracini R. Osteoclastogenesis in peripheral blood mononuclear cell cultures of periprosthetic osteolysis patients and the phenotype of T cells localized in periprosthetic tissues. *Biomaterials* 2010; **31**: 7519-7525
61 **Porter VR**, Greendale GA, Schocken M, Zhu X, Effros RB. Immune effects of hormone replacement therapy in postmenopausal women. *Exp Gerontol* 2001; **36**: 311-326
62 **Grcević D**, Lee SK, Marusić A, Lorenzo JA. Depletion of CD4 and CD8 T lymphocytes in mice in vivo enhances 1,25-dihydroxyvitamin D3-stimulated osteoclast-like cell formation in vitro by a mechanism that is dependent on prostaglandin synthesis. *J Immunol* 2000; **165**: 4231-4238
63 **Adamski J**, Ma Z, Nozell S, Benveniste EN. 17beta-Estradiol inhibits class II major histocompatibility complex (MHC) expression: influence on histone modifications and cbp recruitment to the class II MHC promoter. *Mol Endocrinol* 2004; **18**: 1963-1974
64 **Gao Y**, Qian WP, Dark K, Toraldo G, Lin AS, Guldberg RE, Flavell RA, Weitzmann MN, Pacifici R. Estrogen prevents bone loss through transforming growth factor beta signaling in T cells. *Proc Natl Acad Sci USA* 2004; **101**: 16618-16623
65 **Roggia C**, Tamone C, Cenci S, Pacifici R, Isaia GC. Role of TNF-alpha producing T-cells in bone loss induced by estrogen deficiency. *Minerva Med* 2004; **95**: 125-132
66 **Kim JH**, Kim K, Youn BU, Jin HM, Kim N. MHC class II transactivator negatively regulates RANKL-mediated osteoclast differentiation by downregulating NFATc1 and OSCAR. *Cell Signal* 2010; **22**: 1341-1349
67 **Mueller RB**, Skapenko A, Grunke M, Wendler J, Stuhlmuller B, Kalden JR, Schulze-Koops H. Regulation of myeloid cell function and major histocompatibility complex class II expression by tumor necrosis factor. *Arthritis Rheum* 2005; **52**: 451-460
68 **Masuzawa T**, Miyaura C, Onoe Y, Kusano K, Ohta H, Nozawa S, Suda T. Estrogen deficiency stimulates B lymphopoiesis in mouse bone marrow. *J Clin Invest* 1994; **94**: 1090-1097
69 **An J**, Ribeiro RC, Webb P, Gustafsson JA, Kushner PJ, Baxter JD, Leitman DC. Estradiol repression of tumor necrosis factor-alpha transcription requires estrogen receptor activation function-2 and is enhanced by coactivators. *Proc Natl Acad Sci USA* 1999; **96**: 15161-15166
70 **Yang NN**, Venugopalan M, Hardikar S, Glasebrook A. Identification of an estrogen response element activated by metabolites of 17beta-estradiol and raloxifene. *Science* 1996; **273**: 1222-1225
71 **Manabe N**, Kawaguchi H, Chikuda H, Miyaura C, Inada M, Nagai R, Nabeshima Y, Nakamura K, Sinclair AM, Scheuermann RH, Kuro-o M. Connection between B lymphocyte and osteoclast differentiation pathways. *J Immunol* 2001; **167**: 2625-2631

S- Editor Sun H **L- Editor** Roemmele A **E- Editor** Sun H

World Journal of Orthopedics

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

World J Orthop 2011 March 18; 2(3): 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.

Dr. Andrea Giusti, Department of Gerontology and MusculoSkeletal Science, Galliera Hospital, via Sapeto 11a 18, Genora, 16100, Italy

Gunnar Knutsen, MD, PhD, Associate Professor, Department of Orthopaedic Surgery, University of Tromsø, University Hospital North Norway, 9038 Tromsø, Norway

Miroslav Z Milankov, MD, PhD, Professor, Department of Orthopaedic Surgery and Traumatology, Clinical Center Vojvodina, Medical faculty, University of Novi Sad, Hajduk Veljkova 1, 21 000 Novi Sad, Serbia

Donatela Lippi, Professor, Department of Anatomy, Viale Morgagni, 85, Florence, 50134, Italy

Sang-Hun Ko, Professor, Chairman of Orthopedics, Ulsan University Hospital, University of Ulsan College of Medicine, 290-3, Jeon-Ha dong, Dong gu. Ulsan City 682-714, South Korea

World Journal of Orthopedics

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

World J Orthop 2011 March 18; 2(3): I
ISSN 2218-5836 (online)

Meetings

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 March 18; 2(3): 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

SERIAL PUBLICATION NUMBER

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: +86-10-59081630
Fax: +86-10-85381893

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, book reviews and letters to the editor are published free of charge.