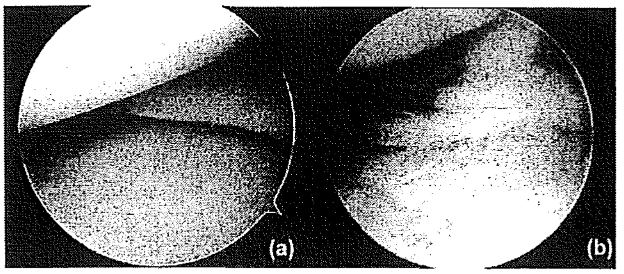

図3　正常膝関節(a)と変形性膝関節症(b)の関節鏡所見．変形性膝関節症では半月板や関節軟骨の変性を認める．

を除去することにより，症状の改善が得られると判断できる場合がよい適応である．OA に伴う滑膜増殖により関節水症が続く症例に対して，関節鏡視下滑膜切除を中心に本手術法が行われることもあるが，変形性変化は残存するため，その効果は限定的である．

2）術前チェック

病歴，診察所見から安静時痛や夜間痛などが主症状でなく，関節運動時の疼痛など機械的な要素が主であることを確認する．術前に単純 X 線だけでなく，MRI (magnetic resonance imaging) 等で関節軟骨，半月板，滑膜などの関節構成体の状態を把握し，機械的因子が現在の症状の主原因であることを確認する．

3）手術方法

通常内側および外側傍膝蓋ポータルより鏡視を行う．まず関節鏡視下に関節構成体の状態を確認する．損傷半月や関節軟骨などが関節内遊離体になっている場合はこれを摘出する．半月板は変性していることが多いが，関節運動に影響する機械的因子になっていない場合は，通常放置する．関節軟骨の部分的剝離を認めることも多いが，これも機械的因子になっていない場合は放置する．滑膜切除を行う場合には電動シェーバーが有用であるが，内外側の谷部や後方の滑膜切除は通常のポータルから行うことは難しいので，必要な場合にはポータルを追加する．マイクロフラクチャーやドリリング，後方解離術などを行う場合はこれを追加するが，本稿では詳細は省略する．

2. 高位脛骨骨切り術 (high tibial osteotomy, HTO)

内反型の OA に対して脛骨中枢部で骨切りを行って下肢全体の軸を外反し，膝関節内側部に加わる荷重を減少することにより，症状の軽減を図るものである（図 4）．本法により術後荷重が軽減された膝関節内側部の軟骨の修復が得られたとする報告もある．

1）適　応

内側コンパートメントの変化を中心とした内反型の OA で，外側コンパートメントや膝蓋大腿関節の変形性変化が強くないものがよい適応である．著しい伸展制限や膝蓋骨低位のある症例は適応が制限される．術後関節軟骨の修復が得られたとする報告はあるものの，荷重条件を変えることが主な目的であり，病変部には手術操作を加えないため OA の根本的な治療ではない．後に述べる人工関節置換術に比べ生物学的な治療であり，年齢が低く人工関節を適応しにくい症例

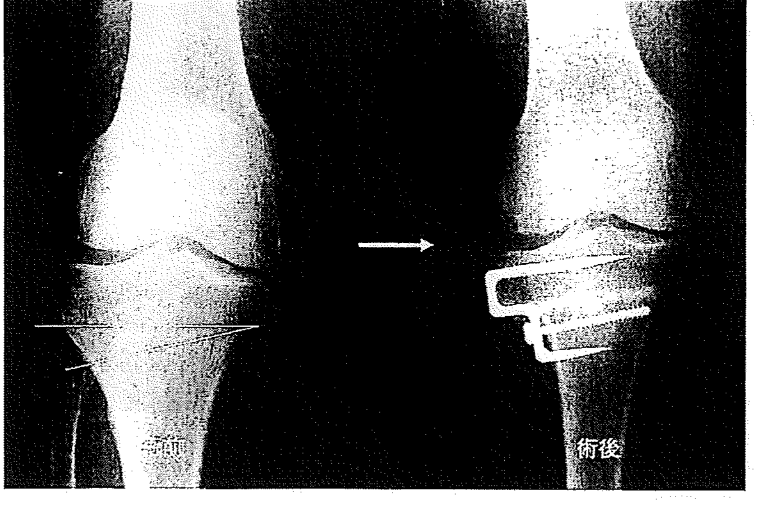

図4　高位脛骨骨切り術(closed wedge osteotomy)．脛骨中枢部で外側を底辺とする三角形の骨片を切除して外反を図る．

に対しても適応されることがある．また，関節内に機械的な疼痛要因が合併する場合には joint débridement を併用することもある．

2）術前チェック

病歴，診察所見から内側部に主症状があることを確認する．術前に単純X線は通常の3方向だけでなく，下肢荷重時（立位）正面像を撮影し，荷重時の膝関節内反変形の程度を定量化して，骨切り角度を計画しておく．通常は荷重時の外反角（FTA, femoro-tibial angle）を計測する．正常下肢の FTA は 173°前後であるが，荷重をより外側に変位させることと，術後の再内反の可能性を考慮して，FTA：167-8° 程度を骨切り目標角度とすることが多い．また，可能であれば MRI 等で関節軟骨，半月板，滑膜などの関節構成体の状態も把握しておく．

3）手術方法

外側部を底辺とする三角形の骨片を切除して外反を図る closed wedge osteotomy と水平に骨切りを行った後，内側部を底辺とする三角形の骨片または人工骨を移植して外反を図る open wedge osteotomy，正面からみてドーム形に骨切りを行い，脛骨末梢部を回転させる dome osteotomy がある[4),5)]．また，脛骨を骨切りするにあたって，腓骨の骨切りも同時に要するが，これも腓骨の中央部で骨切りする方法，中枢 1/3 で骨切りする方法，近位脛腓関節をはずす方法などがある．

Closed wedge osteotomy および open wedge osteotomy は手技的には比較的容易であり，外反角のコントロールもしやすいことが長所である．しかし，closed wedge osteotomy では，膝関節外側部の緩みが生じること，膝蓋骨高位になりやすいこと，骨切り面の外側部の形状が合いにくいため，固定が難しく，脛骨の末梢部が中枢部にめり込んで過外反になりやすい，などの欠点がある．Open wedge osteotomy では，腓骨の骨切りを要さない長所がある反面，大きな矯正は難しいこと，膝関節内側部が過緊張になりやすいこと，膝蓋骨低位になりやすいこと，自家骨を移植する場合には骨採取を要することなどが欠点である．一方，dome osteotomy は骨切りを行った後，術中に外反角度を調整できる長所があるが，手術手技が比較的難しいこと，固定に創外固定を要することが多いことなどが欠点である．

腓骨の骨切り部位は遠位で行うほど，合併症で問題となる腓骨神経損傷が生じにくくなるが，脛骨の骨切り部位と離れると骨切り部の先端の移動距離が大きくなる．また，通常腓骨が早期に再癒合して，脛骨の骨癒合を障害することを防止するため，ある程度の長さを切除することが多い．

3．人工膝関節置換術

OA により荒廃した関節面を切除して，人工物で置き換える手術である．膝関節の内側または外側コンパートメントのいずれか一方だけを置換する単顆置換術（unicompartmental knee arthroplasty, UKA，図 5）

図 5　単顆置換術（UKA）術後の単純X線所見．膝関節の内側コンパートメントだけを置換する．

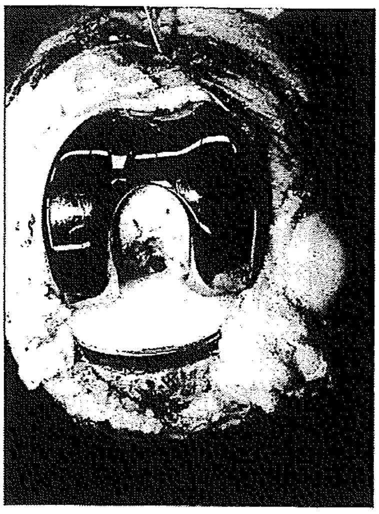

図6　全人工膝関節置換術(TKA)後の肉眼所見．荒廃した大腿骨，脛骨，膝蓋骨関節面を切除しインプラントに置換する．

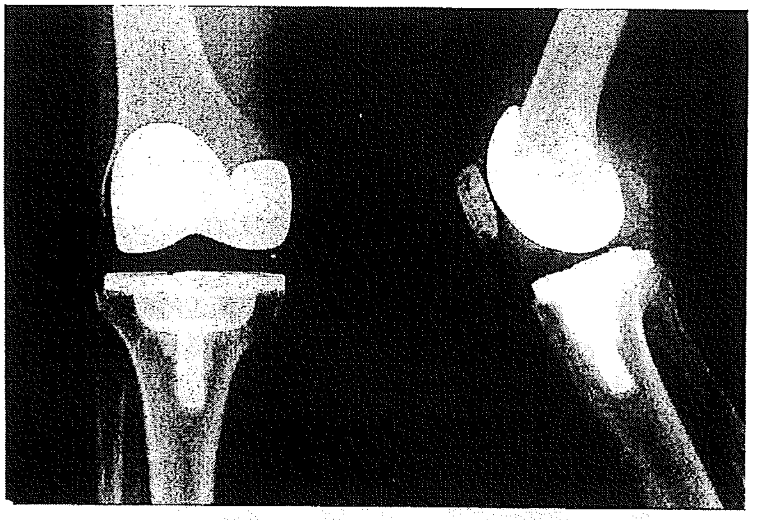

図7　全人工膝関節置換術(TKA)後の単純X線所見．大腿骨，脛骨，膝蓋骨すべての関節面がインプラントに置換されている．

と両方のコンパートメントと膝蓋大腿関節のすべてを置換する全置換術(total knee arthroplasty, TKA, 図6, 7)がある[6),7)]．大腿骨関節面は金属，脛骨と膝蓋骨関節面は高分子ポリエチレンで置き換えるものが多いが，セラミックなどの素材も開発されている．OAによる病変部そのものを置換するため，除痛効果に優れるが，高齢者にとっては侵襲の大きな手術であり，また感染，長期的に人工関節の緩みなどの合併症に十分な注意が必要である．

1) 適　応

OAによる関節面の荒廃が著しく，保存療法や他の手術では十分な効果が得られない場合に選択する．高度の内外反変形や回旋変形，著しい骨欠損，可動域制限の強い例などに対しても，さまざまなオプションの関節や充填用のブロックなどが開発されている．長期的な人工関節の緩みが問題となるので，年齢が低い場合には適応を慎重に決定する．また侵襲の大きな手術であり，全身的にさまざまな合併症を持つ人に対しては慎重に適応を検討する．UKAは明らかに内側または外側コンパートメントのいずれか一方だけの変化が強い場合に適応する．大腿骨顆部の骨壊死後に生じたOAなどは他のコンパートメントの変化が軽い場合が多く，良い適応である．

2) 術前チェック

病歴，診察所見から膝関節痛による日常生活動作の障害程度を確認する．単純X線は下肢荷重時(立位)正面像も撮影し，内側関節裂隙の狭小化の程度，脛骨内側関節面の損傷程度を定量化し，大腿骨および脛骨の骨切り角度を計画しておく．また著しい骨欠損や変形を認める症例では，骨欠損の充填用ブロックや固定用延長ステムなどを術前に計画して用意しておく．

3) 手術方法

通常，傍膝蓋内側皮膚切開で進入する．それぞれの人工関節に専用の骨切りガイドが開発されており，これを用いて術前に計画した通りに大腿骨と脛骨関節面の骨切りを進める．膝蓋骨は置換する方法としない方法があり，置換する場合には骨切りを行い，しない場合には骨棘の切除等を行う．正確な骨切りが完了し，軟部組織のバランスが取れたら，インプラントを挿入する．インプラントの固定は骨セメントを用いる場合と，プレスフィット，すなわち直接固定する方法がある．また，近年，ナビゲーションシステムを用いて，より正確に骨切りを行う試み(図8)や，皮膚切開や大腿四頭筋への侵襲をできるだけ小さく手術を行う最小侵襲人工膝関節置換術(minimally invasive surgery-TKA, MIS-TKA, 図9)[8),9)]が開発され，臨床応用されている．

おわりに

変形性膝関節症は進行すると日常生活でも疼痛を伴うようになる．疼痛を伴う生活はきわめて苦痛であ

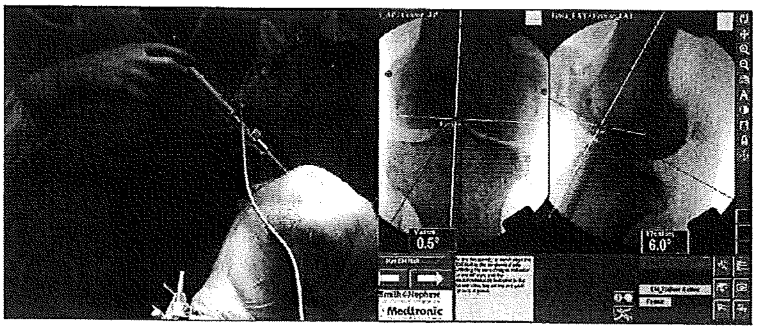

図 8　ナビゲーションを用いた膝関節置換術(膝関節置換術(全人工TKA). 骨切りガイドと骨との間の角度を定量的に表示できる.

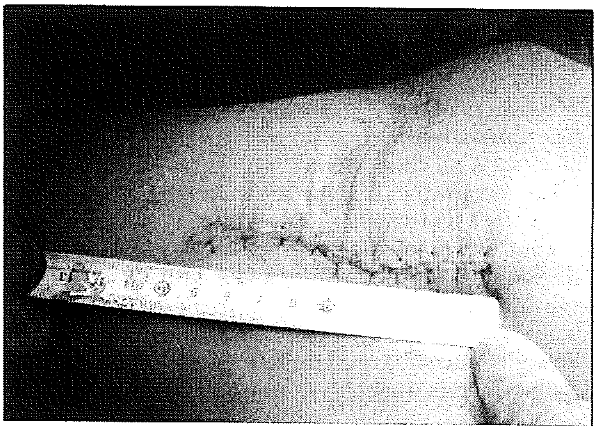

図 9　最小侵襲人工膝関節置換術(MIS-TKA)の皮膚切開. 7-10 cm 程度の皮膚切開で手術が可能である.

り, 解決できるのであれば, 解決すべきである. しかし, 手術療法はさまざまなリスクも伴うため, 手術によるメリットとデメリットを慎重に吟味して適応を決めることが大切である.

文　献

1) 戸山芳昭, 中村耕三, 越智光夫他. 変形性膝関節症に対する手術療法：過去 10 年における手術法選択の推移 —日本整形外科学会認定研修施設を対象とした全国アンケート集計結果—. 日整会誌 2007; 81: 585-9.
2) Yen YM, Cascio B, O'Brien L, et al. Treatment of osteoarthritis of the knee with microfracture and rehabilitation. Med Sci Sports Exerc 2008; 40: 200-5.
3) Moriya H, Sasho T, Sano S, et al. Arthroscopic posteromedial release for osteoarthritic knees with flexion contracture. Arthroscopy 2004; 20: 1030-9.
4) 齋藤知行, 腰野富久. 横浜市大式高位脛骨骨切り術. HTO. 新 OS NOW. 24 膝関節外科 —手術手技のすべて. 岩本幸英他編. 東京：Medical View 社；2004. p.76-82.
5) 井原秀俊. ドーム式. HTO. 新 OS NOW. 24 膝関節外科 —手術手技のすべて. 岩本幸英他編. 東京：Medical View 社；2004. p.64-8.
6) 秋月章. 最小侵襲人工膝単顆置換術. TKA. 新 OS NOW. 24 膝関節外科 —手術手技のすべて. 岩本幸英他編. 東京：Medical View 社；2004. p.121-7.
7) 松野誠夫, 龍順之助, 勝呂徹他. 人工膝関節置換術 —基礎と臨床—. 東京：文光堂；2005.
8) 須田康文, 松本秀男, 大谷俊郎他. 人工膝関節全置換術に対するナビゲーションシステムの応用. 膝 2003; 28: 76-9.
9) 松本秀男, 大谷俊郎, 松崎健一郎他. 大腿四頭筋温存型人工膝関節—手術技法と問題点. 整形外科 2006; 57: 84-8.

Case Report

Double-Concave Deformity of the Polyethylene Tibial Post in Posterior Stabilized Total Knee Arthroplasty

Yasuo Niki, MD,* Hideo Matsumoto, MD,* Fumihiro Yoshimine, MD,†
Yoshiaki Toyama, MD,* Yasunori Suda, MD,* and Scott A. Banks, PhD‡

Abstract: This report describes a unique case of bilateral total knee arthroplasty necessitating revision of the polyethylene insert, which showed prominent marks on the tibial post resulting from repeated *seiza*-style sitting. The patient presented 7 years postoperatively with knee pain and flexion disturbance due to continuous joint effusion persisting for more than 4 months. Proliferating synovia throughout the joint revealed reactive synovitis to polyethylene particles. The retrieved polyethylene inserts displayed double-concave deformity of the tibial post with burnishing and creep in tibiofemoral articulation. The damage pattern of retrieved polyethylene inserts reflected the data from tibiofemoral contact location obtained using a shape-matching technique in the early postoperative phase. This case provides an example of damage to the polyethylene tibial post caused by a floor-sitting lifestyle and the potential clinical sequelae.
Keywords: total knee arthroplasty, deep flexion, polyethylene insert, tibial post, floor-sitting lifestyle, shape matching.

With increasing progress in surgical techniques, implant design, and biomaterials, the ability to achieve greater than 145° of deep flexion is increasingly requested by patients undergoing total knee arthroplasty (TKA), particularly in Asian and Middle Eastern countries. In the late 1990s, several manufacturers developed implants with a high-flex knee design; however, the safety of very deep flexion and the effects of this activity on implant longevity remain unclear. Herein, we report the case of a 69-year–old man for whom Japanese *seiza*-style sitting was an important activity of daily living after bilateral TKA. At 7 years postoperatively, the patient presented with persistent joint effusion of both knees, for which revision of the polyethylene inserts alone resulted in complete recovery. In fact, knee kinematics of the patient during *seiza*-style sitting had been analyzed in the early postoperative phase using model-based shape-matching techniques. The damage pattern of retrieved polyethylene inserts reflected these shape-matching data, providing valuable information on the long-term effects of *seiza*-style sitting.

Case Report

A 63-year–old man underwent bilateral primary TKA with the Stryker Scorpio posterior-stabilized knee system (Stryker Orthopaedics, Mahwah, NJ) in 2000. He recovered without any complications and returned to his original floor-sitting lifestyle, often participating in the tea ceremony, which requires knee flexion greater than 145°. At 3 months postoperatively, routine bilateral radiographs were obtained with the patient in the *seiza* (Japanese-style) sitting posture. Tibiofemoral orientation and contact/separation of the articular surfaces were determined using model-based shape-matching techniques, as previously reported [1]. Briefly, fluoroscopic images were digitized and corrected for static optical distortion. The implant surface model was projected onto the geometry-corrected image, and the 3-dimensional pose was adjusted to match the silhouette of the model to that of the TKA implants in the subject. The results of shape-matching analysis revealed

*From the *Department of Orthopaedic Surgery, Keio University, Shinjuku-ku, Tokyo, Japan; †Department of Orthopaedic Surgery, Tokyo Metropolitan-Ohkubo Hospital, Tokyo, Japan; and ‡Department of Mechanical and Aerospace Engineering, University of Florida, Gainesville, Florida.*
Submitted May 10, 2008; accepted February 8, 2009.
No benefits or funds were received in support of the study.
Reprint requests: Yasuo Niki, MD, PhD, Department of Orthopaedic Surgery, Keio University, 35, Shinanomachi, Shinjuku, Tokyo 160-8582, Japan.

0883-5403/09/2503-0029$36.00/0
doi:10.1016/j.arth.2009.02.012

subtle articular surface separation occurring in the lateral tibiofemoral articulation of both knees, whereas cam/post and medial tibiofemoral articulation showed substantial contact in both knees (Fig. 1). Internal rotation of the tibia during *seiza*-style sitting was 9.5° for the right knee and 13.8° for the left knee, indicating minimum risk of posterior condylar subluxation. Seven years postoperatively, the patient presented with bilateral knee joint effusion, limiting deep flexion of the knees and disturbing his lifestyle. Laboratory testing showed negative results for inflammatory markers suggestive of deep infection, such as C-reactive protein or erythrocyte sedimentation rate, although aspiration of clear yellowish joint fluid indicated a paucity of active inflammatory cells migrating into the joint. According to radiography, metal components were well positioned with no signs of osteolysis or loosening; but joint spaces appeared slightly narrowed, suggesting polyethylene insert wear or creep (Fig. 2).

Joint effusion persisted for 4 months and was considered to be caused by reactive synovitis to wear particles from polyethylene. As metal components were well positioned, only the polyethylene inserts were revised to thicker inserts, bilaterally. Intraoperatively, synovial tissues proliferating throughout the joints were extensively excised. Pathologic findings revealed polyethylene particles surrounded by foreign body giant cells in places in synovia with villous phenotype (Fig. 3). Both retrieved inserts displayed burnishing and dimensional changes (Fig. 4A), which have been reported in 30% of retrievals of this type [2]. The

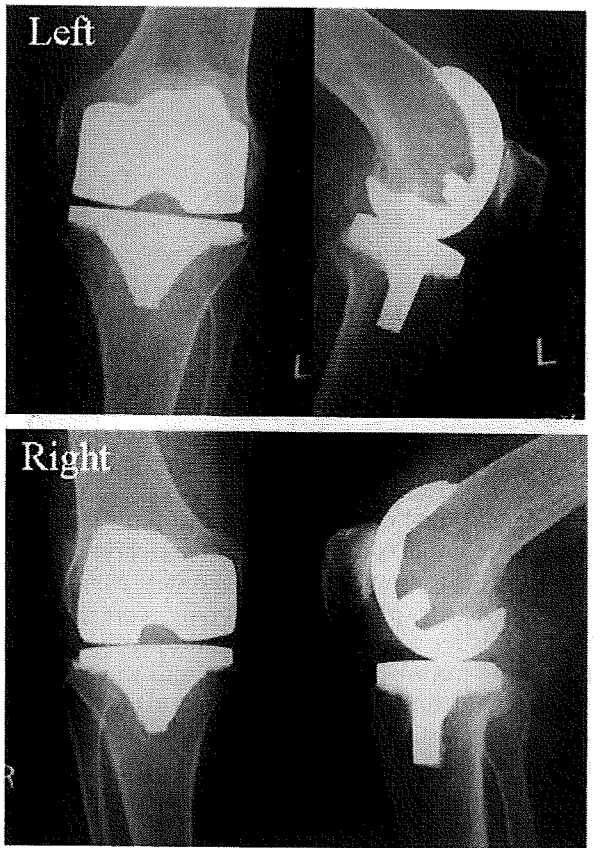

Fig. 2. Radiographs at 7 years postoperatively, suggesting polyethylene insert wear or creep.

	Left	Right
Cum-Post distance	(-)*	(-)
Disengagement (med/lat) [mm]	(-) /0.99	(-) / 0.21
Internal tibial rotation [degrees]	13.8	9.52

*(-), below the lower detection limit

Fig. 1. Shape-matching data of *seiza*-style sitting 3 months after TKA. Left radiographs show 3-dimensional position and orientation of the implant as measured by model-based shape-matching techniques. Right table shows articular surface separation and rotation between polyethylene insert and femoral component.

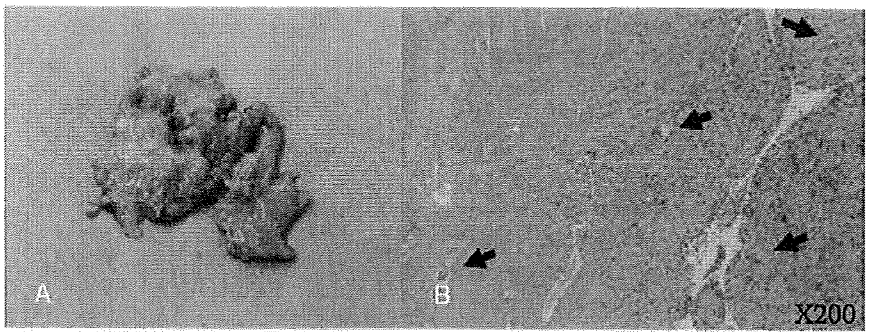

Fig. 3. Synovial granuloma tissue retrieved from the joint capsule (A). Polyethylene wear particles are present throughout the retrieved synovial tissues. Arrows indicate polyethylene particles encapsulated by foreign body giant cells (B).

area of dimensional change was identical to the contact position of femoral condyles defined by earlier shape-matching investigations (data not shown). Minor wear of the top of the post was observed, representing a finding that is reportedly unique to an open-box design and resulting from cement extrusion into the box (Fig. 4B). Prominent findings were a double-concave deformation of the post, suggestive of gradually accumulated dimensional changes resulting from cam/post contact (Fig. 4C). The upper concave surface may have resulted from *seiza*-style sitting with the knee in greater than 145° of flexion, whereas the lower concave surface may have occurred with 60° to 145° flexion. At the 6-month follow-up after insert replacement, joint effusion had disappeared; and the patient had returned to a floor-sitting lifestyle. Clinical scoring according to the Hospital for Special Surgery score had improved from 58 to 95.

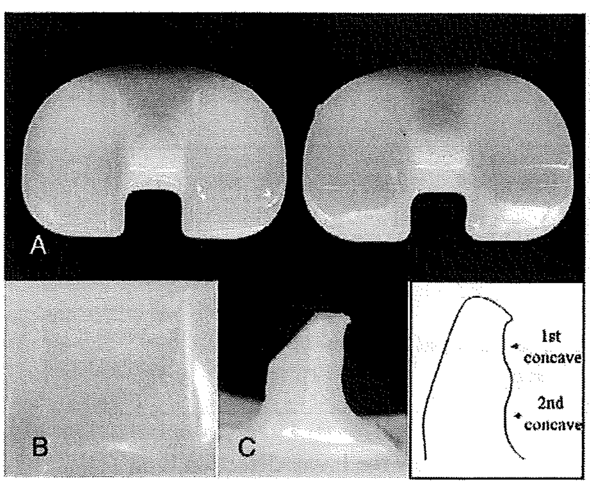

Fig. 4. Polyethylene insert retrieved 7 years postoperatively. Tibiofemoral surfaces display burnishing and dimensional change (ie, creep) (A). Polyethylene post shows abrasion on the top (B) and double-concave deformation in the posterior part suggestive of marking from cam/post contact (C). Schematic representation clearly shows 2 distinct concave surfaces (C, right panel).

Discussion

An earlier study proposed 2 potential risks associated with very deep flexion for the same type of implants used in the present patient [3]. First, large tibial rotation in deep flexion might cause the lateral condyle to overleap the posterior border of the polyethylene insert, leading to breakage of the posterior rim. Fortunately, this did not occur in the present patient, as the tibiofemoral contact position was located anteriorly and internal rotation of the tibia was small. Second, the tibiofemoral articulating surface reportedly separates in more than half of knees at flexion greater than 130°, whereas the cam/post remains in contact even at flexion greater than 130° in most patients [3]. Theoretically, cam/post contact during *seiza*-style sitting might increase the risk of post breakage because the site of concave deformation is moving to the upper part of the post with increasing flexion of the knee. This might arguably represent a limitation of posterior cruciate ligament-sacrificing prostheses with a cam/post design facing the risk of post wear or breakage during *seiza*-style sitting.

Deeply flexed postures increase the risk of polyethylene wear, as tibiofemoral contact occurs at the superior aspect of the femoral condyles in very deep flexion, where contact areas are small. Although histopathology of proliferative synovia revealed substantial numbers of polyethylene particles surrounded by foreign body giant cells, pathologic associations between these particles and continuous joint effusion remained unclear because a 7-year-old well-functioning TKA will inevitably present with certain amounts of wear particles within periprosthetic granulation tissue and surrounding synovia. However, we have previously encountered a case involving a highly damaged polyethylene insert presenting with wear particle–induced synovitis and continuous joint effusion, ultimately developing gigantic popliteal synovial cyst [4]. If such a case were left untreated, accumulation of inflammatory cytokines in joint fluid and increased intraarticular pressure might result in loosening of the prosthesis via periprosthetic osteolysis. In the present case, given that polyethylene insert revision alone soon resulted in the resolution of the joint effusion and limitation of deep flexion, we believe that joint effusion was at least partially attributable to wear particle–induced synovitis.

The risk of wear or fracture of the post has already been highlighted in posterior stabilized implants with an open-box design. Anterior post impingement to the femoral notch occurs with the knee in extension and occasionally causes fracture of the post. This type of impingement has been thoroughly investigated and implicated in increased tibial slope and/or flexed position of the femoral component [5-7]. Conversely, posterior post impingement to the cam reportedly occurs at knee flexion greater than 80° [8], theoretically contributing to the generation of wear particles and/or damage to the post, as a past in vitro experiment showed that cam/post contact force increases with increasing knee flexion [9]. To the best of our knowledge, no previous studies have suggested that very deep flexion can cause post fracture; however, the present case illustrates that repeated very deep flexion, such as in *seiza*-style sitting, may potentiate the risk of post wear and breakage. Future designs for posterior stabilized mechanisms should be awaited to ensure a safe floor-sitting lifestyle, particularly for use in Asian and Middle Eastern countries.

References

1. Banks SA, Hodge WA. Accurate measurement of three-dimensional knee replacement kinematics using single-plane fluoroscopy. IEEE Trans Biomed Eng 1996;43:638.
2. Silva M, Kabbash CA, Tiberi III JV, et al. Surface damage on open box posterior stabilized polyethylene tibial inserts. Clin Orthop 2003;416:135.
3. Kanekasu K, Banks SA, Honjo S, et al. Fluoroscopic analysis of knee arthroplasty kinematics during deep flexion kneeling. J Arthroplasty 2004;19:998.
4. Niki Y, Matsumoto H, Otani T, et al. Gigantic popliteal synovial cyst caused by wear particles after total knee arthroplasty. J Arthroplasty 2003;18:1071.
5. Hendel D, Garti A, Weisbort M. Fractures of the central polyethylene tibial spine in posterior stabilized total knee arthroplasty. J Arthroplasty 2003;18:672.
6. Mauerhan DR. Fracture of the polyethylene tibial post in a posterior cruciate substituting total knee arthroplasty mimicking patellar clunk syndrome: a report of 5 cases. J Arthroplasty 2003;18:942.
7. Mestha P, Shenava Y, D'Arcy JC. Fracture of the polyethylene tibial post in posterior stabilized (Insall Burstein II) total knee arthroplasty. J Arthroplasty 2000;15:814.
8. Li G, Most E, Sultan PG, et al. Knee kinematics with a high-flexion posterior stabilized total knee prosthesis: an in vitro robotic experimental investigation. J Bone Joint Surg Am 2004;86:1721.
9. Li G, Most E, Otterberg E, et al. Biomechanics of posterior-substituting total knee arthroplasty: an in vitro study. Clin Orthop 2002;404:214.

J Orthop Sci (2010) 15:57–63
DOI 10.1007/s00776-009-1410-3

JOURNAL OF
ORTHOPAEDIC SCIENCE

Original article

Rheumatoid arthritis: a risk factor for deep venous thrombosis after total knee arthroplasty? Comparative study with osteoarthritis

Yasuo Niki[1,2], Hideo Matsumoto[3], Akihiro Hakozaki[1], Takeshi Mochizuki[2], and Shigeki Momohara[2]

[1] Department of Orthopaedic Surgery, Keio University, 35 Shinanomachi, Shinjuku-ku, Tokyo 160-8582, Japan
[2] Institute of Rheumatology, Tokyo Women's Medical College, Tokyo, Japan
[3] Institute for Integrated Sports Medicine, Keio University, Tokyo, Japan

Abstract

Background. Recent advances in the understanding of blood coagulation processes favor an inflammatory basis for thrombotic events. In this study, thrombotic risk after total knee arthroplasty (TKA) was assessed and compared between patients with rheumatoid arthritis (RA) and those with osteoarthritis (OA).

Methods. Subjects comprised 199 patients (238 knees) with RA and 156 patients (169 knees) with OA. Serum D-dimer levels were measured before and after the operation. Low-dose unfractionated heparin was given for 7 days when patients had a history of previous venous thromboembolism or had a D-dimer level or ≥10 μg/ml of D-dimer on postoperative day 1. Doppler ultrasonography (DUS) was routinely performed preoperatively and on postoperative day (POD) 7 for diagnosing a deep venous thrombosis (DVT).

Results. D-dimer levels on PODs 0, 1, and 7 were, respectively, 4.6, 37.2, and 11.2 μg/ml for RA and 1.8, 42.3, and 13.6 μg/ml for OA. The incidence of DUS-confirmed DVT was 20.6% in the RA group and 43.2% in the OA group, indicating a much higher incidence of postoperative DVT in OA patients ($P < 0.001$). Interestingly, when patients taking nonsteroidal antiinflammatory drugs (NSAIDs) or those >65 years of age were excluded, the incidence of DVT was comparable in the RA and OA groups. Symptomatic pulmonary embolism and DVT occurred in two and one OA patients and in one and two RA patients, respectively, with one post-discharge DVT included in each group.

Conclusions. The present study revealed that the incidence of DVT following TKA was significantly lower in RA patients than in those with OA. However, when the patients were matched for age and NSAID use, the incidence of DVT was equivalent in the two groups. These findings may allow us to reconsider a prophylactic regimen for venous thromboembolism in patients with RA.

Offprint requests to: Y. Niki
Received: January 5, 2009 / Accepted: September 3, 2009

Introduction

Venous thromboembolism (VTE) is a potentially life-threatening complication in patients undergoing total hip arthroplasty (THA) or total knee arthroplasty (TKA). VTE clinically incorporates signs and symptoms of two interrelated but distinct clinical conditions: deep vein thrombosis (DVT) and pulmonary embolism (PE). The seventh American College of Chest Physicians (ACCP) guidelines for VTE,[1] which are widely accepted evidence-based guidelines concerning the use of VTE prophylaxis, define THA and TKA as having the highest risk of postoperative VTE. The incidence of VTE has so far been considered lower in Japan than in Europe or North America, and VTE has been underdiagnosed and undertreated over the past three decades. However, the incidence is currently increasing and has reached 22.6% for THA and 48.6% for TKA,[2] resulting in increased awareness of the need for VTE prophylaxis in Asian countries.

To date, various risk factors predisposing to VTE have been identified and can be applied to the screening of patients for increased VTE risk prior to surgery.[3] These proven factors comprise heart failure, obesity, age >75 years, history of VTE, varicose veins in the lower extremities, and estrogen therapy; they also include certain inflammatory states, such as certain neoplasms,[4,5] inflammatory bowel disease,[6,7] and septicemia.[8,9]

At present, joint arthroplasty is a promising surgical intervention applicable to patients with several inflammatory arthritides, such as rheumatoid arthritis (RA), ankylosing spondylitis, and psoriatic arthritis. Indeed, these inflammatory arthritides account for a substantial proportion of the primary reasons for performing joint arthroplasty. However, whether inflammatory arthritis is a potential candidate predisposing patients to post-operative VTE remains controversial.

In fact, contradictory results on the association between RA and VTE have been reported in the literature. The main scenarios supporting accelerated thrombosis in RA patients show that active RA exhibits hypercoagulability with reduced fibrinolysis[10] and elevated levels of autoantibodies such as anti-cardiolipin antibodies and anti-phospholipid antibodies.[11–13] Conversely, reports advocating a lower thrombotic risk in RA patients have noted that frequent administration of nonsteroidal antiinflammatory drugs (NSAIDs), younger age distribution, and lower body mass index (BMI) in RA patients may decrease the incidence of VTE.[14–16] The present study assessed and compared thrombotic risk after TKA between patients with RA and those with noninflammatory arthritis, osteoarthritis (OA), to clarify whether RA represents a predisposing factor to VTE following joint arthroplasty.

Materials and methods

Patient characteristics

A consecutive series of 425 knees from 373 patients who underwent primary TKA between October 2003 and June 2007 were enrolled. Among them, 18 knees from 18 patients were excluded from the study for the following reasons: Anticoagulation prophylaxis was contraindicated in eight patients owing to the presence of high bleeding risk or renal impairment; three refused routine anticoagulation therapy; and seven refused postoperative laboratory testing on a routine basis as required by the study protocol. As a result, the RA group comprised 238 knees from 199 patients, and the OA group comprised 169 knees from 156 patients.

Patient demographic characteristics in the two groups are shown in Table 1. The mean age at the time of TKA was 59.9 years (range 25–84 years) in the RA group and 74.2 years (range 40–88 years) in the OA group. The risk of VTE in each patient was individually assessed based on the presence of proven risk factors, as follows: heart failure; obesity (BMI ≥ 30); age >75 years; history of VTE; varicose veins in the lower extremities; use of estrogen therapy; use of warfarin; specific disease conditions including diabetes mellitus, neoplasm, and inflammatory bowel disease. The mean number of risk factors per patient was 1.06 for the RA group and 1.79 for the OA group, indicating a significantly higher VTE risk in the OA group than in the RA group.

As blood rheological properties are closely related to venous circulation and potentially affect susceptibility to VTE, preoperative levels of hemoglobin and hematocrit were measured. The mean values of hemoglobin and hematocrit were, respectively, 12.3 g/dl and 35.3% in the OA group and 11.3 g/dl and 32.5% in the RA group. There was no statistically difference between the two groups (Table 1).

Regarding preoperative oral administration of NSAIDs, in the RA group, 131 patients used NSAIDs daily, 24 patients used them on demand, and 44 patients did not use NSAIDs. In contrast, in the OA group, 9 patients used NSAIDs daily, 44 patients used them on demand, and 103 patients did not use NSAIDs. Antitumor necrosis factor (TNF) inhibitors were administered to 16 patients in the RA group (etanercept, $n = 4$; infliximab, $n = 12$) and no patients in the OA group.

As patient age, BMI, frequency of NSAID use, and number of risk factors at the time of TKA differed significantly between the RA and OA groups (Table 1), patients taking NSAIDs and those ≤65 years of age were excluded from each group, and statistical analyses were performed again. These exclusions were made because the use of NSAIDs and patient age reportedly affect the incidence of VTE.[16] Demographic data for the two groups after these adjustments were made are shown in Table 2.

The study was approved by the institutional human subjective research committee, and informed consent was obtained from all patients participating in the study.

Antithrombotic protocol

Serum D-dimer levels were measured on postoperative days (PODs) 0, 1, and 7. When patients displayed a D-dimer level of ≥10 μg/ml on POD 1, low-dose unfractionated heparin (LDUH) (5000 units) was given subcutaneously three times a day from POD 2 to POD 8. An equivalent dose of LDUH was given to high-risk patients with either a history of previous VTE or three or more risk factors.

Doppler ultrasonography (DUS) was routinely performed in all patients preoperatively and on POD 7 for diagnosing DVT. Warfarin was administered orally to patients with DUS-confirmed DVT, starting on POD 7 and continuing for 3 months. Patients were followed for symptomatic VTE until ≥3 months after TKA.

Bleeding complications were recorded as described previously.[17] They were classified as "major" if clinically overt (clinically apparent bleeding or signs and/or symptoms suggestive of bleeding with confirmatory imaging studies such as ultrasonography or computed tomography) and meeting one or more of the following criteria: involvement of a critical site (intracranial, retroperitoneal, intraspinal, intraarticular, gastrointestinal, pericardial); bleeding index ≥2.0 (calculated as the baseline hemoglobin level, in grams/liter, minus the hemoglobin level at the end of treatment plus the number of units of packed red blood cells or whole blood transfused); need for medical or surgical intervention; fatal bleeding.

Table 1. Demographic characteristics of patients with RA and OA

Characteristic	RA	OA
No. of knees	238	169
No. of patients	199	156
Age (years) (range)*	59.9 (25–84)	74.2 (40–88)
Sex (no. of patients/knees)		
Male	20/17	17/16
Female	218/182	152/140
BMI (range)*	21.8 (14.0–33.9)	25.0 (16.2–33.3)
No. of knees, by no. of risk factors		
0	114	35
1	57	44
2	18	44
3	38	24
4	9	12
5	2	10
Mean*	1.06	1.79
Medications (no. of knees/patients)		
NSAIDs		
None*	47/44	112/103
On demand	32/24	48/44
Daily*	159/131	9/9
Oral steroid*	82/70	0/0
Anti-TNF inhibitor*	18/16	0/0
Preoperative levels of blood rheological parameters[a]		
Hemoglobin (g/dl)	11.3 ± 1.8	12.3 ± 1.5
Hematocrit (%)	32.5 ± 4.6	35.3 ± 3.4
CRP level (mg/dl)[a]		
Preoperative*	1.27 ± 1.87	0.34 ± 0.88
Postoperative day 1	4.83 ± 2.73	4.54 ± 2.84

RA, rheumatoid arthritis; OA, osteoarthritis; BMI, body mass index; NSAIDs, nonsteroidal antiinflammatory drugs; TNF, tumor necrosis factor

* $P < 0.05$, RA vs. OA

[a]Values are expressed as the mean ± SD

Table 2. Demographic characteristics of patients matched for age and NSAIDs non-use

Characteristic	RA	OA
No. of knees	42	102
No. of patients	39	95
Age (years), mean (range)	75.0 (65–84)	75.7 (65–88)
Sex (no. of knees/patients)		
Male	5/4	12/12
Female	37/35	90/83
BMI (range)	23.4 (18.8–29.4)	24.8 (16.8–33.3)
No. of knees, by no. of risk factors		
0	7	14
1	15	30
2	4	35
3	15	13
4	1	7
5	0	4
Mean	1.71	1.82
Medications (no. of knees/patients)		
Oral steroid*	8/6	0/0
Anti-TNF inhibitor	2/2	0/0
CRP level (mg/dl)[a]		
Preoperative	0.39 ± 0.74	0.28 ± 0.45
Postoperative day 1	4.99 ± 2.78	4.78 ± 1.83

* $P < 0.05$, RA vs. OA

[a]Values are expressed as the mean ± SD

Statistical analysis

The RA and OA groups with and without adjustment for age and NSAID use were compared for the following: age; BMI; rate of NSAID use; incidence of DUS-confirmed asymptomatic DVT; incidence of symptomatic DVT or PE; incidence of bleeding complications; rate of LDUH use; and serum D-dimer levels on PODs 0, 1, and 7. Statistical analyses were performed using Student's t-test for continuous variables and a χ^2 contingency table for dichotomous values. $P < 0.05$ was considered statistically significant.

Results

Time course of changes in serum D-dimer levels

Serum levels of D-dimer on PODs 0, 1, and 7 were, respectively, 4.6 ± 0.51, 37.2 ± 2.6, and 11.2 ± 0.46 μg/ml for RA and 1.8 ± 0.41, 42.3 ± 5.5, and 13.6 ± 1.2 μg/ml for OA (Fig. 1). Serum D-dimer levels were thus significantly higher in the RA group than in the OA group preoperatively ($P < 0.05$), whereas similar time courses of D-dimer levels were seen for the two groups postoperatively, although tending to be slightly higher in the OA group than in the RA group.

Incidence of VTE

Preoperatively, DUS-confirmed DVT was found in 21 patients (8.8%) in the RA group and 19 patients (11.2%) in the OA group, with no significant difference between groups (Table 3). On POD 7, the incidence of DUS-confirmed DVT was 20.6% in the RA group and 43.2% in the OA group, indicating more frequent DVT in the presence of OA than in RA ($P < 0.001$). Proximal DVT was identified in eight RA patients (3.3%) and seven OA patients (4.1%), showing no significant difference. All patients were available for follow-up for ≥3 months after TKA and were checked for development of symptomatic VTE. During the first 3 months after TKA, symptomatic PE was found in two patients in the OA group and one patient in the RA group, and symptomatic DVT was found in two patients in the RA group and one patient in the OA group, including one case of postdischarge DVT in each group.

According to the existing literature dealing with comparative analysis of DVT risk between RA and OA, the incidence of DVT has been considered low for RA patients potentially because of the frequent administration of NSAIDs and younger age distribution among patients with RA.[16] Patients using NSAIDs or who were

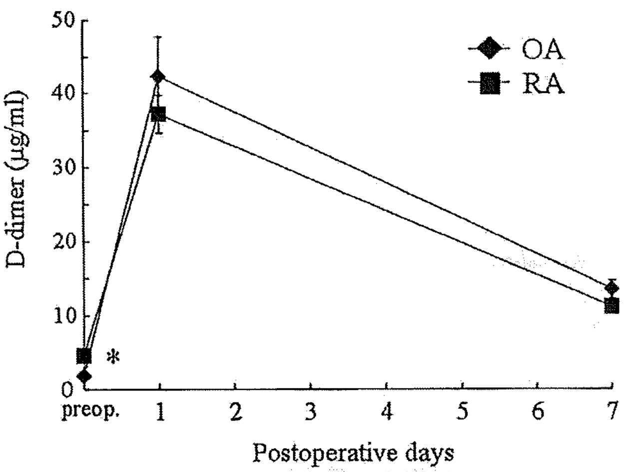

Fig. 1. Time course of plasma D-dimer levels after total knee arthroplasty. Data are given as the mean ± standard deviation. *Preop.*, preoperative. *$P < 0.05$, rheumatoid arthritis (*RA*) vs. osteoarthritis (*OA*)

Table 3. Incidence of VTE and bleeding complications within first 3 months after TKA

	All patients		Patients matched for age and NSAIDs non-use	
Parameter	RA (n = 238)	OA (n = 169)	RA (n = 42)	OA (n = 102)
Asymptomatic DVT (no. of knees)				
Preoperative	21 (8.8%)	19 (11.7%)	4 (9.5%)	10 (9.8%)
Postoperative day 7	49 (20.6%)*	73 (43.2%)	16 (38.1%)	43 (42.2%)
Proximal DVT	8 (3.3%)	7 (4.1%)	2 (4.8%)	4 (3.9%)
Symptomatic DVT (no. of knees)				
In-hospital	1	0	0	0
After discharge	1	1	1	1
Symptomatic PE (no. of knees)	1	2	0	1
LDUH use (%)	67.7	72.5	78.6	72.5
Major bleeding (no. of knees)	1	2	0	1

VTE, venous thromboembolism; TKA, total knee arthroplasty; DVT, deep vein thrombosis; PE, pulmonary embolism; LDUH, low-dose unfractionated heparin

*$P < 0.001$, RA vs. OA

≤65 years of age were therefore excluded from each group to adjust the patient demographics between groups and elucidate the precise effects of the chronic inflammation of RA on the development of VTE. After this adjustment, no significant differences were identified between the RA and OA groups regarding age, sex, BMI, or number of preexisting risk factors for VTE (Table 2).

Interestingly, the incidence of DVT was 38.1% for RA and 42.2% for OA after the adjustments, suggesting that the incidence of DVT was quite similar in the two groups; thus, RA itself does not appear to represent a predisposing factor for DVT. In addition, regarding symptomatic VTE, the incidences of PE and DVT were not significantly different (Table 3).

Approximately 70% of patients in our TKA series received LDUH during the postoperative course according to our screening protocol of anticoagulation therapy (Table 3). Major bleeding complications during LDUH administration were seen in two patients with OA (gastrointestinal bleeding, $n = 1$; surgical site bleeding, $n = 1$) and one patient with RA (gastrointestinal bleeding).

Discussion

As total joint arthroplasties, such as TKA and THA, are becoming promising surgical interventions for treating joint destruction associated with RA and related inflammatory arthropathies, important issues facing the patients undergoing total joint arthroplasty are increasingly highlighted, including postoperative VTE. TKA and THA have been defined as carrying the highest thromboembolic risks according to accumulated evidence, such as the finding that the incidence of DVT after joint arthroplasty can reach 50%, and fatal PE occurs in 1%–6% without thromboprophylaxis.[18] These data have been derived predominantly from patients with OA, however, and the precise thromboembolic risk in patients with RA remains poorly understood.

To date, certain studies dealing with postoperative VTE risk in patients with RA have documented that the incidence of DVT is 3–10 times lower in patients with RA than in patients with OA.[14,15] Another retrospective study of the incidence of postdischarge VTE after joint arthroplasty reported that only 1 of 103 patients with RA developed symptomatic DVT during a 1-year follow-up.[16] These studies reached the identical conclusion that the decreased incidence of symptomatic VTE in patients with RA was attributable to frequent use of NSAIDs with the resulting antiplatelet activity. However, those studies appear to include the following drawbacks: (1) the studies were not prospective investigations; (2) the studies focused only on symptomatic VTE and did not include asymptomatic VTE; and (3) the precise effects of the chronic inflammation in RA on developing VTE were not clarified, as most RA patients used NSAIDs preoperatively. The present study therefore prospectively investigated the incidence of both symptomatic and asymptomatic DVT in patients with RA undergoing TKA, with particular emphasis on comparison between patients with RA and OA, none of whom were using NSAIDs.

According to the results from all patients enrolled, patients with RA displayed significantly higher D-dimer levels preoperatively, reflecting accelerated fibrin formation and fibrinolysis in the preoperative phase due to constitutive inflammation. Conversely, postoperative D-dimer levels were not significantly different between patients with RA and OA. As expected, the incidence of DUS-confirmed DVT on POD 7 in patients with OA was double that in patients with RA, potentially because in our RA series approximately 78% of patients were orally administered NSAIDs both pre- to postoperatively. Interestingly, when patients taking NSAIDs or ≤65-years-old were excluded, the incidence of DUS-confirmed DVT was comparable between the RA and OA groups. Whether chronic inflammatory diseases such as RA are associated with the development of VTE after joint arthroplasty thus remains controversial.

Historically, inflammation has had little to do with the coagulation response; and a traditional view was that the blood coagulation pathway is simply triggered when tissue factor derived from the cell surface of leukocytes, particularly monocytes, comes in contact with factor VII/VIIa in the blood.[19,20] During the 1990s, however, the picture changed in light of new observations that inflammatory mediators such as endotoxin, tumor necrosis factor-α (TNF-α), and CD40 ligand play crucial roles in the activation of tissue factor.[21–23] Recent studies support an inflammatory basis for the blood coagulation process,[24] and chronic inflammatory conditions may shift the hemostatic balance to favor the activation of coagulation, as has been documented clinically in inflammatory bowel diseases including ulcerative colitis and Crohn's disease.[6,7] Although the best known scenario of inflammation-induced hypercoagulation is the induction of tissue factor, other possible mechanisms can be considered, including impairment of the protein C anticoagulant pathway by down-regulating the expression of thrombomodulin and endothelial cell protein C receptor on endothelial cells,[25,26] and up-regulating levels of plasminogen activator inhibitor (PAI)-1 and subsequent impaired ability to remove thrombus (i.e., fibrinolysis).[27] Mounting evidence has proven elevated levels of TNF-α and PAI-1 in patients with RA,[28,29] and these patients are prone to thrombotic complications after joint arthroplasty. However, according to the present study, the incidence of VTE after TKA is basically equivalent between RA and OA patients despite the standardization of risk factors for VTE in the two groups. At present, we believe that these unexpected results can be explained by the fact that (1) the inflammation of RA can be tightly controlled using anti-TNF inhibitors and (2) the pre- and postoperative C-reactive protein (CRP) levels of the RA patients were regulated to levels similar to those in OA patients (Tables 1, 2).

As hemoglobin and hematocrit levels tend to be low in patients with RA, blood rheology should not be overlooked in regard to DVT pathogenesis when considering DVT risk in RA patients. However, whether blood rheology affects a patient's susceptibility to postoperative DVT remains unclear despite the close relation between blood rheological properties and venous circulation. Hemoglobin and hematocrit levels do not appear to have been defined as risk factors for DVT in previous studies.[30,31] The present study, however, could not disregard the influence of these two parameters, as values tended to be lower in RA patients than in OA patients and could not be matched during comparisons of RA and OA. Whether blood rheology represents an alternative etiology for DVT is a potential subject for future studies.

In our TKA series, the overall incidence of DUS-confirmed DVT was 20.6% in the RA group and 43.2% in the OA group, indicating a much lower incidence of postoperative DVT in RA patients. A recent study showed that the incidence of symptomatic VTE in patients with RA undergoing joint arthroplasty was low owing to daily administration of NSAIDs,[16] supporting the present findings. Even though lower DVT risk in RA was attributable to younger age and higher frequency of NSAID usage at the time of TKA — rather than to the disease itself — surgeons should pay close attention to the prophylactic use of anticoagulant therapies for thromboembolic events after TKA in patients with RA.

Finally, our findings must take into consideration three major limitations of this study. First, a multiple regression analysis should have been used to analyze the effects of all independent variables as potential risk factors for VTE. However, in our cohort, LDUH was administered only to the patients with increased risk of VTE based on assessments of their preoperative risk score or their D-dimer level, which created a bias regarding the indication for anticoagulant therapy after TKA in our cohort. As use of anticoagulant therapy is considered to be the most critical factor influencing the incidence of VTE, it is worthless to analyze risk factors of VTE in this cohort. In fact, when a stepwise multiple linear regression analysis was performed in this cohort, use of LDUH was paradoxically defined as a significant risk factor of VTE with the largest odds ratio because LDUH was used in the patients with a high VTE score.

Second, the precise effects of NSAIDs on the incidence of VTE following TKA remain unclear as the present study did not directly confirm whether the reduced incidence of VTE in RA patients was attributed to frequent administration of NSAIDs or the disease itself. The patients should be randomized to use of NSAIDs preoperatively in both RA and OA cohorts, which is a potential subject for future study.

Third, because one investigative group reported that oral steroid use is one of the risk factors for postoperative VTE,[32] we should have elucidated whether steroid use affected the incidence of VTE in our cohort. However, the type, dosage, and duration of steroid use varied considerably from case to case; and the net steroid usage could not be explained by daily steroid dosage at the time of examination. Further studies, including a randomized controlled trial, on the use of NSAIDs or steroid in larger cohorts of RA patients are needed so we can better understand the true magnitude of VTE risk following TKA in patients with RA.

The authors did not receive and will not receive any benefits or funding from any commercial party related directly or indirectly to the subject of this article.

References

1. Geerts WH, Pineo GF, Heit JA, Bergqvist D, Lassen MR, Colwell CW, et al. Prevention of thromboembolism. Chest 2004; 126(suppl):338S–400S.
2. Fujita S, Hirota S, Oda T, Kato Y, Tsukamoto Y, Fuji T. Deep venous thrombosis after total hip or total knee arthroplasty in patients in Japan. Clin Orthop 2000;375:168–74.
3. Russel MW, Taylor DCA, Cumminus G, Huse DM. Use of managed care claims data in the risk assessment of venous thromboembolism in outpatients. Am J Manag Care 2002;8: S3–9.
4. Coussens LM, Werb Z. Inflammation and cancer. Nature 2002;420: 860–7.
5. Aggarwal BB, Shishodia S, Sandur SK, Pandey MK, Sethi G. Inflammation and cancer: how hot is the link? Biochem Pharmacol 2006;72:1605–21.
6. Solem CA, Loftus EV, Tremaine WJ, Sandborn WJ. Venous thromboembolism in inflammatory bowel disease. Am J Gastroenterol 2004;99:97–101.
7. Bernstein CN, Blanchard JF, Houston DS, Wajda A. The incidence of deep venous thrombosis and pulmonary embolism among patients with inflammatory bowel disease: a population-based cohort study. Thromb Haemost 2001;85:430–4.
8. Van Deventer SJ, Buller HR, ten Cate JW, Aarden LA, Hack CE, Sturk A. Experimental endotoxemia in humans: analysis of cytokine release and coagulation, fibrinolytic, and complement pathways. Blood 1990;76:2520–6.
9. Psuja P, Zozulinska M, Turowiecka Z, Cieslikowski W, Vinazzer H, Zawilska K. Plasma markers of hypercoagulability in patients with serious infections and risk of septic shock. Clin Appl Thromb Hemost 2002;8:225–30.
10. So AK, Varisco PA, Kemkes-Matthes B, Herkenne-Morard C, Chobaz-Peclat V, Gerster JC, et al. Arthritis is linked to local and

systemic activation of coagulation and fibrinolysis pathways. J Thromb Haemost 2003;1:2510–5.
11. Seriolo B, Accardo S, Garnero A, Fasciolo D, Cutolo M. Anticardiolipin antibodies, free protein S levels and thrombosis: a survey in a selected population of rheumatoid arthritis patients. Rheumatology (Oxford) 1999;38:675–8.
12. Seriolo B, Accardo S, Fasciolo D, Bertolini S, Cutolo M. Lipoproteins, anticardiolipin antibodies and thrombotic events in rheumatoid arthritis. Clin Exp Rheumatol 1996;14:593–9.
13. Fort JG, Cowchock FS, Abruzzo JL, Smith JB. Anticardiolipin antibodies in patients with rheumatic diseases. Arthritis Rheum 1987;30:752–60.
14. Buchanan RR, Kraag G. Is there a lower incidence of deep venous thrombosis after joint replacement in rheumatoid arthritis? J Rheumatol 1980;7:551–4.
15. Sikorski JM, Hampson WG, Staddon GE. The natural history and aetiology of deep vein thrombosis after total hip replacement. J Bone Joint Surg Br 1981;63:171–7.
16. Van Heereveld HA, Laan RF, van den Hoogen FH, Malefijt MC, Novakova IR, van de Putte LB. Prevention of symptomatic thrombosis with short term (low molecular weight) heparin in patients with rheumatoid arthritis after hip or knee replacement. Ann Rheum Dis 2001;60:974–6.
17. Colwell CW Jr, Berkowitz SD, Lieberman JR, Comp PC, Ginsberg JS, Paiement G, et al. Oral direct thrombin inhibitor ximelagatran compared with warfarin for the prevention of venous thromboembolism after total knee arthroplasty. J Bone Joint Surg Am 2005;87:2169–77.
18. Salzman EW, Hirsh J. The epidemiology, pathogenesis and natural history of venous thrombosis. In: Colman RW, Hirsh J, Marder VJ, Salzman EW, editors. Hemostasis and thrombosis: basic principles and clinical practice. Philadelphia: Lippincott; 1994. p. 1275–96.
19. Rao LV, Rapaport SI, Bajaj SP. Activation of human factor VII in the initiation of tissue factor-dependent coagulation. Blood 1986;68:685–91.
20. Fair DS, MacDonald MJ. Cooperative interaction between factor VII and cell surface-expressed tissue factor. J Biol Chem 1987;262:11692–8.
21. Mackman N. Regulation of tissue factor gene expression in human monocytic and endothelial cells. Haemostasis 1996;26(suppl 1):17–9.
22. Bierhaus A, Zhang Y, Deng Y, Mackman N, Quehenberger P, Haase M, et al. Mechanism of the tumor necrosis factor alpha-mediated induction of endothelial tissue factor. J Biol Chem 1995;270:26419–32.
23. Lindmark E, Tenno T, Siegbahn A. Role of platelet P-selectin and CD40 ligand in the induction of monocytic tissue factor expression. Arterioscler Thromb Vasc Biol 2000;20:2322–8.
24. Esmon CT. The interactions between inflammation and coagulation. Br J Haematol 2005;131:417–30.
25. Conway EM, Rosenberg RD. Tumor necrosis factor suppresses transcription of the thrombomodulin gene in endothelial cells. Mol Cell Biol 1988;8:5588–92.
26. Fukudome K, Esmon CT. Identification, cloning and regulation of a novel endothelial cell protein C/activated protein C receptor. J Biol Chem 1994;269:26486–91.
27. Scarpati EM, Sadler JE. Regulation of endothelial cell coagulant properties: modulation of tissue factor, plasminogen activator inhibitors, and thrombomodulin by phorbol 12-myristate 13-acetate and tumor necrosis factor. J Biol Chem 1989;264:20705–13.
28. Maini RN, Elliott M, Brennan FM, Williams RO, Feldmann M. Targeting TNF alpha for the therapy of rheumatoid arthritis. Clin Exp Rheumatol 1994;12(suppl 11):S63–6.
29. Kopeikina LT, Kamper EF, Koutsoukos V, Bassiakos Y, Stavridis I. Imbalance of tissue-type plasminogen activator (t-PA) and its specific inhibitor (PAI-1) in patients with rheumatoid arthritis associated with disease activity. Clin Rheumatol 1997;16:254–60.
30. Vayá A, Mira Y, Martínez M, Villa P, Ferrando F, Estellés A, et al. Biological risk factors for deep vein thrombosis. Clin Hemorheol Microcirc 2002;26:41–53.
31. Banyai S, Banyai M, Koppensteiner R. Blood rheology in deep venous thrombosis: relation to persistent and transient risk factors. Thromb Res 2002;15;107:101–7.
32. Gangireddy C, Rectenwald JR, Upchurch GR, Wakefield TW, Khuri S, Henderson WG, et al. Risk factors and clinical impact of postoperative symptomatic venous thromboembolism. J Vasc Surg 2007;45:335–41.

The Journal of Arthroplasty Vol. 25 No. 2 2010

Extension Limitation in Standing Affects Weight-Bearing Asymmetry After Unilateral Total Knee Arthroplasty

Kengo Harato, MD, Takeo Nagura, MD, PhD, Hideo Matsumoto, MD, PhD, Toshiro Otani, MD, PhD, Yoshiaki Toyama, MD, PhD, and Yasunori Suda, MD, PhD

Abstract: The aim of this study was to evaluate weight-bearing condition after unilateral total knee arthroplasty (TKA) during standing and to examine whether the condition affects knee kinetics during gait in both limbs. Twenty-five patients, who underwent unilateral TKA for symptomatic bilateral osteoarthritis and who were on average 74 years old, participated. As a result, operated limbs became dominant in 80% of the patients. The other 20%, who had lack of knee extension during standing, showed more weight bearing in nonoperated knees. Furthermore, extension limitation in the operated knee in standing led to mechanical overload in the contralateral limb during gait. Therefore, to avoid progression of the osteoarthritis in the contralateral knee, it is important to acquire full extension in the operated knees during standing after unilateral TKA. **Keywords:** unilateral total knee arthroplasty, weight-bearing asymmetry, standing, gait analysis, extension limitation, quadriceps muscle strength.

Severe knee osteoarthritis (OA) often limits the elderly people to perform normal activities of daily living. Symptomatic knee OA is found in approximately 14.4% of men and 28.4% of women older than 45 years, and 87% of knee OA occurs bilaterally [1,2]. Total knee arthroplasty (TKA) has traditionally been performed as an effective treatment for these patients, by relieving pain, restoring function, and correcting deformity [3,4]. Gait analysis is widely used to evaluate dynamic function of both osteoarthritic and replaced knee joint [5-7]. As described in the previous gait analysis studies, abnormal joint loading is indicated in patients with knee OA [8-10]. The patients with medial knee OA have increased knee adduction moment during walking. According to previous studies, pain relief was accompanied by knee adduction moment after use of nonsteroidal anti-inflammatory drug in patients with knee OA [11-13]. In addition, Hurwitz et al [11] showed that decreases in pain were associated with an increase in knee joint loading during level walking and indicated that the change in pain levels was inversely correlated with the change in knee joint loading. Therefore, pain could be a protective mechanism against increased joint loads; and subjective pain may result in reduced loading of the affected joint. Thus, increased joint loads should be observed after TKA comparing with those of contralateral OA because pain level is reduced. On the other hand, it is possible that subjective pain in contralateral OA knee can be frequently reduced after unilateral TKA. Although we often experienced this phenomenon, little attention has been paid to evaluate weight-bearing condition in both limbs after the surgery.

We hypothesize that the knee joint after TKA would act as a dominant limb and have more weight bearing than contralateral nonoperated OA knee in relaxed standing because compensatory mechanics against painful OA knee is basically observed. The aim of this study was to evaluate weight-bearing condition in both limbs after unilateral TKA during standing and to examine whether the surgery affects the loading rate and other gait parameters in contralateral OA knee using gait analysis.

From the Department of Orthopedic Surgery, Keio University, Tokyo, Japan.
Submitted October 5, 2008; accepted February 3, 2009.
This study was supported by The General Insurance Association of Japan.
Reprint requests: Kengo Harato, MD, Department of Orthopedic Surgery, Keio University, 35 Shinanomachi, Shinjuku, Tokyo 160-8582, Japan.

0883-5403/08/2502-0011$36.00/0
doi:10.1016/j.arth.2009.02.003

Materials and Methods

Participants and Gait Analysis System

Twenty-five patients (22 women and 3 men), who underwent unilateral TKA for bilateral symptomatic knee osteoarthritis and who were 67 to 84 years old

Table 1. Demographic Data of 25 Patients Undergoing Unilateral TKA (Mean ± Standard Deviation)

	Patients (n = 25)
Age	74.1 ± 5.5
BMI (kg/m²)	26.0 ± 3.0
Sex (female/male)	22/3
Implant (CR Flex/LPS Flex)	6/19
Follow-up period (mo)	14.7 ± 9.4

(mean, 74 years), participated in the current study. Cruciate-retaining or posterior-stabilized component design (NexGen CR Flex or LPS Flex, Zimmer, Warsaw, IN) were used by a single surgeon (TO). We confirmed that replaced knee acquired full extension after the procedure in the operation room. Patients underwent a standard rehabilitation program that consisted of early range of motion and weight-bearing exercises as tolerated. Radiographic grades of knee OA in nonoperated knees were at least grade 3 severities according to the Kellgren-Lawrence grade [14], including 7 knees of grade 3 and 18 knees of grade 4. Patients who had any symptoms in either the hip or ankle joint were excluded. Demographic data of 25 patients are presented in Table 1.

After an informed consent, all subjects were tested at our gait laboratory using 6 retroreflective markers, a 5-camera system (120 frames per second; Pro-reflex, Qualisys, Gothenburg, Sweden), and a force plate (sample frequency, 120 Hz; Type 4060-10, Bertec, Columbus, OH) at an average of 15 (4-36) months after surgery. Six markers were placed at the lateral aspect of the iliac crest, greater trochanter, lateral joint line of the knee, lateral malleolus, lateral aspect of the calcaneus, and head of the fifth metatarsal [15]. Clinical assessment was done using Hospital for Special Surgery (HSS) score, and passive range of motion was examined. All methods and procedures were also approved by our institution's ethics committee.

Motion Analysis

The patients performed relaxed standing, placing 1 foot on a force plate for 5 seconds until subjects became stable and relaxed (Fig. 1A); and thereafter, they were asked to walk on a level floor for about 10 m at their preferred speed. Relaxed standings were measured in each patient twice. Walking trials included warm-ups, and the trials were measured several times until clear contact with the force plate was achieved in each trial. Because there is a single force plate in the laboratory, the measurements for each leg were undertaken independently. The knee kinetics was calculated using an inverse dynamics approach [16].

Evaluation of Loading Asymmetry

During relaxed standing, knee resultant force (percentage of body weight [%BW]) was calculated on bilateral knees of all patients. Definition of dominant side limb was based on the evaluation of loading asymmetry according to these forces: TKA dominant, knee resultant force was greater on TKA side than OA side; or OA dominant, knee resultant force was greater on OA side than TKA side.

Analysis of Factors Affecting the Loading Asymmetry

To analyze the factors that affect the weight-bearing condition in both limbs, patients' backgrounds were compared between TKA-dominant group (group A) and OA-dominant group (group B). Because side-to-side differences of weight distribution in standing would lead to the gait asymmetry as previously described in the literature [17,18], the following parameters were also evaluated in each group: knee flexion angles (degrees) in standing and at heel strike on each knee, peak values of net knee adduction and extension moment (%BW Height) on each knee, and maximum axial knee loading rate (%BW per second) on OA knees during gait. *Maximum axial loading rate* was defined as maximum slope of the axial force at the knee during first 10% of stance phase. The *axial force at the knee* was defined as the intersegmental resultant force at the knee resolved along the long axis of the shank, taking into account the ground reaction force, the weight of the shank, and the inertial forces (Fig. 1B) [19].

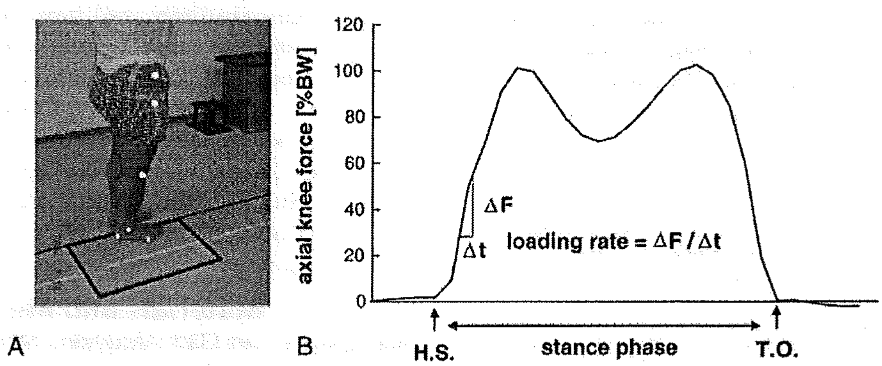

Fig. 1. (A) Subjects performed relaxed standing, placing 1 foot on a force plate, and level walking thereafter. (B) *Maximum axial loading rate* (%BW per second) was defined as maximum slope of the axial force during first 10% of stance phase.

Statistical Analysis

An average value of 2 trials was calculated. Statistical difference between TKA and OA knees in each group was evaluated using Wilcoxon *t* test. In addition, Mann-Whitney *U* test was used to determine the differences between groups in TKA or OA knees. Categorical valuables were analyzed by χ^2 test or Fisher exact test. *P* values less than .05 were considered as significant. All statistical analyses were done with the use of SPSS Version 11 for Microsoft Windows (SPSS, Chicago, IL).

Results

Weight-Bearing Asymmetry

Weight-bearing asymmetry was seen among the patients, as 20 patients were allocated to TKA dominant (group A) and 5 patients were OA dominant (group B). In group A, the averages of knee resultant forces (%BW) were 53.4 ± 9.8 on TKA side and 34.8 ± 6.7 on OA side. On the contrary, those were 39.1 ± 6.7 on TKA side and 50.0 ± 6.3 on OA side in group B. Each patient in both groups had relatively large side-to-side difference that was more than 5%BW (Table 2).

Factors Affecting Asymmetrical Loading

Concerning the demographic data, there were no statistical differences between the groups, including age, body mass index (BMI), total HSS score, passive range of motion, and other categorical valuables (Table 2). When comparing pain scores of HSS on TKA side in both groups, there was no difference, as the scores were 28.7 ± 2.3 in group A and 27.0 ± 4.4 in group B. Furthermore, pain scores on OA side were 21.8 ± 3.8 in group A and 23.0 ± 5.7 in group B; and those were not significantly different between the groups.

Results of knee flexion angles during relaxed standing are presented in Fig. 2. In group A, operated knees were significantly more extended than OA knees during relaxed standing, although operated knees were significantly more flexed than OA knees in group B. Particularly, operated knees had less knee extension in group B than in group A.

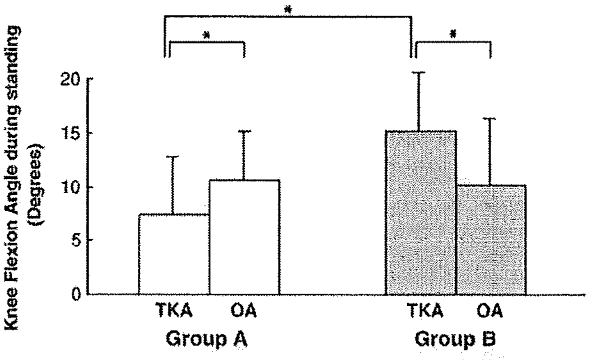

Fig. 2. Knee flexion angle (degrees) during relaxed standing in each group (*P <05).

Knee flexion angles at heel strike were not significantly different between the knees in each group (Table 3), although the angle on TKA side in group B was relatively larger than that in group A. Net knee adduction and extension moment are also presented in Table 3. The TKA side had less net knee adduction moment than the OA side, but the moments were not significantly different between TKA knees or OA knees in both groups. Net knee extension moments in group B were significantly smaller than those in group A, when comparing the moments between the TKA knees or OA knees. Maximum axial knee loading rate (%BW per second) on OA side during gait is found in Fig. 3. Those on OA knees in group B were significantly larger than those in group A. We confirmed that all the data obtained from gait analysis in the current study were reproducible.

Discussion

Our hypothesis that TKA side has dominant loading in relaxed standing was confirmed in 20 of 25 patients (80%). Although many studies have concentrated on the role of high flexion in TKA [20-22], few have

Table 2. Patient Data in Each Group (Mean ± Standard Deviation)

	Group A (n = 20)		Group B (n = 5)		Statistical Significance
	TKA Side	OA Side	TKA Side	OA Side	
Knee resultant force in standing (%BW)	53.4 ± 9.8	34.8 ± 6.7	39.1 ± 6.7	50 ± 6.3	NS
Age	74.3 ± 5.2		72.8 ± 6.3		NS
BMI (kg/m^2)	26.1 ± 3.4		25.9 ± 1.3		NS
Sex (female/male)	19/1		3/2		NS
Implant (CR Flex/LPS Flex)	4/16		2/3		NS
Follow-up period (mo)	14.5 ± 9.4		15.7 ± 9.7		NS
Radiographic OA grade (grade 3/grade 4)		5/15		2/3	NS
Total HSS score	91 ± 4.2	81 ± 12.1	90.3 ± 6.7	82.5 ± 8.3†	
HSS pain score	28.7 ± 2.3	21.8 ± 3.8*	27 ± 4.4	23 ± 5.7†	
Passive range of motion (extension)	1.3 ± 3.7	5.2 ± 8.5	3.3 ± 6.9	4.0 ± 6.1	NS
Passive range of motion (flexion)	118.1 ± 13.3	120.6 ± 17.3	116.7 ± 4.8	123.7 ± 13.3	NS

NS indicates not significant.
*P less than .05 between TKA and OA side in group A using Wilcoxon *t* test.
†P less than .05 between TKA and OA side in group B using Wilcoxon *t* test.

Table 3. Knee Kinematics and Kinetics During Level Walking (Mean ± Standard Deviation)

	Group A (n = 20)		Group B (n = 5)		Statistical Significance
	TKA Side	OA Side	TKA Side	OA Side	
Knee flexion angle (°) at heel strike	3.2 ± 1.8	5.6 ± 2.4	7.0 ± 1.5	5.7 ± 3.5	NS
Knee adduction moment (%BW Height)	2.8 ± 2.2	4.0 ± 0.8*	2.4 ± 1.4	3.9 ± 0.5†	
Knee extension moment (%BW Height)	1.5 ± 1.1	1.9 ± 1.2	0.8 ± 0.5‡	0.7 ± 0.6§	

**P* less than .05 between TKA and OA side in group A using Wilcoxon *t* test.
†*P* less than .05 between TKA and OA side in group B using Wilcoxon *t* test.
‡*P* less than .05 between TKA side in group A and TKA side in group B using Mann-Whitney *U* test.
§*P* less than .05 between OA side in group A and OA side in group B using Mann-Whitney *U* test.

concentrated on the importance of knee extension [23,24]. From our results, ability to extend the knee joint during standing was considered to be a key factor to decide loading condition in both limbs. Previous studies have shown that knee extension limitation of greater than 15° in standing would cause balance impairment and lead to mechanical overload to contralateral knee during gait [17,18,25]. In our study, asymmetrical loading in both limbs may result from less extension and quadriceps muscle weakness in the operated knees during relaxed standing. In particular, replaced knees in group B could not extend fully during standing; and knee extension limitation greater than 15° in standing was observed, even if knee flexion contracture was not detected by physical examination. On the other hand, static alignment (ie, knee adduction moment) and subjective pain were not factors to affect the loading condition. These results indicate that, if the operated knee has enough extension in standing, the operated limb becomes dominant. On the contrary, if extension limitation is seen in the operated knee in standing, the limb would not have dominant loading. Because postoperative passive range of motion was not significantly different between the groups, the cause of the extension limitation in standing should not be flexion contracture; and it might be other factors such as quadriceps strength. In fact, significantly smaller extension moments in operated knees were detected in OA-dominant group than in TKA-dominant group (Table 3).

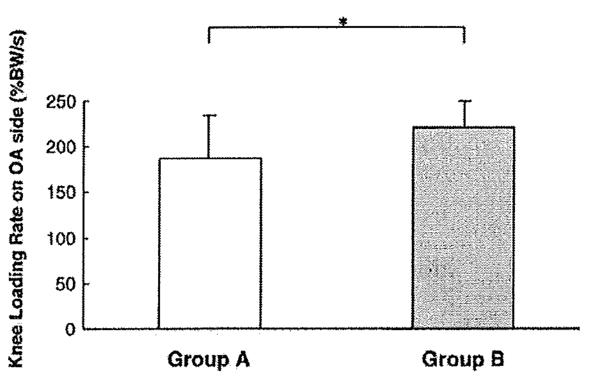

Fig. 3. Maximum knee loading rate (%BW per second) on OA side during level walking in each group (*$P < .05$).

Quadriceps muscle strength is an important consideration in gait characteristics after TKA. Yoshida et al [26] indicated that, when the operated limb had a very weak quadriceps, patients would depend on the nonoperated side to compensate by placing greater forces on the nonoperated leg during gait. Thus, retraining program that encourages the patients to use improvements in quadriceps strength with greater knee extension during standing can be effective.

The patients with medial knee OA have increased knee adduction moment during walking, and a primary strategy of the treatment is to reduce the moment [27]. After unilateral TKA in patients with bilateral knee OA, net knee adduction moments in TKA are significantly smaller than those in nonoperated knees [28]. This fact is related to static alignment (varus deformity) [29]. On the other hand, the adduction moment in patients with medial knee OA can be reduced by walking more slowly [27]. These gait changes basically appear to be associated with *increased loading rates*, defined as increased slopes of the ground reaction force curve immediately after heel strike during walking [30,31]. Although the knee forces reported in the present study were measured indirectly, the axial loading rate was considered to be good estimates of the actual loading rates at the knee. According to previous studies, higher loading rates have been shown to generate more surface fissuring of cartilage than lower loading rates [32]; and surface fissures in the cartilage can propagate mechanically if the joint surface is subjected to rigorous repetitive loading [33]. Mechanical overload in the contralateral osteoarthritic knee can be a factor to progress the disease severity. Therefore, it is important to examine the ability to extend the replaced knee in standing as a postoperative evaluation after unilateral TKA.

Conclusion

After unilateral TKA in patients with bilateral symptomatic OA, TKA knees had dominant weight bearing in 80% of patients, although the other 20% who had extension limitation in standing put more weight on OA side with greater loading rate during walking. Extension limitation in the operated knee in standing may lead to mechanical overload in the contralateral osteoarthritic knee, which can be a factor to progress the disease severity. Therefore, the ability to extend the replaced knee in standing is important as postoperative function after unilateral TKA.

Acknowledgment

The authors gratefully acknowledge the valuable contribution of Yuji Kuroyanagi, MD, and Yoshimori Kiriyama, PhD.

References

1. Davis MA, Ettinger WH, Neuhaus JM, et al. Knee osteoarthritis and physical functioning: evidence from the NHANES. I. Epidemiological followup study. J Rheumatol 1991;18:591.
2. Gunther KP, Sturmer T, Sauerland S, et al. Prevalence of generalised osteoarthritis in patients with advanced hip and knee osteoarthritis: the Ulm Osteoarthritis Study. Ann Rheum Dis 1998;57:717.
3. Bourne RB, Laskin RS, Guerin JS. Ten-year results of the first 100 Genesis II total knee replacement procedures. Orthopedics 2007;30:83.
4. Harato K, Bourne RB, Victor J, et al. Midterm comparison of posterior cruciate-retaining versus -substituting total knee arthroplasty using the Genesis II prosthesis. a multicenter prospective randomized clinical trial. Knee 2008;15:217.
5. McClelland JA, Webster KE, Feller JA. Gait analysis of patients following total knee replacement: a systematic review. Knee 2007;14:253.
6. Mandeville D, Osternig LR, Chou LS. The effect of total knee replacement on dynamic support of the body during walking and stair ascent. Clin Biomech 2007;22:787.
7. Levinger P, Webster KE, Feller J. Asymmetric knee loading at heel contact during walking in patients with unilateral knee replacement. Knee 2008;15:456.
8. Sharma L, Song J, Felson DT, et al. The role of knee alignment in disease progression and functional decline in knee osteoarthritis. JAMA 2001;286:188.
9. Kerrigan DC, Jennifer LL, Goggins J, et al. Effectiveness of a lateral-wedged insole on knee varus torque in patients with knee osteoarthritis. Arch Phys Med Rehabil 2002;83:889.
10. Sharma L, Hurwitz DE, Andriacchi TP, et al. Knee adduction moment, serum hyaluronan level, and disease severity in medial tibiofemoral osteoarthritis. Arthritis Rheum 1998; 41:1233.
11. Hurwitz DE, Ryals AR, Andriacchi TP, et al. Knee pain and joint loading in subjects with osteoarthritis of the knee. J Orthop Res 2000;18:572.
12. Schnitzer TJ, Popovich JM, Andriacchi TP, et al. Effect of piroxicam on gait in patients with osteoarthritis of the knee. Arthritis Rheum 1993;36:1207.
13. Blin O, Pailhous J, Lafforbue P, et al. Quantitative analysis of walking in patients with knee osteoarthritis: a method assessing the effectiveness of non-steroidal anti-inflammatory treatment. Ann Rheum Dis 1993;49:990.
14. Kellgren LH, Lawrence JS. Radiological assessment of osteoarthritis. Ann Rheum Dis 1957;16:494.
15. Nagura T, Dyrby CO, Andriacchi TP, et al. Mechanical loads at the knee joint during deep flexion. J Orthop Res 2002;20: 881.
16. Andriacchi TP, Galante JO, Fermier RW. The influence of total knee-replacement design on walking and stair-climbing. J Bone Joint Surg [Am] 1982;64A:1328.
17. Harato K, Nagura T, Suda Y, et al. A gait analysis of simulated knee flexion contracture to elucidate knee-spine syndrome. Gait Posture 2008;28:687.
18. Harato K, Nagura T, Suda Y, et al. Knee flexion contracture will lead to mechanical overload in both limbs—a simulation study using gait analysis. Knee 2008;15:467.
19. Andriacchi TP, Johnson TD, Hurwitz DE, et al. Musculoskeletal dynamics, locomotion, and clinical applications. In: Mow VC, Huiskes R, editors. Basic orthopaedic biomechanics and mechano-biology. 3rd ed. Philadelphia: Lippincott Williams & Wilkins; 2005. p. 91.
20. Bellemans J, Banks S, Victor J, et al. Fluoroscopic analysis of the kinematics of deep flexion in total knee arthroplasty. Influence of posterior condylar offset. J Bone Joint Surg [Br] 2002;84B:50.
21. Dennis DA, Komistek RD, Stiehl JB, et al. Range of motion after total knee arthroplasty: the effect of implant design and weight-bearing conditions. J Arthroplasty 1998;13:748.
22. Kurosaka M, Yoshiya S, Mizuno K, et al. Maximizing flexion after total knee arthroplasty. the need and pitfalls. J Arthroplasty 2002;17:59.
23. Ritter MA, Lutgring JD, Davis KE, et al. The role of flexion contracture on outcomes in primary total knee arthroplasty. J Arthroplasty 2007;22:1092.
24. Meneghini RM, Pierson JL, Bagsby D, et al. Is there a functional benefit to obtaining high flexion after total knee arthroplasty? J Arthroplasty 2007;22:43.
25. Potter PJ, Kirby RL, MacLeod DA. The effects of simulated knee-flexion contractures on standing balance. Am J Phys Med Rehabil 1990;69:144.
26. Yoshida Y, Mizner RL, Ramsey DK, et al. Examining outcomes from total knee arthroplasty and the relationship between quadriceps strength and knee function over time. Clin Biomech 2008;23:320.
27. Mundermann A, Dyrby CO, Andriacchi TP, et al. Potential strategies to reduce medial compartment loading in patients with knee osteoarthritis of varying severity: reduced walking speed. Arthritis Rheum 2004;50:1172.
28. Nagura T, Otani T, Suda Y. Is high flexion following total knee arthroplasty safe? Evaluation of knee joint loads in the patients during maximal flexion. J Arthroplasty 2005;20:647.
29. Hurwitz DE, Ryals AB, Andriacchi TP, et al. The knee adduction moment during gait in subjects with knee osteoarthritis is more closely correlated with static alignment than radiographic disease severity, toe out angle and pain. J Orthop Res 2002;20:101.
30. Radin EL, Yang KH, Riegger C, et al. Relationship between lower limb dynamics and knee joint pain. J Orthop Res 1991;9:398.
31. Messier SP, Loeser RF, Hoover JL, et al. Osteoarthritis of the knee: effects on gait, strength, and flexibility. Arch Phys Med Rehabil 1992;73:29.
32. Ewers BJ, Jayaraman VM, Banglmaier RF, et al. Rate of blunt impact loading affects changes in retropatellar cartilage and underlying bone in the rabbit patella. J Biomech 2002;35:747.
33. Kerin AJ, Coleman A, Wisnom MR, et al. Propagation of surface fissures in articular cartilage in response to cyclic loading in vitro. Clin Biomech 2003;18:960.