AME Medical Review 002

Key Leaders' Opinion on Orthopaedics

Editors: Qing Jiang
Freddie Fu
Shiro Ikegawa

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Will scholarly journals perish?

Will scholarly journals perish? This is a question that has puzzled me for years.

The introduction of online journals results in the inevitable recession of print journals. The uprise of the open access journals has been changing the structure of scholarly journals ceaselessly. What keeps me thinking is the open access of clinical trials data. What would be the bigger picture if open access to clinical trials data becomes the mainstream?

It is interesting that with the primary bottleneck lying in the availability of open data, the Big-data Clinical Trial (BCT) seems to stay where it was in spite of the increasingly popularity of "Big Data" among scientists. It has to be the fact that without open data, a statistical analysis is restricted to a particular area (or several areas). Even with big enough data, the study can only be termed as "research with big data sets" rather than "big data research", which are totally different concepts. Big Data is constituted by a plurality of dimensions. On one hand, for an individual (e.g., a patient), the relevant data covering his/her disease course is big enough; on the other hand, for the entire population, as more as individuals (e.g., patients) are expected to be included, to contains all the elements just like the "universe set" in set theory; by doing so, scientists expect to carry out the so-called clinical studies in real-world settings.

Why do the real-world-based clinical trials so appealing? It is understandable that the results and conclusions are likely to be altered in studies targeting the same issue using the same research method with sample size changed. In addition, the probability of such a "likely" is quite high. In many top journals, it is a common phenomenon that some authors tend to validate the results of one study in another population using the same research method. However, if the results are "validated" in one population, it only means that they are "repeatable". Will the results also be repeatable in the second, third, and more populations? If the attempts are not continuing, which should be, the "validation" is equivalent to "self-deception" in a sense.

When clinical research data is open accessed, we can easily integrate data from multiple centers for statistical analysis and meanwhile "validate" the results in multiple populations. If this is the case, then another question arise: can everyone easily publish his/her results/papers in high-profile journals such as the *New England Journal of Medicine*? My answer is NO.

When the open access to clinical research data becomes mainstream, we can easily find the constant update of database on the Internet. Simply by clicking on a button, we obtain the statistical results of the most current data. A further button click would display the validation results based on a specific population. The database would be updated at a certain period of time (e.g., 1 month or 1 day), and the statistical results would "likely" also be changed accordingly. At that time, the questions may change to "would any researchers publish their findings in a journal?" Well, even if someone is still keen to write such articles, journals may be reluctant to publish them because of the indefiniteness of the findings with the risk of being overturned at anytime.

Eventually here it comes the serious question: will scholarly journals perish? My answer is still NO. Then in what way the scholarly journals would probably lead to?

During my Business Administration course, my teacher distributed to us an article from the Case Study column of the *Harvard Business Review*. In this highly respected journal, articles in this column often present one case first, followed by the comments from two experts. These comments could either support or oppose each other. My teacher asked us to study the case, read through the comments and then form our own point of views on the case. He encouraged us to interpret the case from different perspectives independently in what form that I found pretty practical.

The course brought a possible answer to me. When the open access to clinical research data becomes mainstream, the entire publishing industry, especially the publication of "scholarly journals", would eventually experience revolutionary change. It may no longer focus on the rigid and cold outcomes but it would definitely cares more about the reflection on the problems, update of insights, and integration of science and arts.

AME Medical Review Series is a production of the above thinking. As an attempt, we decided to invite experts internationally to provide their views on a specific topic to share their insights with more clinicians and thus benefit more patients. The first chosen topic for the series is the currently controversial one: conventional surgery versus stereotactic body radiotherapy for

the early stage lung cancer. As the first book to the series, we hope it would give you a glance at the coming changes.

The book series will be written by a group of individual experts who are willing to contribute medical reviews and comments to individuals who are interested in clinical research and medical reviews specifically. The book in your hand may possibly be on a heavy subject but we do hope it is presented in an easier way. It will be more than great if it brings you some thoughts and inspire you in some way.

Stephen D. Wang
Founder and CEO,
AME Publishing Company

Preface

It is our tremendous pleasure to edit this book *Key Leaders' Opinion on Orthopedics* with massive assistance from Dr. Dongquan Shi. Internationally renowned experts in the field have been invited to give their insightful views on current controversial topics, new skills and technologies chosen to be included in the book. We are glad to hear its Chinese version will soon come into being with the help of young Chinese clinicians and researchers serving as translators to the book.

With exploration of numerous pioneers, significant progresses have been made aiming less invasive during surgery and more cost effective for implant materials with new surgical skills and technologies coming out. Progress in basic science of orthopedic on the other hand, makes a better vision and knowledge of the mechanism of disease and its development. Experience and knowledge shared between global colleagues also boost the progress in a good way.

For orthopedic surgeons all around however, it is a too heavy work to collect and absorb all information shared, not is it an easy work even to catch up progresses made, or new concepts and skills in a timely manner. Thus it is our goal for this book to collect some essential new concepts and skills together and invite renowned experts into discussion to form their insight views for our readers. All selected articles are concise and precise ones towards a specific topic or subject, from different experts.

In this book *Key Leaders' Opinion on Orthopedics*, 3D printing in orthopedics was firstly bring forward, followed by the topic of tranexamic acid reducing blood loss in knee arthroplasty. The topic of reported outcome and patients' satisfaction was discussed significantly then. More other clinical and basic research topics are covered from the advantage of Spinal anesthesia to genetic research of adolescent idiopathic scoliosis.

Hope orthopedic surgeons and researchers find this book with insightful views of different experts helpful and referential. Based on feedback from our readers, we will keep making update of the progress on orthopedics in this form.

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A leader is one who knows the way, goes the way, and shows the way. — John Maxwell

The field of orthopaedics, like all of medicine, is filled with a myriad of different opinions on multiple topics. These various opinions drive the field of orthopaedics forward by encouraging research projects to prove and disprove different viewpoints. The leaders of the field that contributed to this book guide us on how to conduct practice using evidenced based medicine to guide us in improving patient care.

This book on Key Leaders' Opinion on Orthopaedics covers a variety of current hot topics in orthopaedics that spans multiple fields. In total joint arthroplasty, the topics of anesthesia, patient satisfaction, tranexamic acid, patient reported range of motion, obesity, complications, and implant types, including the Charnley hip, are covered. For pediatric orthopaedics, adolescent idiopathic scoliosis is covered in depth. On the other end of the age spectrum, geriatric care and co-management of hip fracture patients demonstrates improved outcomes. Sports injuries are also covered, including anterior cruciate ligament reconstruction and arthroscopic partial menisectomies in knees, and tennis elbow and Latarjet procedure in shoulder/elbow. Finally, articles include basic science research, such as 3D printing for bone regeneration, tendon and cartilage repair, platelet-rich plasma, and hyluronate injections.

The hope is that ideas derived from key leaders in the field of orthopaedics will spur others to drive research forward. The end goal is to provide the best benefits to our patients; by engaging in thoughtful conversation, we are leading the way.

Antonia F. Chen, MD/MBA

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Preface

I'm honored to write the foreword for *Key Leaders' Opinion on Orthopaedics*, edited by famous esteemed colleagues as Qing Jiang, Freddie Fu and Shiro Ikegawa.

First of all it's a great pleasure for me to present a list of renowned authors from all over the world: from China to Italy, from Austria to Singapore, from Croatia to the USA, from Turkey to France, from Spain to Brazil, from Greece to Iran, from Germany to Taiwan. Each contributing author has a special interest in the selected topic and every author has given his influential opinion by literature analysis and by own results' discussion; by this way, the reader can have a clear idea about important topics of modern orthopaedic science.

Later, the topics are extremely interesting and essential for a correct update; in fact, the book's arguments concern a large list of modern orthopaedic subjects: surgical techniques and tips, technological annotations, patient reported outcome measures and patient expectations, biological notes, epidemiological science, anesthesiological evaluations, etc.

The Editors have done a marvellous job of choosing topics covering a lot of aspects of orthopaedic science: this book will provide comprehensive evidence based information on several sectors. The authors, instead, share with the reader their knowledge and experience, and so the present book is an important tool for daily job and an useful instrument to remain current and worldwide correlated.

I think this book will be very useful for all orthopaedic surgeons, residents and fellows to improve the future clinical practice: this is a book to maintain in our bookcase and to enjoy.

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An increasingly elderly population, combined with the growth in proportion of obese population, will inevitably lead to a rise in the number of patients requiring total joint arthroplasty surgeries. By 2030, the number of total knee arthroplasty performed will increase five fold compared with 2005 figures.

The content of this book addresses two important topics in total knee arthroplasty. Firstly, reducing blood loss with tranexamic acid. Tranexamic acid is considered the holy grail for perioperative blood management in total knee arthroplasty. With topical application, its popularity among surgeons has been increasing rapidly. Although the ideal route of administration remains debatable, most will agree that topical application is effective yet easy to administer and safe. With its emergence, the need for and cost effectiveness of routine preoperative type and screen has also been called into question.

Secondly, patient reported outcome and patients' satisfaction. Patient reported outcome measure may be more important than physician derived outcome score and has been increasingly used in recent years. There are two aspects to consider when dealing with patients' satisfaction: determinants of satisfaction and components of satisfaction. Patients' satisfaction can be improved by modifying the elements from these two categories.

This book also covers other relevant clinical topics including the strengths of regional anaesthesia in total hip arthroplasty and geriatric care in elderly hip fracture patients, as well as translational topics such as genotyping for adolescent idiopathic scoliosis and 3D printing in orthopaedic surgery. While 3D printing continues to develop and innovate, its place in orthopaedic surgery remains to be seen. Nonetheless, this is one advancement with huge potential for personalized implants and customized jigs.

Professor Qing Jiang, Professor Freddie Fu and Professor Shiro Ikegawa are prominent, well respected figures in their respective field of practice. I congratulate the editors for bringing together the experts' opinions on various important, updated orthopaedic surgery topics in this book. I am confident the readers will find these experts' opinions insightful and perhaps practice changing.

Jerry Yongqiang Chen, MBBS
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Editorial

Application of 3D printing in orthopedics: status quo and opportunities in China

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The 3D printing technology is penetrating the healthcare field at an astonishing rate. Although there is still a long way to go to realize organ printing and despite the constantly existing ethical and technical changes (1), the 3D printing can form 3D supporting structures in a controllable manner and has shown charms in fields such as tissue engineering and regenerative medicine along with the advances in cell printing and bio-printing and the innovation of printing materials (2-4). In the clinical settings, 3D printing, as a novel additive manufacturing technique, is mainly applied in orthopedics and stomatology (5). A group of 3D printing-based patient-specific osteotomy instruments, orthopedic implants, and dental implants have been licensed by the US Food and Drug Administration (FDA) and Caritas Europa (CE) for clinical use. The orthopedics in China does not lag behind the Western countries in terms of patient number, operation volume, and surgical skills; however, the Western countries have much advanced orthopedic devices, in particular the implants, than China. The 3D printing technology may provide a chance for the Chinese orthopedists and technicians to independently develop innovative medical devices to catch up with their Western counterparts.

Using the rapid prototyping manufacturing (RPM) to facilitate surgery design

Based on imaging techniques such as computed tomography (CT) and magnetic resonance imaging (MRI), the 3D images of the bones can be re-constructed; then, the prototypes of the bones can be obtained using the layered manufacturing technique (LMT) for teaching, presentation, and surgical design. Based on the symmetry of the human anatomy, or by using the human anatomy data in database, we can also reverse or mimic the 3D images of the bones at the missing parts, so as to assist the conventional mechanical processing to manufacture bone prostheses that can be implanted into human body. These two rapid prototyping manufacturing (RPM) techniques have been quite mature and commonly applied in surgery design. By using the RPM techniques, the Ninth People's Hospital of Shanghai Jiaotong University School of Medicine has applied the custom-made prosthesis for the hemipelvic reconstruction after hemipelvectomy and for the reconstruction of serious acetabular bone defect in hip revision surgery (6,7). They took a lead in this field; however, confined by the 3D metal printing technology, the implanted prostheses were still manufactured by conventional techniques. Along with the advances in 3D printing technology and the drop of forming equipment prices, an increasing number of doctors began to use 3D printing for the medical education and for the design and presentation of complex surgeries.

Design and application of 3D printing-based instruments

While the role of patient-specific instrumentation in total knee replacement remain controversial (8,9) (particularly, no evidence on its effectiveness in improving the long-term outcomes has been available), it does have some notable advances such as shorter operative time, improved the accuracy of alignment, and simplified complex surgical procedures. All the major international artificial joint companies have marketed their corresponding products for clinical use. In China, however, the higher cost (an addition USD 1,000 is needed for each case) and longer duration

(it takes 4 weeks from imaging to instrumentation) limit its application. Currently, some domestic artificial joint manufacturers have initiated R&D in this field, and some products have been piloted in some hospitals. Obviously, the patient-specific instrumentation also has a learning curve and is designed for experienced surgeons; thus, it can not completely replace the traditional surgical tools. In addition to the field of artificial joints, the design and application of 3D printing-based instruments in fields including spinal surgery, trauma, and orthopedics have shown special values. Researchers from Kunming General Hospital have demonstrated the efficacy and accuracy of a novel rapid prototyping drill template for cervical pedicle screw placement in cadaver spine specimens (10); also, satisfactory effectiveness has been achieved in their clinical practices (11).

R&D of 3D printing-based orthopedic metal implants

Development of metallic implants and personalized prostheses is the most important and most valuable direction when applying the 3D printing in the field of orthopedics. This is determined by the materials, equipment, and manufacturing capabilities available for 3D printing. The commonly used metal materials including Ti6Al4V, cobalt-chromium alloy, and stainless steel can be used for 3D printing and manufacturing. The preciseness and efficiency of high-energy 3D printing equipment such as electron beam and laser beam can meet the requirements for manufacturing small parts or achieving high-scale production. Under the computer-aided design, the 3D printing can rapidly manufacture shaped implants; meanwhile, it can also produce size-controllable micro-pore structures. These micro-pore structures can lower the elastic modulus of metal materials and decrease the stress shielding at the solid parts of the implants and can promote the integration between metal and bones at the surface of the implants. The unique feature makes R&D of orthopedic implants become more promising. Researchers from Peking University Third Hospital have developed an artificial vertebral body fabricated by electron beam melting using the microporous 3D printing; animal study has demonstrated that the artificial vertebral body can be well integrated with the surrounding bones (12). Also, research has shown that the roughened titanium screws prepared with 3D printing demonstrated a high degree of osseointegration and increased torsional resistance to extraction over smooth titanium screws (13). In 2010, FDA approved the InteGrip®, an acetabular cup manufactured by Exactech with a titanium alloy with a porous surface manufactured using 3D printing; in 2013, FDA approved the Tesera® Standalone anterior lumbar interbody fusion cage, which was manufactured by Renovis using 3D printing. However, the actual outcomes of the use of porous structures (instead of the conventional bone grafting) and the bone integration efficiency still require further verifications in long-lasting studies, in particular when they are used for the interspinous fusion.

Basic research

Due to their innate biological inertness, the metal materials can not be easily integrated with the host bones. Currently, one of the hot research topics is the modification in the nature of the porous surfaces of the 3D printing-formed metals. The aims of these studies are to promote the osseointegration efficiency of the porous surfaces of the metals; or, they may be used as stent materials to be loaded with other functional materials and drugs (e.g., producing anti-bacterial surfaces). The research teams from the Fourth Military Medical University Affiliated Xijing Hospital and the Shanghai Jiaotong University (14,15) have successfully promoted the osteointegration under diabetic conditions using chitosan/hydroxyapatite composite coating on 3D printing-based porous titanium surfaces. These studies have overcome the weakness of 3D printing materials and the manufacturing techniques, and thus expanded the application of 3D printing in orthopedics. Indeed, while the 3D printing of biodegradable materials is another hot research topic, there is still a considerable distance to go before clinical translation.

In summary, the application of 3D printing in orthopedics is experiencing a rapid translation from bench to bedside. Only a "real world" clinical translation can reveal the value and future of 3D printing. Currently, a major limiting factor may be the policies and regulations from the government, particularly those on the manufacturing of the 3D printing-based patient-specific implants. Luckily, the government has made great efforts on this issue, and some improvements have occurred. Nevertheless, 3D printing provides a great opportunity for the orthopedic implantable medical devices manufacturing in China to catch up with the advanced countries.

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Footnote

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Editorial

Editorial on the original article entitled "3D printing of composite calcium phosphate and collagen scaffolds for bone regeneration" published in the *Biomaterials* on February 14, 2014

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Abstract: The paper entitled "3D printing of composite calcium phosphate and collagen scaffolds for bone regeneration" published in the *Biomaterials* recently illuminated the way to make particular scaffolds with calcium phosphate (CaP) powder, phosphoric acid, type I collagen and Tween 80 in low temperature. After the optimal concentration of each component was determined, the scaffolds were evaluated in a critically sized murine femoral defect model and exhibited good material properties. We made some related introduction of materials applied in 3D printing for bone tissue engineering based on this article to demonstrate the current progress in this field of study.

Keywords: Three-dimensional (3D) print; bone tissue engineering; material; scaffolds

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It is known that the body itself cannot heal the large-scale bone defects although the osseous tissue has well self-healing abilities (1). To overcome this clinical obstacle, autografts and allografts are the two common treatment options. However, both the two operations have limitations including the amount of graft material, donor site morbidity, high risk of infection, chronic pain and lengthy rehabilitation (2).

Due to these complicated reasons, methods of synthesizing and/or regenerating bone to restore, maintain or improve its function *in vivo* have become hot research topics in bone tissue engineering (3). Materials and structures are the two crucial factors that could have significant influences on biocompatibility, mechanical strength and cell viability of scaffolds. Scaffolds made by appropriate materials in three-dimensional (3D) biocompatible structures can mimic the properties of extracellular matrix and provide a template for bone tissue formation *in vivo* through biochemical and mechanical interactions (1,3).

A paper entitled "3D printing of composite calcium phosphate and collagen scaffolds for bone regeneration" published in the *Biomaterials* expounded a kind of new method of making scaffolds with 3D structure in low temperature by composite materials including calcium phosphates (CaPs), type I collagen, Tween 80 (a non-cytotoxic surfactant) and phosphoric acid (4). This study gave an interpretation of the production and identification of materials as well as the *in vivo* testing through a series of rigorous experiments.

To made the composite powder consisting of hydroxyapatite (HA) and α-tricalcium phosphate (α-TCP), the solution contained $Ca(NO_3)_3{\cdot}4H_2O$, $(NH_4)_2HPO_4$ and carbohydrazide inside was combusted at 500 ℃ and subsequently calcined at 1,300 ℃. The binder solution for 3D printing was composed of different concentration of type I collagen, phosphoric acid and Tween 80, which enhanced the mechanical strength of the materials without compromising the biocompatibility. The authors demonstrated some results of cell viability, maximum flexural stress and micro-CT to explain how they determine the optimal binder solution acidity and powder particle size.

The scaffold was made of CaP powder with a size ranging from 30 to 150 μm through a ZPrinter 450 under low temperature and selectively bound by the 8.75 wt% phosphoric acid solution containing 0.25 wt% Tween 80 and 1.5 wt% collagen which was delivered by a HP thermal inkjets. According to the results of the scanning electron micrographs, the 3D printed scaffolds confirmed pore sizes in the range of 20-50 μm with layer thickness of 89 μm. For the purpose of determining the functional performance of type I collagen, which is one of the key structure proteins of the bone extracellular matrix attributing to its assembling into fibers, some scaffolds were bound by the solution without collagen but were coated with a 0.5 wt% neutralized collagen gel that dried into a film on the surface.

The *in vivo* massive bone defects' healing was evaluated by a murine femoral defect model. A 2 mm osteotomy was created at the femoral mid-shaft in 13-15 weeks female mice and an allograft or a 3D printed scaffold [calcium phosphate scaffolds (CPS), CPS with collagen binder, CPS with collagen coated] was placed into the defect to heal for 9 weeks. X-rays was taken weekly to monitor the progress of bone healing and micro-CT was used to measure the mineralized volume, mineral density and mineral content. The biomechanical properties, especially torsion, were tested by using an EnduraTec TestBench instrument.

Although the maximum flexural strength, toughness and cell viability improved in both CPS with collagen binder and CPS with collagen coated in *in-vitro* studies, the result differed in *in-vivo* experiment. The scaffolds coated with collagen tended to facilitate less new bone formation and ingrowth as measured by the mineral content and scaffold engraftment despite the levels of new bone formation was similar between allografts and 3D printed scaffolds. Compared with 3D printed scaffolds, the allografts had the greatest net mineralized volume and higher maximum torque values otherwise the slower period of dissolving or resorbing. However, host-host unification was observed in none of the 3D printed scaffolds or allografts. Cause for this phenomenon could be the sufficient osteoconductive and insufficient osteoinductive of scaffolds, which resulted in bone formation into the engraftment with incomplete healing.

CaPs are common substitutes in bone tissue engineering due to they are osteoconductive and good mechanical strength. The most commonly processing method with this material is high temperature sintering (5,6) to achieve higher mechanical strength but less bioactivity as nearly all the bioactive substances cannot suffer the temperature as high as 1,200 ℃ or higher. An *in vitro* study showed that scaffolds made by biphasic calcium phosphate (BCP) containing HA as well as TCP in varying ratios were cytocompatible and enhanced the cell viability and the cell proliferation, as compared with pure TCP (6). To maintain the biological activity, dicalcium hydrogen phosphate and a bioactive glass were mixed with CaPs during the heat treatment, the reactions between these three components can generate the phases $CaNaPO_4$ and $CaSiO_3$ with bioactive potential of biodegradation (5). Human mesenchymal stem cells (hMSC) associated with sintered BCP particles induced osteoclastogenesis and osteogenesis after implanted in the paratibial muscles of nude mice after 4 weeks (7). On the other hand, low or normal temperature 3D printing provides the potential to create composite scaffolds with proteins, growth factors and collagen to attain the combinational therapies of inducing new bone formation as well as enhancing osteoconductive and osteoinductive characteristics (8).

As with CaPs, HA is another inorganic material widely used in almost all kinds of 3D printing like direct ink writing, laser-assisted bioprinting, selective laser sintering (SLS), selective laser melting (SLM) and robotic assisted deposition (8). A kind of water based binder solution with layer thickness ranging from 100 to 300 μm is considered as the optimal condition for making scaffolds and the bending strength ranging from 0.69 to 76.82 MPa based on diverse rapid prototyping (RP) techniques (9-12). Ceramic scaffolds made up of HA powder in 3D structure exhibited good cell viability as well as good proliferation behavior (13). In a previous study published in 2012, capillaries and vessel formation that accompany the homogeneous osteoconduction from central channels have been observed in 3D-printed HA blocks with the application of bone morphogenetic protein 2 (BMP-2) (14), which can be regarded as another successful example for combinational therapies. The attachment, proliferation and osteogenic differentiation as well as the expression of angiogenic factor of adipose derived stem cells were be systematically investigated while cultured with HA bioceramic scaffolds with nanosheet, nanorod and micro-nano-hybrid surface topographies (15).

Apart from inorganic materials, synthetic polymers such as polycaprolactone (PCL), poly lactic-coglycolic acid (PLGA), polylactic acid (PLA), polyethylene glycol (PEG), poly L-lactic acid (PLLA) and polypropylene (PP) are widely used in scaffold development (8) within orthopedics due to the highly biocompatible and degrades into harmless by-products metabolized in the tricarboxylic acid cycle of

these polymers (16). The preferred option of processing method is fused deposition model (FDM), another kind of RP technology, which allow complex shapes for scaffolds' fabrication directly from a computer aided design (CAD) file to accurately mimic the different void dimensions of cortical bone or cancellous bone (16,17). Direct ink writing, SLS, stereolithography (SLA) and robotic assisted deposition are also suitable for polymers (8). Since the diversity of characteristics and manufacturing methods between inorganic materials and polymers, scaffolds made by polymers offer low mechanical strength while good biocompatibility (4). A cranial bone defect model in female Danish Landrace pigs was utilized to verify the application of PCL, the result demonstrated that the purely PCL scaffold without any cells, growth factors or BMP significantly induce bone formation and osteoconductive effect as well as slight degradation of scaffold volume *in vivo*, although the osseointegration and biocompatibility were not as pronounced as the autografts *in vitro* (16). Compared with other polymer scaffolds, permeability in PCL scaffolds increased with higher pore volume and resulted in better bone regeneration, blood vessel infiltration and compressive strength *in vivo*. Combined application of rhBMP-2 and collagen with PCL/PLGA scaffolds showed the best healing quality without inflammatory response at 8 weeks as well as controlled release of rhBMP-2 up to 28 days after implantation in a rabbit radius defect model (18). To heal the rat femur massive full-thickness defect with critical-size, a uniquely PLGA scaffold seeded with MSCs pre-differentiated *in vitro* into cartilage-forming chondrocytes was fabricated and exhibited excellent bone union with biomechanical strength ranging from 75% to 100% compared with normal rat femur (2).

Some commonly used materials were not mentioned in this paper like alginate, chitosan (19,20) and so on. Scaffolds can be made in more precise layer thickness, pore size, porosity and Young's modulus with combined application of various materials due to the rapid development of the 3D printing technology in biomedicine. Fabrication of scaffolds with not only biological activity but also mechanical strength in low or normal temperature has become the hot topic in current research of bone tissue engineering.

Generally speaking, much more kinds of biological or synthetic materials can be applied to make grafts with controllable structure, size as well as shape through very diverse 3D printing technologies for the application of bone tissue engineering with the development of materials science and the numerical control technology.

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Editorial

Topical intra-articular and intravenous tranexamic acid to reduce blood loss in total knee arthroplasty

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Different blood loss prevention protocols have been adopted after total knee replacement (TKR) because bleeding is a major complication of TKR and transfusions is frequently required (1). Increased bleeding has been associated with delayed recovery, increased complications, increased costs and decreased patient satisfaction.

Methods used for blood preservation are hemodilution, intraoperative and postoperative blood salvage and reinfusion, hypotensive anesthesia or epidural anesthesia, transfusion of pre-donated autologous blood, use of antifibrinolytic agents and erythropoietin. These treatments had been demonstrated to reduce postoperative blood loss in total knee arthroplasty (TKA) (2) but are associated with high costs and complications.

Obviously the most appropriate solution is to enhance hemostasis and vessels sealing at site of operation. The use of tranexamic acid (TXA) in primary TKR is today widely accepted. Several studies in the last 2 years confirm TXA efficacy for decreasing blood loss and no increased complications and costs.

Nevertheless there are concerns regarding potential risks of its use, modality and way of application, right time of infusion and above all dose of TXA applied is often different in each work.

Many RCT studies support efficacy and safety of intravenous (IV) use but there are concerns regarding IV administration of TXA in some settings, and topical application may be considered an alternative with less risk than IV use.

In a recent article published in *The Journal of Bone and Joint Surgery Am*, Gomez-Barrena and colleagues (3) compare topical intra-articular TXA with two IV doses of TXA in preserving blood loss in patients undergoing TKA.

The objective of the present double-blind, randomized noninferiority trial was to assess the efficacy and safety of topical intra-articular application of 3 g of TXA compared with IV administration of two 15-mg/kg doses during primary unilateral TKR with cemented implants. The blood transfusion rate and drain and estimated postoperative blood loss were the efficacy end points; safety was assessed on the basis of the complications.

Authors present methods of the study satisfactorily; it is conduct in a rigorous way and statistically correct. Criteria inclusions in the study, methods of randomization and double blind analysis, surgical technique and materials are well explained. From January to October 2013, 78 patients undergoing TKR were randomized to receive either topical TXA (the experimental group, n=39) or IV TXA (the control group, n=39). No significant differences of composition features between the groups randomized were found.

No transfusion was performed in either group, confirming no inferiority for the primary efficacy end point (transfusion rate). Similarly, also for secondary efficacy end points involving blood loss there were no significant differences (in drain blood loss at 24 h or in estimated blood loss at 48 h or 5 days). Decreases in the hemoglobin level were similar in the two groups. The possibility of superiority with respect to the blood loss end points was also investigated by comparing both drain and estimated blood loss. Although non-inferiority was confirmed, no clear superiority was detected.

The mean length of stay in the hospital was similar and less than 4 days in both groups, the range of motion of the knee 48 h postoperatively and the range of motion 1 month

postoperatively was similar.

There were no differences between groups in the safety outcome, no pulmonary embolism (PE) was noted. Two patients in the experimental group and none in the control group had a clinical suspicion of deep venous thrombosis (DVT), only one present a Doppler confirmation of a superficial venous thrombosis in the femoral vein at postoperative day 30. Non inferiority of topical TXA was demonstrated for all outcomes examination at four months postoperatively. Minor adverse events were equivalent (3).

These results are similar to other in literature and are very important to manage blood loss after TKR. Verification of noninferiority in this study provides ample evidence for use of 3 g of topical intra-articular TXA in TKA with cement with predictable efficacy and safety. The results in the patients treated with topical intra-articular TXA were consistent with those in several trials (4-8) and a meta-analysis (9) in which topical TXA was compared with placebo.

Nevertheless authors underline some limitations of the study: as no transfusion was needed in either group, the analysis can not confirm superiority of either treatment with respect to blood loss, and larger studies may be necessary. Also, the estimation of blood loss at 48 h postoperatively may have been unreliable because of hemodilution, with the estimate at 5 days being more accurate. This randomized controlled trial could have had a third arm in which only placebo was administered. However, today is not possible because ethical issues regarding placebo use have been raised because of the results of prior TXA studies (10) with an increased risk of transfusion. Finally, this clinical trial had little capacity to detect differences in adverse events; large cohort studies would be required to investigate that outcome.

According to this study and recent literature some points need to be analysed and in some cases these problems remain today without a correct answer yet.

Efficacy

TXA is widely accepted today as an effective and safe method to reduce blood loss after primary TKA. TXA use is supported by studies with a level of evidence of I that confirm its efficacy for decreasing blood loss (11-14).

Safety and way of administration

Safety have been confirmed in studies comparing TXA treatment against placebo (5-8), but in many studies that showed equivalent safety, TXA is used in patients groups that were selected to exclude complicated patients at risk of DVT, with thromboembolic or heart disease. So, there are concerns regarding IV administration of TXA in some settings, and topical administration may be considered a good alternative that is potentially less risky than systemic administration.

The results of several RCT (4-8) and a meta-analysis (9) involving primary cemented TKR confirmed significantly lower transfusion rates and blood loss (5) in patients treated with topical TXA compared with placebo. Retrospective and cohort studies (15,16), containing a large number of patients, have also confirmed the efficacy of topical TXA.

Contraindications that limit the IV use of TXA include a history of a thromboembolic or ischemic event such as PE, DVT, ischemic cerebrovascular accident, acute myocardial infarction, or ischemic retinopathy. The TXA level in peripheral blood was significantly lower after topical intra-articular administration than after IV administration (7), and this may increase safety. So at the end topical administration has the advantages of easiness of application, maximum concentration at the site of bleeding, minimising its systemic absorption and, consequently, concerns about possible side effects.

The efficacy of topical TXA administration compared with placebo during TKR has been confirmed in trials with various dosages and routes of administration, including tissue impregnation with 1.5 or 3 g of TXA before knee closure (7), delivery of 2 g into the wound (4), or intra-articular delivery of 2 g through the drain (6).

However, concerns regarding possible differences in efficacy according to the route of administration were raised because in one study application of 2 g of topical TXA in the joint before closure failed to achieve a significant reduction in blood transfusion (17).

Therefore, it remains unclear whether the efficacy of topical TXA administration in TKR is equal to or less than that of IV administration.

In conclusion for the way of administration, topical intra-articular TXA could be helpful to patients with contraindications to systemic TXA, as absorption from the joint is very low.

Dosage

In literature there are many studies that underline efficacy of IV infusion of TXA but what is the right dosage is now unclear. Many authors use a 10-20 mg/kg dosage from 1 to 3 times during and after surgery with comparable results (18).

Levine *et al.* in a prospective randomized controlled trial

suggest that a single 1 g dose can be used with the same efficacy as a weighted 20 mg/kg dose (19). It is simple to understand as a uniform dose can be simpler for routinely use in TKA.

Also efficacy of topical TXA administration has been confirmed in trials with various dosages and routes of administration, including tissue impregnation with 1.5 or 3 g of TXA.

Jang *et al.*, in their retrospective study about intra-articular injection of TXA, find that reduction in haemoglobin levels was significantly greater in placebo group than in 1,500 mg TXA group and the 3,000 mg group, with a significative difference between the two TXA groups, so they suggest a dose dependent effect of TXA on blood loss (20).

In addition, it is simple to understand that it is easier for the surgeons to administer a single intraarticular TXA dose, rather than have a control of the one or more IV doses administered by the anesthesiologist during surgery and by other colleagues some hour after operation; so a simplier application may also facilitate wider use of topical TXA during surgery.

Adverse events

We have already analysed possible complications related to use of TXA and what are patients with contraindication to IV administration while analysing ways of administration.

Studies involving IV or topical TXA administration revealed no increase in DVT or overall VTE rates in randomized controlled trials (7,17) or intra-articular administration, prospective cohort studies, retrospective studies, or systematic reviews and meta-analyses (9,12). Systematic use of Doppler ultrasonography (7) revealed no significant difference in the rate of thromboembolism after topical TXA administration.

It is important to underline that in all study analysed, TXA is used in patients groups that were selected to exclude patients with risk of history of DVT e PE, with thromboembolic or heart disease. So doubts are present in clinical practice yet, above all regarding IV administration of TXA for complicated patients, and topical administration may be considered a good alternative that is potentially less risky than systemic administration.

Costs

TXA use, either IV than topical, has undoubted advantages with significant decreases in length of stay, no pre-donated blood units preparation, blood bank costs, and total direct costs to the hospital for the TKR. Indirect cost savings would also result from the avoidance of transfusions that result in complications requiring additional treatment and an increased length of stay.

In conclusion, this randomized controlled trial indicated that a single topical intra-articular dose of 3 g of TXA was not inferior to two 15-mg/kg IV TXA doses. Both regimens were equally efficacious and safe with respect to avoiding blood transfusion, and they achieved equal control of blood loss without complications.

In recent literature some studies presents still better effectiveness of IV administration so we need further study to affirm that topical administration has the same efficacy of IV infusion. But there is no doubt that topical administration could be helpful to patients with contraindications to systemic TXA.

Further research is required to find TXA optimum dose either for IV than topical use. If IV and topical uniform doses are confirmed TXA use can be easier for routinely surgery.

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Editorial

Tranexamic acid and orthopedic surgery—the search for the holy grail of blood conservation

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Over the last decade an increasing amount of literature regarding the perioperative use of tranexamic acid (TXA) for bleeding control in orthopedic surgery has been published (1-6). While clinical trials found promising results regarding the reduction of blood loss and therefore a reduced rate of blood transfusions, concerns regarding prothrombotic adverse events including deep vein thrombosis, myocardial infarction, pulmonary embolism and cerebrovascular events have continued to dampen the enthusiasm and thus recommendations for wide spread use (7).

In clinical practice, this concern has thus lead to avoidance of the use of TXA in a large group of patients. Especially those with a history of coronary artery disease and stent-implantation or those having suffered a stroke are frequently considered to be potentially at increased risk for adverse events due the potential of TXA to promote clotting. These safety concerns are based on the inhibition of fibrinolysis and as a consequence the interference of TXA with the coagulation cascade. So far, there is a lack of clinical trials large enough to not only proof efficacy but also at the same time support the safety of TXA in this patient population. This dilemma is further complicated by the fact that the groups considered at risk for thromboembolic complications may be the same as those at increased risk for ischemic adversities in the setting of increased blood loss. Thus the question arises if in the setting of competing pathophysiologic mechanisms "at risk" patients could "in sum" benefit from the use of TXA, as anemia and higher blood transfusion rates are considered predictors for a worse cardiovascular outcome after surgery (8-10).

In this contentious environment, researchers have tried to address the question of safety in various ways. Given the problems faced with designing clinical trials with large enough sample sizes to identify differences in low incidence outcomes, investigators have turned to population-based administrative datasets in recent years to answer important questions such as those concerning outcomes in various clinical settings. Despite limitations including their retrospective nature, the availability of limited clinical details and the risk of cofounding, considerable benefits include the very large sample sizes providing results from "real world" practice among patient populations from hundreds of hospitals that are not subject to strict and often artificial inclusion and exclusion criteria of perspective, randomized trials.

Poeran *et al*. recently explored these advantages in the context of TXA administration in major joint arthroplasty. The group showed that the use of TXA in patients undergoing total hip or knee arthroplasty was not only effective but also potentially safe. Among 872,416 patients from 510 hospitals in the United States the authors reported reduced odds for blood transfusion by more than 60%. Patients who received TXA had lower rates of the following outcomes: allogeneic or autologous transfusion (7.7% *vs*. 20.1%, P<0.001), thromboembolic complications (0.6% *vs*. 0.8%, P=0.0057), overall complications (1.9% *vs*. 2.6%, P<0.001), need for mechanical ventilation (0.1% *vs*. 0.2%, P=0.0003), and admission to an intensive care unit (3.1% *vs*. 7.5%, P<0.001). Also, median cost of hospital stay was lower for TXA recipients, P<0.001 (3). Importantly,

while showing clear efficacy, no significantly increased risk for complications including for thromboembolic events (odds ratio 0.85 to 1.02), acute renal failure (0.70 to 1.11)—an ongoing concern with the use of antifibrinolytics since the aprotinine was taken off the market—and overall complications (0.75 to 0.98) was found (3). Overall complications included among others the event of acute myocardial infarction. This is important as the pathogenesis of a perioperative myocardial infarction is driven by insufficient myocardial oxygen supply, rupture of coronary artery plaques as well as platelet activation. If surgical bleeding is reduced by the use of TXA, tachycardia and a decrease in hemoglobin responsible for insufficient myocardial oxygen supply might be prevented (11). In this context, preliminary data using the same dataset, may suggest that no increased risk was found among those with a history of coronary artery disease, but more research is clearly needed in this arena. While providing these data, the authors also pointed out that TXA, although increasing in popularity was used in only 11.2% of all patients studied in 2012. Further, they noted, that while TXA seems to be safe on a population basis, more research into its effects among subpopulations is needed.

An additional approach to address safety issues with TXA focuses on attempts to reduce systemic levels of the drug by topical application at the surgical site. In this context, Gomez-Barrena *et al*. recently published results of a clinical trial in The Journal of Bone and Joint Surgery regarding the use of topical TXA compared to an intravenous application in patients undergoing primary total knee arthroplasty (6). The authors performed a phase III, single center, double-blind, randomized, controlled trial to proof the non-inferiority of topical TXA (3 g of TXA in 100 mL saline solution) with two intravenous doses of TXA (15 mg/kg in 100 mL saline solution), one dose before tourniquet release and another 3 hours after surgery. The primary outcome was defined as the need for postoperative blood transfusion. Secondary outcomes included blood loss through the drain at 3 and 24 hours, the postoperative hemoglobin level at 24 hours, 48 hours, and approximately 5 days after surgery, estimated blood loss (determined by the difference between the preoperative hemoglobin level and the lowest postoperative level). Moreover, complications and severe adverse events, the length of stay in the hospital, and postoperative changes in active range of motion of the knee were included in their evaluation. The sample size was calculated for a maximum expected transfusion rate of 5%, being aware of a zero transfusion rate from prior studies in total knee arthroplasty (12-14). For the primary end point, a total of 39 patients per arm provided 99% power to demonstrate non-inferiority at a one-sided level of significance of 0.025. No significant statistical difference was found for the primary end point (blood transfusion rate was 0 for both groups), neither for the secondary efficacy outcomes (drain blood loss at 3 and 24 hours, estimated blood loss 48 hours and 5 days after surgery). In addition, decreases in hemoglobin levels at 24 hours, 48 hours, and approximately 5 days were similar in both groups (–2.3, –3.1, and –2.0 g/dL in the topical intra-articular TXA group, and –2.5, –3.4, and –2.6 g/dL in the IV TXA group, respectively).

The approach using topical TXA may provide an elegant way to overcome the problem of potentially increased systemic clotting risk, especially in the patient population of concern discussed above. However, while the hypothesis that systemic TXA levels could be reduced compared to the scenario where TXA is administered intravenously, thus leading to a reduction in systemic clotting risk warrants further investigation, both because (I) it remains unknown which levels can be considered safe and (II) pharmacodynamic data derived from large patient samples are rare. Interestingly, some evidence suggests that topically administered TXA in doses of 1.5 and 3 g can reach mean plasma levels of 4.5 and 8.5 mg/L (12). Plasma concentrations one hour after intravenous administration of 10 mg/kg TXA have produced mean values of 18 mg/L (15). While topically administered TXA seems therefore to result in lower plasma concentrations, one must consider that levels between 5-10 mg/L are considered to be therapeutically active (16), thus making it at least in theory possible that even the topical approach has systemic effects and potentially side effects. In addition, the possibility that a higher local concentration of TXA when administered topically could lead to increased local complications at the operative site should also be considered and investigated. Several clinical trials and meta-analysis have shown the benefit of intravenous TXA compared with placebo in orthopedic surgery. More recently, a meta-analysis by Zhao-Yu *et al*. showed no significant differences for intra-articular use of TXA in patients undergoing total knee arthroplasty compared to placebo in regard of deep vein thrombosis or pulmonary embolism (17). However, Gomez-Barrena *et al*. could show the non-inferiority of topically administered TXA (3 g TXA in 100 mL saline) compared to a regime using two times 15 mg/kg of TXA intravenously in patients undergoing total knee arthroplasty. This leads the

latter author to state that continuing to use a placebo group is raising ethical questions with regards to the published literature.

One other important aspect seems to be the economical advantage of TXA in the orthopedic patient population. Its ability to reduce the overall hospital costs associated with total hip or knee arthroplasty seems promising. In addition to the drugs low cost (approximately $6 per vial), Poeran *et al*. could show a significant reduction in median hospital costs in patients receiving TXA (3). With regards to the increase in total joint arthroplasties in the United States and elsewhere over the next decades, an economically efficient approach to joint arthroplasty procedures is indispensible (18,19).

In conclusion, the overwhelming evidence to date suggests that TXA is effective in reducing blood loss and the need for blood transfusions in the setting of joint arthroplasty surgery. Data on perioperative safety are emerging and look promising, however questions remain regarding populations at risk for thromboembolic complications and thus more research is needed. In the meantime, approaches should be sought to identify the lowest possible dose and safest route of administration. Topical administration of TXA may offer benefits over the intravenous approach in terms of reducing systemic plasma levels while not affecting its effectiveness, but nevertheless adequately powered studies are needed to draw firm conclusions regarding safety. In the meantime, the use of TXA is likely to increase in popularity due to its clinical and cost benefits, however risks and benefits need to be assessed continuously as new information emerges, especially among those at risk for adverse events. A critical and frequent reassessment of available data is imperative in order to assure an evidence-based approach to the appropriate use of TXA.

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Footnote

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Editorial

Intra-articular versus intravenous tranexamic acid in primary total knee replacement

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We commend Gomez-Barrena *et al.* on their recent study entitled "Topical intra-articular compared with intravenous tranexamic acid to reduce blood loss in primary total knee replacement: a double-blind, randomized, controlled, noninferiority clinical trial". The study was well-designed and appropriate statistical analysis was performed. They compared 39 patients who received 3 grams of intra-articular tranexamic acid (TXA) with another 39 patients who had two doses of 15 milligrams/kilogram of intravenous TXA (one dose before tourniquet release and another three hours after surgery). There was zero incidence of blood transfusion. The visible blood loss as measured in the drain output at 24 hours postoperatively and the invisible blood loss estimated using the Nadler formula at 48 hours postoperatively were comparable in both groups of patients. They conclude that intra-articular TXA according to their described protocol demonstrated noninferiority when compared with intravenous TXA (1).

Total knee replacement (TKR) is a cost-effective and efficacious treatment modality for severe osteoarthritic knees. Growth in the proportion of obese population, combined with the increase in demand from an ageing population, will inevitably lead to a rise in the number of patients requiring TKR. This number is expected to increase five-fold by 2030.

However, TKR can be associated with significant blood loss with 10-38% of patients requiring allogenic blood transfusion perioperatively. Serious complications associated with blood transfusion include viral infections, transfusion-related reactions and fluid overload. Furthermore, transfusions significantly increase the length of hospital stay and hospital cost. The risks and costs of blood transfusion, together with challenges in obtaining sufficient labile blood products, have generated interest in blood-conserving strategies. These include hypotensive anaesthesia, intra-operative blood salvage as well as the use of erythropoietin and anti-fibrinolytic agents.

TXA is a synthetic anti-fibrinolytic agent that competitively inhibits the activation of plasminogen to plasmin, an enzyme that degrades fibrin clots, fibrinogen, procoagulant factors V and VIII. At higher concentration, TXA also acts directly to inhibit plasmin activity. Consequently, there is a decrease in proteolytic action on the fibrin monomers and fibrinogen, which results in clot stabilization. The trauma of surgery activates fibrinolysis by promoting the release of tissue plasminogen activator. Although the body naturally inhibits fibrinolysis by 24 hours after surgery, anti-fibrinolytic agents such as TXA can block the activation of plasminogen to plasmin earlier and thereby decreasing the perioperative blood loss.

The use of intravenous TXA in TKR has been a common practice. It can be given as a: (I) preoperative dose before tourniquet inflation; (II) intraoperative dose before deflation of the tourniquet; (III) postoperative dose three hours after surgery; or (IV) various permutations combining these three doses. TXA, when given intravenously, has a wide distribution throughout the extracellular and intracellular compartments. It diffuses rapidly into the synovial fluid until the concentration of TXA in the synovial fluid equals that of its concentration in the serum. Its biological half-life is 3 hours in the joint fluid and 90% of it is eliminated within 24 hours by glomerular filtration. Meta-analyses have shown that intravenous TXA effectively reduces the perioperative blood loss and incidence of blood transfusion after TKR, without increasing the risk of thromboembolic

events (TEE) (2-6). However, many common medical conditions including renal impairment, cardiovascular diseases, cerebrovascular conditions and the concurrent presence of hormonal treatment may preclude the use of intravenous TXA at the time of surgery (7).

Giving intra-articular TXA during TKR has only started to gain popularity in recent years. It can be given as a topical wash or into the knee joint after wound closure via the drain. Compared to intravenous administration, advocates of intra-articular TXA believe the benefits include ease of administration, ability to achieve maximum concentration at the bleeding site and minimal systemic absorption. Furthermore, the use of tourniquet in TKR results in negligible intraoperative blood loss but notable postoperative blood loss, which is the ideal scenario for using intra-articular haemostatic agents intraoperatively. A recent meta-analysis by Alshryda *et al*. which included nine randomised controlled trials in TKR found that intra-articular TXA significantly reduced the rate of blood transfusion, without an increase in the incidence of TEE (8).

Despite several studies proving the efficacy of both intra-articular and intravenous TXA in reducing blood loss after TKR, the ideal route of administering TXA will remain a topic for ongoing debate and controversy in the upcoming years.

Four other recent studies also concluded that the two routes of administration are comparable for blood transfusion incidences after TKR (9-12). Their findings support the postulation that the therapeutic effect of TXA becomes apparent when proteolysis of plasmin prematurely dissolves the fibrin clot. As TXA works at active bleeding site of the wound rather than within the blood vessels, its presence within the clot is considered effective irrespective of the route of administration. However, there are two recent studies that favoured intra-articular TXA to intravenous administration (13,14), while another study reported significantly lower blood transfusion incidence with intravenous TXA (15).

Huang *et al*. compared 92 patients who received 3 grams of intravenous TXA during TKR with another 92 patients who had 1.5 grams of intra-articular TXA combined with 1.5 grams of intravenous TXA. Interestingly, while both groups had similar effectiveness in reducing blood transfusion rate, patients in the intra-articular-intravenous combined group had significantly lesser drainage volume, lesser postoperative knee pain, lesser knee swelling, shorter length of hospital stay and higher short-term satisfaction (16).

The conflicting findings across these studies are possibly contributed by: (I) the variation in surgical techniques using conventional intra- and extramedullary jigs or computer-assisted surgery; (II) the variation in dosing regimen for intravenous TXA, with some studies giving one dose while others giving three doses; (III) the variation in indications for blood transfusion across hospitals.

Wang *et al*. promptly performed a meta-analysis of six prospective randomized controlled trials and cohort studies comprising 679 patients (739 knees) to evaluate the efficacy of intra-articular versus intravenous TXA in primary TKR. They found no significant difference between the two routes of administration in terms of blood loss, blood transfusion requirements and TEE (17).

From the hospital administrators' point of view, the cost savings associated with the use of TXA in TKR is of paramount importance. The cost of intra-articular TXA is as little as $6 in some countries but it has proven to shorten hospital stay by a mean of 1.2 days (18,19). While the pharmacy cost is higher with the routine use of TXA, the blood bank cost and total direct hospital cost were lower. A recent study by Moskal *et al*. found that the total direct hospital cost (the combined cost of TXA and blood transfusion) was $39.14/TKR, $82.59/TKR and $84.90/TKR for intra-articular, intravenous and without TXA respectively. Similarly, the man-hour cost (the time required to successfully deliver a unit of blood and to address transfusion complications) was zero in the intra-articular group as none of the patients required blood transfusion, as well as 0.007 man-hour/TKR and 0.13 man-hour/TKR for the intravenous and without TXA groups respectively. They concluded that intra-articular TXA has the potential to achieve larger cost saving and decrease hospital man-hour/TKA (20).

While we acknowledge the authors of these studies for their contribution to our current knowledge, there remains no consensus regarding the ideal route of administrating TXA. To yield greater insight into the debate of intra-articular versus intravenous TXA in primary TKR, the need for a multi-centered randomized controlled trial with standardize operative and transfusion protocols or a meta-analysis with significantly larger sample size comprising only randomized controlled trials is clearly evident.

Nonetheless, the current evidence appears to suggest that the efficacy of intra-articular TXA in reducing perioperative blood transfusion incidence is not inferior to intravenous TXA, with no additional safety concerns. We recommend intra-articular TXA as an alternative to surgeons caring for TKR patients in whom intravenous TXA is cautioned.

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Footnote

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Editorial

Tranexamic acid for the reduction of blood loss in total knee arthroplasty

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Abstract: *The Journal of Arthroplasty* recently published a paper entitled "The Efficacy of Combined Use of Intraarticular and Intravenous Tranexamic Acid on Reducing Blood Loss and Transfusion Rate in Total Knee Arthroplasty". Tranexamic acid (TXA) is an antifibrinolytic drug whose administration during the perioperative period either by intravenous route or topically applied to the surgical field has been shown to reliably reduce blood loss and need for transfusion in patients undergoing total knee arthroplasty (TKA). Although randomized trials and meta-analyses did not show an increase in thromboembolic events, concerns remain about its repeated systemic application. The authors of the study introduced a novel regimen of TXA administration combining a preoperative intravenous bolus followed by local infiltration at the end of surgery with the idea of maximizing drug concentration at the surgical site while minimizing systemic antifibrinolytic effects. The combined dosage regimen appears to be more effective than single dose local application in reducing blood loss and transfusion rate without any complications noted.

Keywords: Total knee arthroplasty (TKA); tranexamic acid (TXA); systemic; topical

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Total knee arthroplasty (TKA) is among the most commonly performed orthopedic procedures. With the ageing of the population, increase in life expectancy and our ability to more effectively manage comorbidities in the perioperative period, the number of people undergoing joint replacement surgery has been steadily increasing over the last decades and that trend is going to continue into the foreseeable future. Only in the US it is estimated that by the year 2030 almost 3.5 million total knee arthroplasties will be performed annually (1).

Orthopedic surgery accounts for a significant proportion of all perioperative packed red blood-cell transfusions, with arthroplasty accounting for nearly 40% of transfusions in orthopedic patients (2). It is known that perioperative anemia and RBC transfusions are associated with increased healthcare resource utilization, hospital length of stay, delayed recovery and higher rates of postoperative morbidity and mortality (3,4).

Various techniques have been introduced to reduce blood loss in the perioperative period and perioperative antifibrinolytic therapy is recommended as part of a comprehensive perioperative blood management strategy (5). The use of antifibrinolytic agents is based on the fact that surgical trauma besides promoting clot formation by activating the intrinsic and extrinsic coagulation cascades also leads to a concomitant activation of plasminogen inducing a state of hyperfibrinolysis accelerating clot degeneration and increasing surgical site bleeding.

Tranexamic acid (TXA) is a synthetic analogue of the amino acid lysine that reversibly occupies lysine-binding sites on plasminogen preventing its binding to the surface of fibrin and activation, resulting in inhibition of fibrinolysis (6).

Since the pioneering work of Hiippala and Benoni and colleagues (7,8) many prospective randomized studies and meta-analyses have confirmed the effectiveness of TXA to reduce perioperative blood loss and the need for allogenic and autologous blood transfusion in patients undergoing TKA (9). The most widely reported dosage regimen is

systemic TXA administration by one initial intravenous bolus followed by another bolus or continuous infusion (10). However, to date there are no prospective randomized studies specifically designed and adequately powered to assess the safety of perioperative systemic TXA administration.

Recent reviews and meta-analyses have found no increased risk of thromboembolic events and renal failure with systemic TXA administration (11). The largest such analysis in orthopedic patients was recently published by Poeran and colleagues (12). In a retrospective cohort study encompassing over 870,000 cases of elective total knee or hip arthroplasty in 510 US hospitals perioperative intravenous TXA administration was not associated with increased risk of complications including a composite of thromboembolic complications, acute renal failure, cerebrovascular events, myocardial infarction and in-hospital mortality. Besides adding incremental evidence of safety of TXA use in orthopedic patients this study is also significant because patients receiving intravenous TXA were stratified into groups according to dose categories (none, ≤1,000, 2,000 and ≥3,000 mg). TXA use was significantly associated with a decreased need for allogeneic or autologous blood transfusions [odds ratio (OR) varying from 0.31-0.38 by dose category], and allogeneic blood transfusions (OR, 0.29-0.37), with no significantly increased risk for complications: thromboembolic complications (OR, 0.85-1.02), acute renal failure (OR, 0.70-1.11), combined complications (OR, 0.75-0.98), and admission to an intensive care unit (OR, 0.73-1.01). The authors concluded that 2,000 mg TXA seemed to have the best effectiveness and safety profile.

Despite these encouraging observations regarding safety of TXA use, repeated administration of an antifibrinolytic drug in elderly patients undergoing surgery which promotes a hypercoagulable state and who often are frail with comorbidities putting them at increased risk of DVT (e.g., diabetes, obesity, cardiovascular disease) still raises concerns. In order to address this issue, studies to establish the safety and effectiveness of topical TXA administration have been conducted. The idea is to maximize drug concentration at the site of surgery by intraoperative local infiltration resulting in negligent systemic absorption (13) and by doing so reducing or avoiding completely a generalized antifibrinolytic effect while retaining the beneficial effects on minimizing blood loss. Indeed, topical application has proven to have at least comparable effects to intravenous TXA on controlling blood loss (14,15). In a recently published meta-analysis of 14 randomized controlled trials (11 in knee replacement, two in hip replacement and one in both) which investigated the effect of topical TXA on blood loss and rates of transfusion Alshryda and colleagues found that indirect comparison of placebo-controlled trials of topical and intravenous TXA indicates that topical administration is even superior to the intravenous route without any significant difference in complication rates (16).

In a prospective randomized controlled study investigating various TXA routes of administration and dosage regimens Maniar and colleagues found a single topical dose of TXA to be more effective compared to a single systemic dose. However, the same study concluded that the most effective TXA dosage regimen consists of two intravenous doses, a preoperative one followed by an intraoperative one (17).

Lin *et al.* (18) recently published an interesting study introducing the concept of combining two modes of TXA administration. They randomized 120 patients undergoing primary TKA into three groups. One group received a single 1.0 g dose of TXA in 20 mL saline intra articularly after joint capsule closure (topical group); the second group received a combination of intravenous injection of 1.0 g TXA 15 minutes before skin incision followed by local intra-articular application of 1.0 g after joint capsule closure; and the third group received only 20 mL normal saline by local intraoperative infiltration (control group). Outcome parameters were postoperative hemoglobin levels, Hb drop calculated as the difference between preoperative and Hb values at postoperative days 1 and 3, total drain amount at 24 h after surgery, calculated total blood loss and transfusion rate. As expected, the mean total blood loss was significantly lower in both the topical and combined groups compared to placebo (705.1±213.9 *vs.* 578.7±246.9 *vs.* 948.8±278.5 mL, respectively; P<0.001) as was total drain amount (110.9±61.3 *vs.* 56.8±34.6 *vs.* 211.9±121.9 mL; P<0.001). There was also a significant difference in transfusion rates when comparing the two TXA groups to controls (3 *vs.* 0 *vs.* 15%; P=0.009) as well as in amount of blood transfused (12.5±79.1 *vs.* 0 *vs.* 62.3±167.4 mL; P=0.008). There was no significant difference when comparing mean total blood loss among the two TXA groups although there is a trend in favor of the combined regimen (P=0.063). The same holds true when comparing transfusion rates among those two groups. The study protocol also provided for screening patients for clinical signs of deep venous thrombosis (including Homan's sign and leg swelling) up to 3 months after surgery. The authors recorded no complications, including thromboembolic events during the follow up period. Of interest is the finding that in the combined

group the postoperative Hb levels were significantly higher and the postoperative Hb drop smaller when compared to the topical and control group. Total drain amount in the combined group was also lower when compared to the other two groups (P<0.001 for both). These findings are suggestive of a combined protocol consisting of an initial intravenous bolus followed by local infiltration at the end of surgery is more effective then local infiltration alone. Although further studies with larger numbers of patients are needed to compare this new combined regime to other modalities of TXA administration in TKA and corroborate its effectiveness and safety, the authors should be complimented on the innovative approach.

Conclusions

The need to optimize healthcare resource utilization and patient outcome in the light of evidence of serious adverse effects of perioperative anemia and allogenic blood transfusion and increasing demand for knee replacement surgery in an ageing, comorbidity laden population has led to the development of strategies aimed at reduction of perioperative blood loss and transfusion requirements.

Although the efficacy of TXA in reducing blood loss in TKA has been well established, there is still uncertainty about the optimal route of administration and despite meta-analyses supporting its safety concerns remain regarding risk of thromboembolic events with higher systemic concentrations and prolonged intravenous application. According to recent randomized studies local surgical site infiltration seems to be at least non-inferior to intravenous application of TXA in reducing blood loss during TKA.

For the concerned practitioner a regimen combining an initial preoperative intravenous bolus with local application by surgical site infiltration at joint closure seems to offer an effective and safe alternative to the more traditional approach using repeated IV administration of TXA. This combined regimen possibly maximizes the benefits of both systemic and local TXA application without exposing the patient to a prolonged increase in systemic antifibrinolytic activity.

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Footnote

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Editorial

Efficacy of combined use of intraarticular and intravenous tranexamic acid in total knee arthroplasty

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Introduction

Tranexamic acid (TXA) has come to light as an effective method to decrease blood loss and transfusion rates in total knee arthroplasty (TKA) without increasing the risk of thromboembolic events (TEE) (1). Many initial studies utilized intravenous (IV) TXA and more recently topical TXA has also been shown to be effective (2,3). In these studies, various dosing regimens have been used for both IV and topical TXA. Some have attempted to find the most beneficial regimen, demonstrating better results with two IV doses compared to a single IV dose (4,5). Others have compared various topical regimens to IV regimens, often comparing single topical doses to one or two IV doses (6-8). These have often shown similar results between IV and topical TXA; however, comparison is difficult due to variance in the regimens used (quantity of TXA, number of doses, route of topical administration). Our standard practice is to administer one gram IV prior to incision and one gram IV at initiation of closure. This provides an effective, easily reproducible routine for the entire surgical team.

Methods

In their study, Lin *et al*. have performed a prospective randomized controlled trial to investigate the effects of a combined regimen using both IV and topical TXA (9). They randomly assigned 120 patients to one of three groups: (I) one gram TXA in 20 milliliters (mL) normal saline injected intra-articularly via two deep drains after arthrotomy closure; (II) one gram TXA IV 15 minutes prior to tourniquet inflation combined with one gram TXA injected intra-articularly as in group 1; and (III) control group with 20 mL normal saline injected intra-articularly via two deep drains after arthrotomy closure. They utilized a tourniquet in all cases which was inflated prior to skin incision and deflated after wound closure. All drains were clamped for one hour after injection and removed after 24 hours.

Results

Their outcomes included postoperative hemoglobin (Hgb) levels, Hgb drop, total drain output, total blood loss, and transfusion rate. They provided a transfusion for any Hgb less than 8.0 grams/deciliter (g/dL) or symptomatic patients with Hgb less than 9.0 g/dL. They demonstrated a significant improvement in Hgb level, Hgb drop, and total drain amount with the combined group compared to both the topical and control groups. Both TXA groups also had a significant decrease in total blood loss and transfusion rates compared to the control group. Although the combined group had a lower mean total blood loss compared to the topical group, mean difference of 126 mL, this was not statistically significant (P=0.063). Six patients in the control group required transfusion, one in the topical group, and none in the combined group. No patient experienced a TEE within 3 months of surgery.

Discussion

This supports previous studies demonstrating an increased effect with multiple doses compared to a single dose of TXA (4,5), but with a novel regimen. We agree with the importance of administering TXA prior to tourniquet inflation and skin incision. This allows TXA to rise to a therapeutic level within the joint before the fibrinolytic cascade is initiated by the surgical trauma. This initial dose

may be especially important for surgeons who choose to perform TKA with no or reduced tourniquet usage as they experience increased intraoperative blood loss compared to surgeons who use a tourniquet throughout the entire surgery.

As noted above, the authors found some statistically significant improvements with the combined regimen in addition to a trend in lower total blood loss compared to the topical only group. Unfortunately, due to a lack of comparison with an established IV—only regimen in this study, one is unable to fully assess the efficacy of this combined regimen. We consider transfusion to be the clinically relevant manifestation of blood loss as it is a medical treatment which carries its own risks and costs to both the patient and the hospital (10). The small number of patients and low transfusion rates make it difficult to fully evaluate this clinically relevant measure in this study. The authors recognize these weaknesses and could more fully analyze the efficacy of their combined regimen in a subsequent study with larger patients groups comparing all possible TXA administration regimens (topical only, IV only, combined IV and topical).

As mentioned by the authors, one appeal to using topical TXA is due to concern of a theoretical increased risk of TEE (defined as deep vein thrombosis (DVT), pulmonary embolism (PE), myocardial infarction (MI), or cerebrovascular accident (CVA). This concern primarily arises from previous case reports attributing various TEE to TXA use; these include cerebral thrombosis (11), arterial thrombosis (12), acute renal failure (13), and ischemic stroke (14). Rydin and Lundberg reported intracranial thrombosis in two women after taking 1 to 4.5 g of TXA daily during menstruation for 1 year (11). At the time of thrombosis both women were found to have a thrombocytosis, another plausible explanation for their thrombosis as was recognized by the authors of the report. A second report was of a woman who died of an arterial thrombosis after using antifibrinolytics daily for a total of 6 years; during 3 of these 6 years she took 6 g of TXA daily (12). The authors of the report did not believe TXA to be relevant in the patient's thrombosis, as she had discontinued its use 4 months prior to the event and she was also found to have Takayasu's arteritis, a known thrombogenic condition. Another report presented a patient who received 500 mg TXA daily for 3 days to treat uterine bleeding after undergoing an abortion (14). In addition to having been recently pregnant, the patient was also found to be heterozygous for the methylene—tetrahydrofolate reductase C677T gene. Homozygous patients with this mutation are known to have an increase in ischemic strokes (15), but whether there is an increased risk in heterozygous patients is not fully understood (14).

The above case reports include the use of TXA, but its direct relationship with the observed TEE remains unclear at best. TXA is an antifibrinolytic medication which prevents clot breakdown and not a prothrombotic medication. In two early studies Astedt found that TXA did not affect fibrinolytic activity within human vein walls (16) or the large heart arteries or coronary vessels of the rat (17). This is important as the fibrinolytic activity of the vessel wall is more influential in preventing thrombosis than the fibrinolytic activity in the blood stream itself (16). Furthermore, during TKA Benoni *et al*. found significantly increased fibrinolytic activity in blood taken from the wound bed when compared to that found in the peripheral venous blood (18). They also found that TXA decreased the fibrinolytic activity within the wound bed without affecting peripheral fibrinolysis.

Many randomized trials and meta-analyses from various surgical disciplines have contributed evidence demonstrating the safety of TXA (19). A meta-analysis of placebo controlled randomized studies demonstrated no increased risk of TEE in patients undergoing cardiac surgery who received significantly higher doses of TXA than those used in TKA (20). Other studies investigating TXA in high risk cardiac surgery included patients with a history of TEE and demonstrated no increased rate of TEE postoperatively (21,22). Conversely, almost all orthopedic studies, including Lin *et al*.'s, have excluded patients with a history of prior TEE. This exclusion criterion has persisted in orthopedics despite the uncertainty of the associations seen in the aforementioned case reports, multiple meta-analyses demonstrating no increased risk of TEE with TXA in TKA, and the significantly lower dose administered in TKA compared to that used in cardiac surgery. The recently published results showing our experience with IV TXA in patients with a history of previous TEE demonstrated no statistically significant increase in the rate of TEE with IV TXA (23). There was a significantly increased risk of postoperative TEE in patients with a history of previous TEE, but there was no statistically significant additional increase in risk when TXA was used in these patients.

Nevertheless, for those hesitant to use IV TXA in the setting of previous TEE, topical TXA provides an attractive route of administration with decreased, but not zero, systemic absorption. Wong *et al*. measured systemic TXA levels at a single time point after topical administration, finding

mean plasma levels of 4.5 and 8.5 mg/L approximately 80 minutes after application of 1.5 g and three grams respectively (2). In comparison, Pilbrant *et al*. found a mean plasma TXA level of 25.3 mg/L 90 minutes after administering 1 g TXA IV (24). The mean plasma level decreased to less than 10 mg/L approximately four hours after IV administration. Studies have shown topical TXA to effectively decrease blood loss during TKA (2,3), and others have shown comparable results to single dose IV TXA regimens (6,7). Thus, in patients with previous TEE, topical TXA presents an effective option to decrease blood loss, but the absorption of topical TXA may vary throughout the postoperative period and warrants further study.

At this time, we continue to use our standard IV TXA regimen in all total joint arthroplasty patients, including those with a history of previous TEE. This paper by Lin *et al*. provides additional evidence supporting increased efficacy with two doses of TXA compared to one. However, this study is unique, comparing their combined IV and topical regimen to a single topical dose. Again, we agree with Lin *et al*. on administering TXA prior to the initiation of traumatic fibrinolysis, thus inhibiting the initiation of this enzymatic reaction at the surgical site. Then, the second TXA dose, be it IV or topical, can be administered prior to the second time of increased fibrinolysis associated with the release of the tourniquet. We congratulate the authors on a well-executed study and look forward to continued investigation into the best use of TXA in order to provide maximal benefit to all patients.

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Footnote

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Editorial

Spinal anesthesia: the new gold standard for total joint arthroplasty?

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The study by Basques *et al*. (1) is one in a series of studies that have demonstrated that regional anesthesia is more advantageous than general anesthesia for total hip arthroplasty (THA) patients. Previous studies have shown a multitude of advantages including decreased cost, complications, infections and improved pain control. A randomized study comparing forty patients found that total costs per case were almost halved in the spinal group in comparison to the general anesthesia group. This was a result of both less cost for anesthesia and less cost for recovery. In the same study there was no relevant difference in anesthesia times. Patients in the general anesthesia group were admitted to the PACU with a higher pain score and needed more analgesics than patients in the spinal group (2). Spinal anesthesia has also demonstrated fewer complications in comparison to general anesthesia. A meta-analysis of ten independent trials found a significant decrease in DVT, PE, surgical time, blood transfusion (3). Another study similarly found a 25% decrease in intra-operative blood loss and 50% reduction of intraoperative transfusion and a 20% lower total transfusion requirements (4). General anesthesia has been associated with higher risk of surgical site infection as well as perioperative hyperglycemia in comparison to spinal anesthesia (5,6).

This study based out of the Yale University School of Medicine identified 20,936 patients from the American College of Surgeons National Surgical Quality Improvement Program (ACS-NSQIP) database, where 60.9% of the surgeries were done under general anesthesia and 39.1% of the THAs were performed under spinal anesthesia. When compared with spinal anesthesia, they found general anesthesia for THA had longer operative and postoperative recovery room time. More importantly, general anesthesia was associated with prolonged postoperative ventilator use (odds ratio: 5.81), cardiac arrest (odds ratio: 5.04), stroke (odds radio: 2.51), unplanned intubation (odds ratio: 2.17), and blood transfusion (odds radio: 1.34). No difference was found in preoperative room time, postoperative length of stay or readmission. Given that the study was a retrospective review and not randomized, one would be concerned for potential selection bias of patients, however, the study was done with a propensity-adjusted multivariate analysis.

The ACS-NSQIP database collects data from more than 370 participating hospitals in the United States. It is a clinical database that is validated and has risk-adjusted methodology to compare observed to expected outcomes for a wide variety of surgeries. The ACS-NSQIP database was started in the Veterans Health Administration (VHA) in the mid-1980's when the VHA was criticized for their high operative mortality. Comparative validation studies have confirmed high reliability and comparability (7). The methodology is based on labor-intensive manual review with trained abstractors, but is not available to all hospitals. A trained nurse abstractor reviews clinical documentation for 150 variables including preoperative patient demographics, risk factors, procedure, and 30-day complications on a monthly, systematic, random sample of patients undergoing a particular operation.

Basques' report is one of the first large, multicenter studies comparing operating room times, length of stay, adverse events and readmission between elective THA patients who received general versus spinal anesthesia. Study results indicate that patients who receive spinal anesthesia had better outcomes, regardless of preoperative medical comorbidities. The most novel observation is the higher overall adverse event rate of 23.5% for patients undergoing general anesthesia compared to 19.7% for those undergoing spinal anesthesia (odds ratio: 1.31).

A shortcoming of this study is that it suggests that the cause of different outcomes is solely dependent on the type of anesthesia administered. While neuroaxial anesthesia is

associated with hypotension that may reduce blood loss and decrease operative time, it is not the only factor associated with reduced operative time and reduced adverse events. Unfortunately, the study does not assess the effect of surgeon and medical center case volumes. Higher volume arthroplasty surgeons and medical centers that perform a large volume of THAs often use spinal anesthesia. Could it be that more experienced surgeons, skilled anesthesiologists, well-trained assistants and experienced postoperative care accounted for the difference in outcomes? The published data on the 'volume' effect indicates that it is of at least the same magnitude as the 'anesthetic' effect (8-12). Of note, most surgeons doing hip and knee arthroplasty do less than ten such cases per year, which could affect the outcomes of the database study (8).

In order to conclude that the choice of anesthetic solely determines the outcomes listed in this study, it will be necessary to show a reduction in adverse outcomes in a prospective, randomized controlled study within a homogenous population of high volume medical centers and arthroplasty surgeons. However, this study gives credence to other studies in literature that support the use of spinal anesthesia over general anesthesia in elective THA cases.

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Footnote

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Editorial

General versus spinal anesthesia in joint arthroplasties

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Over the last decades demographic changes and high success rates have continued to increase the utilization of total joint replacements with estimates of continued dramatic growth (1,2). It has become obvious that given this often elderly and comorbidity ridden patient population joint arthroplasties have exerted significant medical and economic stresses on the health care system. In this context, the identification of intervention with the goal to improving perioperative outcomes has become more important than ever.

In a recent population based study, Basques *et al.* conducted an analysis including nearly 21,000 total hip arthroplasty recipients who either had neuraxial or general anesthesia (3). The main goal of this investigation was to compare postoperative adverse events and utilization of hospital resources among the two anesthesia techniques. General anesthesia was utilized in about 61% of the cases. These patients, were younger, had less comorbidities but an increased BMI compared to the neuraxial cohort. The authors found that higher odds for complications were associated with the use of general anesthesia. Compared to neuraxial, general anesthesia was associated with higher odds for any adverse event in general [odds ratio, 1.31 (95% CI, 1.23-1.41); P<0.001] as well as specific adversities such as prolonged postoperative ventilator use [odds ratio, 5.81 (95% CI, 1.35-25.06); P=0.018] and unplanned intubation [odds ratio, 2.17 (95% CI, 1.11-4.29); P=0.024], cardiac arrest [odds ratio, 5.04 (95% CI, 1.15-22.07); P=0.032] and the need for blood transfusions [odds ratio, 1.34 (95% CI, 1.25-1.45); P<0.001]. Further, the utilization of general compared to neuraxial anesthesia was associated with increased operative and postoperative room time, although no differences were found for length of hospital stay and odds for readmission.

These results are in concordance with a significant number of recent population based studies which have shown that the choice of anesthesia technique might significantly contribute to the improvement of perioperative outcomes. Numerous studies strongly support the notion that choosing regional instead of general anesthesia may improve not only medical perioperative outcomes but positively affect resource utilization (4-7). Resulting benefits range from decrease of blood transfusion use and mechanical ventilation need to reduced mortality risk.

Given these findings, however, it is intriguing that among various data sets the utilization of neuraxial anesthesia has been found to be fairly low compared to the general anesthesia approach. In the study by Basques *et al.*, as in other publications on the topic, about 40% of the patients or less received neuraxial anesthesia (3,7). While the reasons for this underutilization remain largely unknown (8) an additional point for concern in light of the consistently better outcomes reported with neuraxial anesthesia are variations in care and disparities in anesthesia practice showing differences in its application among patient subgroups and hospitals (9-11).

The study by Basques *et al.* further deserves to be put in the context of the recent emergence of large database anesthesia related outcomes research (3). Although the subject of differential outcomes among anesthesia types has been the subject of numerous clinical studies, these have rarely reached sufficient power to allow for the reaching of meaningful conclusions and lacked external validity. Meta-analytical approaches allowed for pooling of data thus allowing for the examination of larger cohorts, but at the expense of including studies spanning over multiple decades

questioning relevance in today's practice. Further, these analyses only allowed for the study of limited outcomes as available in the individual investigations. Irrespectively, these publications also suggested improved outcomes with regional versus general anesthesia (7,12).

With the advent of large database research, many previous limitations regarding sample size and external validity could be overcome and data from real-world practice could be examined without the constraints of often unrealistic inclusion and exclusion criteria of randomized controlled trials. These advantages however come at the expense of the inability to determine causality. Thus, despite of the overwhelming number of studies supporting the use of neuraxial anesthesia, the lack of answers regarding causal relationships has been the reason why controversy still persists in this matter (13-15). In addition, comorbidities, surgical pathologies and complications are based on ICD-9 coding which can be burdened by coding bias despite all quality checks. Further, anesthesia technique represents only one of many perioperative interventions influencing overall outcomes and residual confounding certainly exists.

Therefore, the interpretation of results from database research and other studies favoring neuraxial anesthesia has to be made carefully. Taking prevalent disparities into account and differences in clinical practice of regional anesthesia, superiority of regional anesthesia could be subject to confounding. The question whether regional anesthesia might represent a surrogate marker for a "specific type of perioperative" clinical practice remains unknown. Furthermore, the issue whether the avoidance of general anesthesia or the implementation of neuraxial anesthesia itself confers a positive effect, remains debatable (12), although studies including cohorts that received a combination of both approaches have been suggested to fair better than general only patients.

In the face of these limitations only a large multicenter prospective pragmatic trial may offer the definitive answer to the remaining questions regarding causality and mechanisms. Until such studies are performed—which may be never given the enormous scope and cost—clinicians should take comfort in the fact that virtually no studies have found inferior outcomes associated with neuraxial when compared to general anesthesia.

In conclusion, assuming that the positive outcomes related to neuraxial anesthesia are causally related a wider utilization among the over 1 million patients undergoing joint arthroplasty annually in the United States alone might produce a significant impact on the health care system as a whole (1).

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Footnote

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Editorial

General compared with neuraxial anesthesia for total hip and knee arthroplasty

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Spinal anesthesia has been used for total hip replacement (THR) since 1970s (1). In recent decades and in light of growing body of evidence supporting better outcome of THR and total knee replacement (TKR) with the use of neuraxial anesthesia, this type of anesthesia has become more popular among anesthesiologists and surgeons (2-7). A recent study by Memtsoudis *et al*. (7), using the Premier database and reviewing 382,236 joint arthroplasty procedures, revealed that general anesthesia was by far the most frequent type of anesthesia used for joint arthroplasty as approximately 75% of the procedures were performed under general anesthesia. So it seems that the use of neuraxial anesthesia for total joint arthroplasty (TJA) is still limited to high volume specialized centers and less frequently used in other centers. The reason for the lack of universal adoption of regional anesthesia may be many. Barriers such as patient's fear of spinal anesthesia, the lack of adequate experience or the lack of familiarity with the regional anesthesia techniques, and administration of perioperative anticoagulation to patients that prevents the use of regional anesthesia may be some of the factors (7).

There is ample evidence that supports the superior outcome of neuraxial anesthesia, in terms of reduced perioperative complications and mortality compared to general anesthesia for patients undergoing THR or TKR (4,5,7-10). In a study by Hunt *et al*. (9) using the National Joint Registry for England, Wales and Northern Ireland, spinal anesthesia, but not epidural anesthesia, reduced the risk of 90-day mortality after THR (10). Similarly, the study by Memtsoudis *et al*. (7) demonstrated that neuraxial anesthesia was associated with a lower risk of 30-day mortality and perioperative complications in joint arthroplasty patients.

Lower rate of perioperative morbidity and mortality using the neuraxial anesthesia is most likely due to the lower rate of perioperative complications particularly thromboembolic events, cardiac issues (4) and deep surgical site infection (SSI) (5). It has been well defined that neuraxial anesthesia reduces perioperative blood loss, and the need for subsequent red blood cell (RBC) transfusion, because of its ability to provide hypotension through vasodilatation (3,11). In addition, neuraxial anesthesia allows for optimal muscle relaxation that facilitates expeditious surgery and reduction in operative time. This is particularly important as increased operative time and allogeneic transfusion are risk factors for SSI in TJA patients (12). General anesthesia on the other hand may result in hemodynamic fluctuations (uncontrolled hypotension and hypertension), arrhythmia, and also affect the coagulation pathway that can result in an increased risk of thromboembolic events and cardiac arrest (4). There are other beneficial effects of neuraxial anesthesia. Patients are likely to have better early postoperative cognitive function (13), and better postoperative pain control that leads to a reduction in opioid consumption and consequently lower risk of nausea/vomiting and ileus (6).

In conclusion, there is ample evidence to support the notion that administration of neuraxial anesthesia during TJA is associated with lower morbidity and mortality. The numerous beneficial effects of neuraxial anesthesia should prompt the orthopedic and anesthesia community to seek wider adoption of this anesthesia technique for patients undergoing TJA.

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Footnote

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Editorial

What can we learn from AOANJRR 2014 annual report?

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Australian Orthopaedic Association National Joint Replacement Registry (AOANJRR) was founded in 1998. It was introduced in a staged manner commencing in South Australia on the 1st of September, 1999 and fully implemented across the country by mid 2002. In June 2009, Federal Parliament passed legislation to enable the government to recover funding costs from the orthopaedic industry. All data is validated against information reported to the government and by using this approach the AOANJRR obtains information on over 98% of hip and knee replacements undertaken in Australia, which is almost a complete dataset of hip and knee replacements.

There are four types of data collected for each joint replacement. Type I data includes patient's identification, basic patient details, type of joint replacement, primary or revision arthroplasty, details of the prostheses, and the identity of the hospital and surgeon. This data is the basic and minimum data set required, it also has been proven to be the most useful to date. It can be analyzed for survival rate/revision rate for different arthroplasties, which can be interpreted in all aspects of arthroplasty, particularly in the quality and utility of different prostheses. Type II data is about additional data on the patient, which includes: perioperative treatment (antibiotics and anticoagulants), comorbidities, the American Society of Anesthesiologists Physical Status classification system (ASAs) score, surgical approach, the use of computer-assisted surgery and many more. This data is widely collected by many joint registries and can provide useful clinic information that can direct clinical treatment perioperatively. Type III data includes post-operative clinical assessment as well as patient-reported pain, function and satisfaction. Type IV data includes radiographic data which is heavily utilised by surgeons. The usability of the later two types of data are not fully disclosed or extensively reported. This is due to the labour intensive requirements for collecting these two types of data. For this reason the last two types of data are usually the focus of institutional registries and not the national joint registry.

Many hospitals or medical care groups hold their own database for joint replacements, these institutional registries collect all types of data and can give precise and valuable information including reports of longitudinal institutional experience and individual case findings, which are especially useful for unusual complications or comorbidities. This data has been used to influence changes in clinical practice with improvement in clinical care. These institutional registries, therefore, are excellent platforms for clinical prospective and retrospective research. Compared to the institutional registries, the national joint registry has the ability to provide more valuable information for national health care insurance and policy makers, such as: (I) very detailed information on patterns of implant usage and performance; (II) surveillance of implants performance that is nation wide and across all surgeons; (III) identification of the behavior of new implants with the ability to detect earlier outlier implant performance, which is almost impossible using smaller institutional based registries. AOANJRR was the first registry to demonstrate the high failure rate of large head (greater than 32 mm) metal-on-metal (MOM) prostheses (1), this alarm was confirmed by other national registries and finally induced a worldwide recall of ASR by the Depuy Company as well as other large head MOM devices.

AOANJRR collects type I and II data for the annual national report, with the time of first revision and national

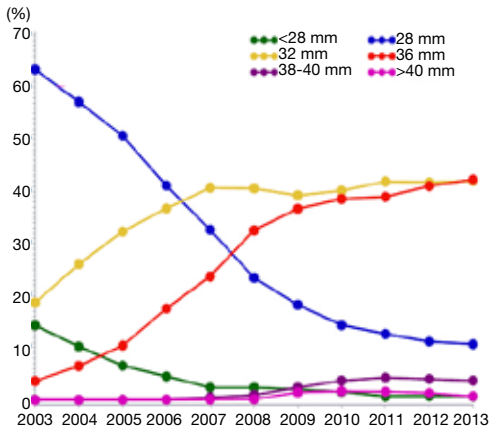


Figure 1 Primary total conventional hip replacement by procedure year and head size.

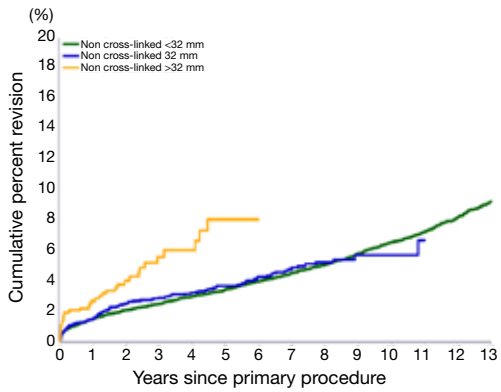


Figure 2 Cumulative percent revision of primary total conventional hip replacement using non cross-linked polyethylene by head size (primary diagnosis OA).

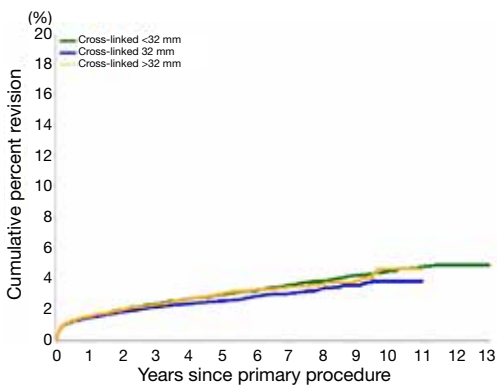


Figure 3 Cumulative percent revision of primary total conventional hip replacement using cross-linked polyethylene by head size (primary diagnosis OA).

mortality used as key measures, these data can estimate the revision rate of each procedure by Kaplan-Meier analysis, these results provide the guidance for health care policy of the Australian government. In the 2014 annual report, there are 891,208 primary and revision hip and knee replacements, which increased by 91,393 arthroplasties compared to the 2013 annual report. The annual report from AOANJRR shows the data and results from the previous year, it does not attempt to explain the meaning of these results, and allows for subjective interpretation of the results by different surgeons or groups depending on their personal understanding. Therefore, the following results are the data from authors' views and readers are encouraged to interpret these results from their own experiences.

The 2014 annual report contains 410,767 hip replacements, with an additional 40,180 replacements compared to the 2013 annual report. Hip arthroplasty has gained great success after Charley invented the low-friction joint that was thought to be the greatest advance in orthopaedic surgery of the 20th century. With new philosophy, technique and implants, there have been some advancement in recent years, whether these new theoretic innovations correlate into real clinic advantage still under investigation. In this paper, we report on the results from AOANJRR and share our opinion on how they relate to best practice in China.

For total hip replacements, dislocation is the most common complication in first four years and the second most common complication overall (25.0%). Large femoral head size has been demonstrated to increase the stability of hip and decrease resultant dislocation rate. For this reason 32 and 36 mm femoral head sizes are now used more frequently for THA, and ≤28 mm heads has become much less common in recent years (*Figure 1*). Larger femoral heads are associated with thinner liners and increased wearing which are negative factors for survivorship. The introduction of cross-linked polyethylene has been beneficial to the outcome of THA. The AOANJRR reports that the rate of revision increases with head size for non cross-linked polyethylene implants. For cross-linked polyethylene, 32 mm head size has the lowest revision rate and there is no difference between less than 32 mm and greater than 32 mm (*Figures 2,3*). This phenomenon is also the same for ceramic on ceramic bearing surfaces. Furthermore, the results even show that head sizes larger than 32 mm are not associated with a reduced rate of revision for dislocation (*Figure 4*). Following these data and

Primary Diagnosis	Head Size	N Revised	N Total	1 Yr	3 Yrs	5 Yrs	7 Yrs	10 Yrs	13 Yrs
Osteoarthritis		**1798**	**33660**	**0.5 (0.4, 0.5)**	**0.7 (0.6, 0.7)**	**0.8 (0.7, 0.8)**	**0.9 (0.9, 1.0)**	**1.1 (1.1, 1.2)**	**1.4 (1.2, 1.5)**
	≤28mm	1121	86468	0.6 (0.6, 0.7)	0.9 (0.9, 1.0)	1.1 (1.1, 1.2)	1.3 (1.2, 1.4)	1.5 (1.5, 1.6)	1.8 (1.6, 1.9)
	32mm	410	79308	0.4 (0.3, 0.4)	0.5 (0.4, 0.6)	0.5 (0.5, 0.6)	0.7 (0.6, 0.7)	0.7 (0.7, 0.8)	1.1 (0.6, 2.1)
	36mm	251	61744	0.3 (0.3, 0.4)	0.4 (0.4, 0.5)	0.5 (0.4, 0.6)	0.5 (0.5, 0.6)	0.6 (0.5, 0.8)	
	>36mm	16	6140	0.2 (0.1, 0.4)	0.3 (0.2, 0.4)	0.4 (0.2, 0.8)			
Fractured Neck Of Femur		**164**	**10610**	**1.3 (1.1, 1.6)**	**1.7 (1.4, 1.9)**	**1.8 (1.5, 2.1)**	**1.9 (1.6, 2.3)**	**2.1 (1.7, 2.6)**	
	<28mm	72	3227	1.6 (1.2, 2.2)	2.3 (1.8, 2.9)	2.5 (2.0, 3.2)	2.7 (2.1, 3.4)	2.9 (2.3, 3.7)	
	32mm	57	4332	1.2 (0.9, 1.6)	1.5 (1.1, 1.9)	1.5 (1.1, 1.9)	1.5 (1.1, 1.9)	1.5 (1.1, 1.9)	
	36mm	33	2826	1.1 (0.8, 1.6)	1.2 (0.9, 1.7)	1.2 (0.9, 1.7)	1.5 (1.0, 2.4)		
	>36mm	2	230	0.4 (0.1, 3.0)	1.0 (0.3, 4.2)				
Osteonecrosis		**118**	**9010**	**1.0 (0.8, 1.2)**	**1.2 (1.0, 1.5)**	**1.4 (1.1, 1.7)**	**1.5 (1.2, 1.8)**	**1.7 (1.4, 2.1)**	**1.8 (1.4, 2.3)**
	≤28mm	73	3863	1.2 (0.9, 1.6)	1.6 (1.2, 2.1)	1.8 (1.4, 2.3)	1.9 (1.5, 2.4)	2.2 (1.7, 2.8)	2.3 (1.8, 3.0)
	32mm	24	2957	0.8 (0.5, 1.2)	0.8 (0.5, 1.2)	0.9 (0.6, 1.3)	0.9 (0.6, 1.3)	1.2 (0.6, 2.1)	
	36mm	17	2025	0.8 (0.5, 1.3)	0.9 (0.6, 1.5)	0.9 (0.6, 1.5)	0.9 (0.6, 1.5)		
	>36mm	4	165	2.5 (0.9, 6.5)	2.5 (0.9, 6.5)				
Developmental Dysplasia		**42**	**3258**	**1.0 (0.7, 1.4)**	**1.2 (0.9, 1.6)**	**1.4 (1.0, 1.9)**	**1.4 (1.0, 1.9)**	**1.5 (1.1, 2.1)**	**1.5 (1.1, 2.1)**
	≤28mm	29	1495	1.6 (1.0, 2.3)	1.8 (1.2, 2.6)	1.9 (1.3, 2.7)	2.0 (1.4, 2.8)	2.1 (1.4, 3.0)	2.1 (1.4, 3.0)
	32mm	9	1029	0.6 (0.3, 1.3)	0.7 (0.3, 1.5)	1.2 (0.6, 2.3)	1.2 (0.6, 2.3)	1.2 (0.6, 2.3)	
	36mm	4	656	0.5 (0.2, 1.4)	0.7 (0.2, 1.8)	0.7 (0.2, 1.8)	0.7 (0.2, 1.8)		
	>36mm	0	78	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)				
Rheumatoid Arthritis		**58**	**3039**	**1.0 (0.7, 1.4)**	**1.6 (1.2, 2.2)**	**1.7 (1.3, 2.2)**	**1.9 (1.4, 2.5)**	**2.2 (1.7, 3.0)**	**5.0 (3.0, 8.2)**
	≤28mm	43	1572	1.2 (0.8, 1.9)	2.1 (1.5, 3.0)	2.1 (1.5, 3.0)	2.3 (1.7, 3.3)	2.8 (2.0, 3.9)	5.8 (3.5, 9.4)
	32mm	9	950	0.5 (0.2, 1.3)	0.8 (0.4, 1.7)	1.0 (0.5, 2.0)	1.2 (0.6, 2.4)	1.2 (0.6, 2.4)	
	36mm	6	482	1.1 (0.5, 2.6)	1.4 (0.6, 3.1)	1.4 (0.6, 3.1)	1.4 (0.6, 3.1)		
	>36mm	0	35	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)				

Note: All procedures using metal/metal prostheses with head size larger than 32mm have been excluded

Figure 4 Cumulative percent revision for dislocation of primary total conventional hip replacement by primary diagnosis and head size.

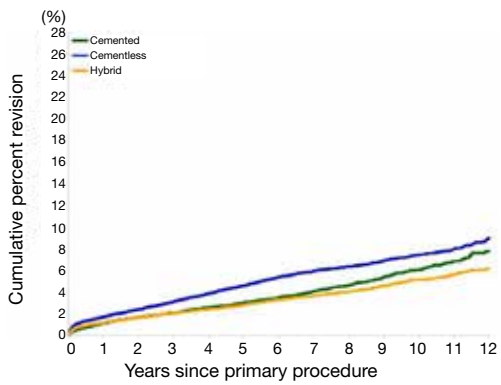


Figure 5 Cumulative percent revision of primary total conventional hip replacement by fixation (primary diagnosis OA).

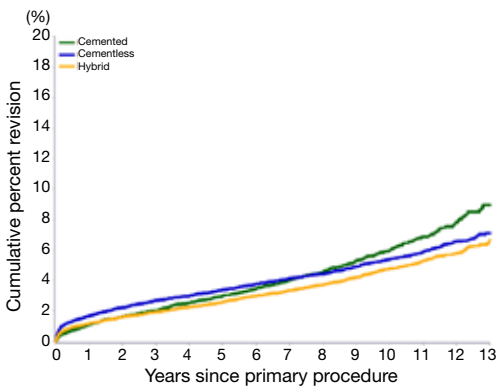


Figure 6 Cumulative percent revision of primary total conventional hip replacement by fixation (primary diagnosis OA).

the reality of our country, we suggest 32 mm metal femoral heads are the treatment of choice for Chinese patients due to its relative lower price and better survival.

Over recent decades, the data from the joint registry supports cemented fixation. The 2013 report also showed cemented fixations had lower revision rates compared to cementless fixation (*Figure 5*). After advancements in surgical skills and technique as well as implant improvements, the 2014 report appears to provide a breaking point in this argument. The hybrid fixation is still the best choice in THA for OA, but cementless fixation demonstrates an advantage after 3 years (*Figure 6*). The cumulative revision at 13 years is 6.7% for hybrid, 7.1% for cementless and 9.0% for cemented fixation (*Figure 7*). Following these results, we suggest a cementless acetabular cup for all cases, and then surgeon's preference for either a

Fixation	N Revised	N Total	1 Yr	3 Yrs	5 Yrs	7 Yrs	10 Yrs	13 Yrs
Cemented	824	19695	1.1 (1.0, 1.3)	2.1 (1.9, 2.3)	3.0 (2.8, 3.3)	4.0 (3.7, 4.4)	6.0 (5.5, 6.4)	9.0 (8.1, 9.9)
Cementless	4551	136311	1.7 (1.6, 1.8)	2.7 (2.6, 2.8)	3.4 (3.3, 3.5)	4.1 (4.0, 4.3)	5.4 (5.2, 5.6)	7.1 (6.7, 7.6)
Hybrid	2211	77768	1.2 (1.1, 1.3)	1.9 (1.8, 2.0)	2.6 (2.5, 2.7)	3.4 (3.2, 3.5)	4.8 (4.5, 5.0)	6.7 (6.1, 7.3)
TOTAL	7586	233774						

Note: All procedures using metal/metal prostheses with head size larger than 32mm have been excluded

Figure 7 Cumulative percent revision of primary total conventional hip replacement by fixation (primary diagnosis OA).

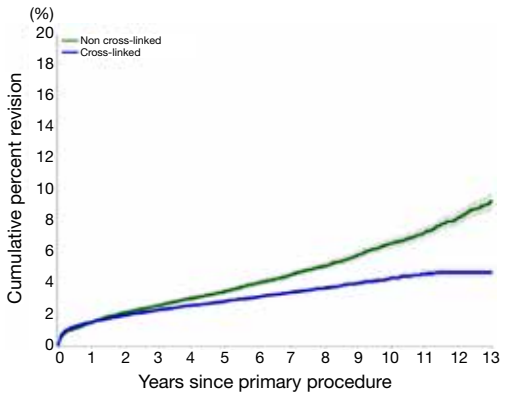


Figure 8 Cumulative percent revision of primary total conventional hip replacement by type of polyethylene (primary diagnosis OA).

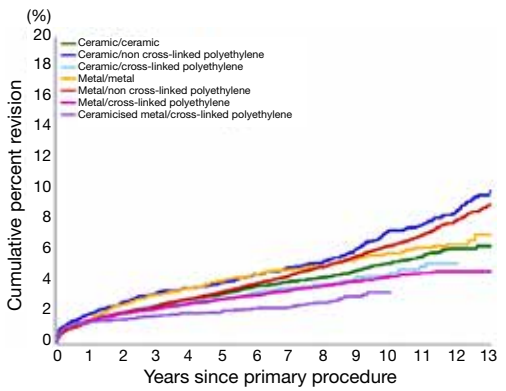


Figure 9 Cumulative percent revision of primary total conventional hip replacement by bearing surface (primary diagnosis OA).

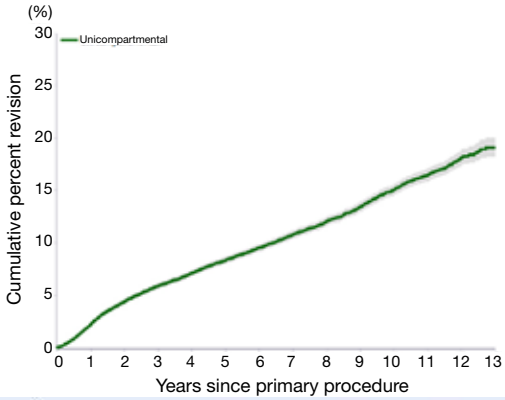
cemented or cementless femoral stem.

In the area of bearing surfaces, it has been demonstrated that the cross-linked polyethylene (XLPE) is superior to non cross-linked polyethylene (*Figure 8*), this advantage increases with time and the cumulative revision rate at thirteen years is 4.7% and 9.2% respectively. Although the ceramic bearing surface has large theoretical advantages of less wearing, this advantage has not correlated into clinic advantage, metal/XLPE has the lowest revision rate (4.7%) compared to the alternatives over a 13-year cumulative revision rate (*Figure 9*). Following these data and the reality of our country, we recommend a 32 mm metal femoral head with XLPE as the treatment of choice for Chinese patients because of its relative lower price and better survival.

The 2014 annual report contains 480,440 knee replacements, with an additional 51,212 replacements compared to the 2013 annual report. Although knee replacement is mature technique useful in treating many clinical problems for all kinds of patients, there are still some controversies to be resolved.

Unicompartmental knee arthroplasty (UKA) has become more and more popular in adult reconstruction, the advocators believe it is less invasive, allows quicker rehabilitation and better satisfaction compared with total knee replacements. Unicompartmental knee arthroplasty is rare in Australia compared with other countries in the world with only 41,250 (8.59%) over 13 years and the use of UKA continues to decline. In 2013, the number of UKA decreased by 2.7% compared to 2012 and 49.5% compared to 2003. As a percentage of all knee arthroplasties, UKA has decreased from 14.5% in 2003 to 4.1% in 2013. The reason for this phenomenon is that the revision rate of UKA is much higher than TKA, the cumulative revision rate of UKA's undertaken for osteoarthritis was 19.1% at 13 years (*Figure 10*), and this revision rate is unacceptably high compared to TKAs (6.8% for OA at 13 years). The first reason for revision is not the progression of OA, which surgeons were concerned about, but the loosening/lysis of the prosthesis (45.3%).

The need for patellar replacement in TKA is still a question that has not been solved over the decades. The 2013 annual report disclosed a lower rate of revision following primary total knee replacement when patellar prosthesis is used. This data has undergone detailed analysis in the 2014 annual report. For rheumatoid arthritis, the



Knee Class	N Revised	N Total	1 Yr	3 Yrs	5 Yrs	7 Yrs	10 Yrs	13 Yrs
Unicompartmental	4310	40809	2.2 (2.1, 2.4)	5.9 (5.6, 6.1)	8.3 (8.1, 8.6)	10.8 (10.5, 11.2)	15.1 (14.6, 15.5)	19.1 (18.2, 20.0)

Figure 10 Cumulative percent revision of primary unicompartmental knee replacement (primary diagnosis OA).

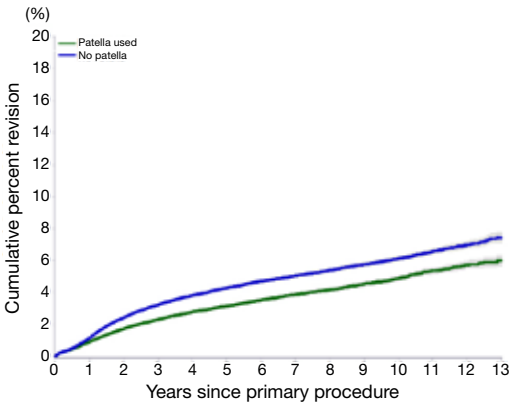


Figure 11 Cumulative percent revision of primary total knee replacement by patella usage (primary diagnosis OA).

revision rate for patella replacement versus no patella replacement was 5.4% and 6.0% at 13 years respectively, which is of no statistical significance. For osteoarthritis, the revision rate for patella use versus no patella use was 6.0% and 7.4% respectively (*Figure 11*). The higher rate of revision when patella prosthesis is not used was due to, increased revision for patellofemoral pain, pain, and patella erosion, as patellofemoral pain was rare with a patella replacement (*Figure 12*).

Whether the surgeon needs to resect the PCL during TKA has also been debated for decades. The choice for PCL resection affects the stability of the implants; cruciate retention (CR) implants have less stability than cruciate sacrificing (CS) implants. In China, CS implants are the more popular choice, but in Australia, CR implants are the first choice except for more complicated cases, the reason for this is the revision rate of CS implants is always higher than CR implants (*Figure 13*). When we consider both the stability of the knee and patella replacements, the results from the AOANJRR demonstrate that CR TKA with a patella replacement have the lowest revision rate compared to the other three combinations (*Figure 14*).

Fixed bearing prosthesis have been utilised in clinic for decades and produces wonderful results, but there exists a paradox between compatibility and constriction, higher compatibility brings out higher constriction which will cause greater loosening. Mobile bearing surfaces were invented to resolve this problem, allowing a combination of high compatibility while limiting constriction. Mobile bearing, therefore, theoretically appears to be the better choice in TKA. The AOANJRR reports do not support these theoretical merits. The data demonstrates that the revision rate of mobile bearing prostheses is higher than fixed bearing prostheses (*Figure 15*). This is the reason why fixed bearing is still the treatment of choice in Australia.

We have discussed some topics that continue to be widely debated worldwide, these topics have yet to reach a consensus and require further investigation. The data from the joint registry have many more cases than clinical trials and meta-analysis because they are generated from national databases, making the findings more compelling when the government formulates healthcare policy. In Australian public hospitals where the government covers all the healthcare expenses, the surgeon should use reliable implants and would be required to justify their reason for choosing an implant with higher revision rates. Although

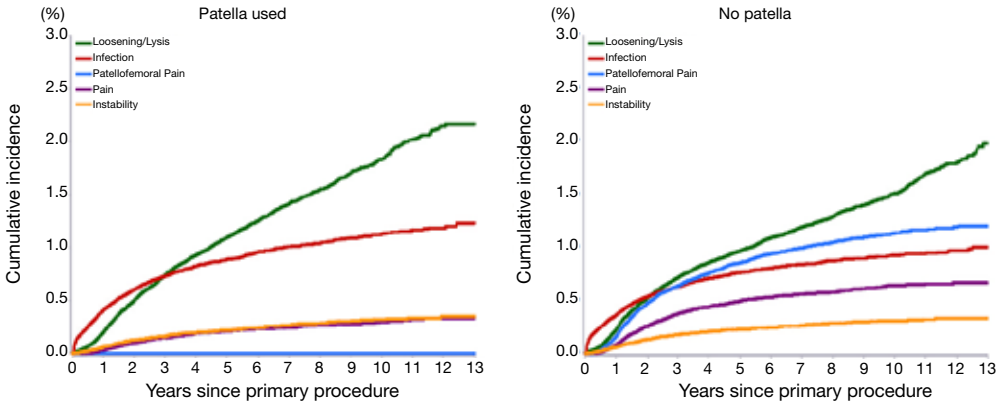


Figure 12 Revision diagnosis cumulative incidence of primary total knee replacement by patella usage (primary diagnosis OA).

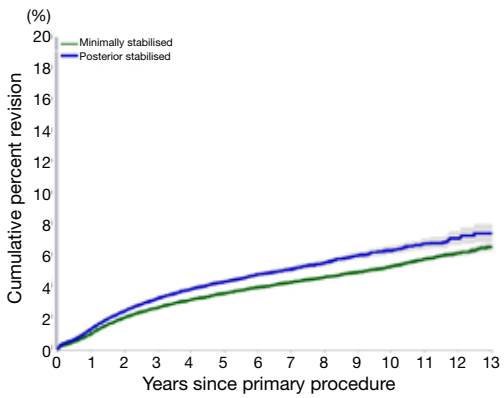


Figure 13 Cumulative percent revision of primary total knee replacement by stability (primary diagnosis OA).

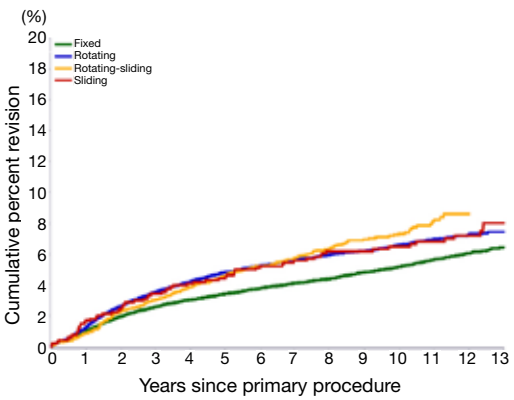


Figure 15 Cumulative percent revision of primary total knee replacement by bearing mobility (primary diagnosis OA).

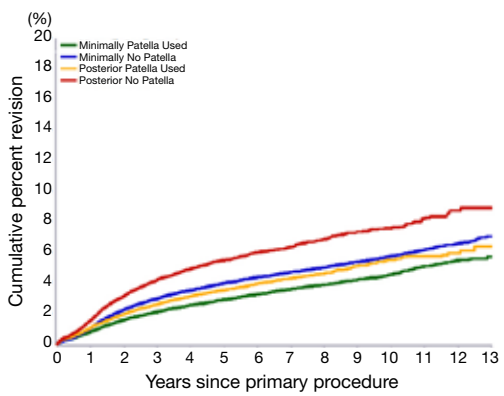


Figure 14 Cumulative percent revision of primary total knee replacement by stability and patella usage (primary diagnosis OA).

the data reports from the AOANJRR are not legally binding mandates dictating surgeon choice of prosthesis, they do give surgeons valuable information that cannot be elucidated through clinic trial and meta-analyses alone.

The joint registry does not give the surgeons the answers to all the clinical questions and the data from the joint registry cannot tell surgeons the functional outcomes of the operations. The joint registry also does not analyse all the radiographs during the operation and follow-up. The joint registry is not a good platform for clinic research as it can only give us retrospective data, although the data can be retrieved much more quickly than these through clinic trials. For this reason there will always be a need for

ongoing clinical trials looking for answers to specific clinical questions.

A new difficult situation has been raised, the data in the AOANJRR regarding revision rate is calculated using Kaplan-Meier analysis, but in recent articles in Clinical Orthopaedic Related Research (CORR) some researchers have found the Kaplan-Meier analysis may overestimate the risk of revision in arthroplasty (2,3). Although we have not confirmed the conclusions from these articles, it is definitely a question worthy of further investigation. Fortunately, AOANJRR has reported on this problem and the need to consider competing risk with death particular as the follow up time increases. However, it is important to understand that the relative comparison remains whether or not the risk is overestimated as it is overestimated equally in all groups being compared.

Another limitation of this article is all the data analysed is from the AOANJRR, where the data is derived from Australia, which is inherently different to the Chinese race and culture. There are some differences between the two races, such as a higher BMI in Australia and a lower incidence of osteoarthritis in China where the main indications for THA is femoral neck fractures and femoral head avascular necrosis. Most of AOANJRR data is from THA for osteoarthritis and so there may be some differences in outcomes among different diagnoses. Furthermore, Chinese patients often have more serious deformities and functional problems prior to undergoing the total joint arthroplasty because of the differences in healthcare systems that also impacts on the results and revision rate of arthroplasties.

We must emphasize that our analysis and interpretation of the AOANJRR are based on the authors' personal understanding and clinical knowledge. All the data are from AOANJRR 2014 annual report, the readers can download the free report from the official website and check the data you are interested in. We are happy to discuss differences of opinion if you have some alternative suggestions.

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Footnote

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Editorial

Meeting patient expectations and ensuring satisfaction in total knee arthroplasty

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Introduction

Osteoarthritis (OA) of the hips and knees is estimated to be the fourth leading cause of functional disability globally. OA is strongly associated with ageing and the Asian region is indeed aging rapidly. The morbidity burden of OA in Asia is significantly increasing (1). In Asia, there is a greater demand for a pain-free knee joint of good range of motion due to cultural, religious or simply lifestyle reasons. Asians are more likely to squat and kneel for prolonged periods of time. Prolonged squatting has been suggested to account for a significant variation in prevalence of knee OA between Chinese subjects from Beijing, China and White subjects participating in the Framingham OA study (2). Total knee arthroplasty (TKA) has been thought to be the definitive solution for chronic mechanical knee pain secondary to OA. the definitive solution for chronic mechanical knee pain secondary to OA. The number of TKAs performed has been increasing steadily over the years according to the national registry in Seoul, Korea (3), as with the rest of the Asia-Pacific region. However, patients' expectations of TKA outcomes seem to differ from the measured outcomes of the surgery (4). Most expected patient-reported outcomes were improvement in pain, restoration of function and resolution of need for assistive devices. There is a significant difference between actual and expected activities after TKA for OA. While TKA relieves pain and restores function beyond doubt, several studies have showed that only 82-89% of patients expressed satisfaction after their primary total knee replacement (5-12). Patient satisfaction is fast becoming an important tool for assessing outcome of TKA (13). However, patient satisfaction is a complex phenomenon that is affected by many elements that determine health-related quality of life (14). This is influenced by the patient's cultural, social and psychological make as well. It is well known that many cultural practices in Asia requires the patient to kneel and/or squat and the ability to achieve this post-TKA will undoubtedly have some impact of patient satisfaction scores. Good clinical and functional outcome as determined by clinicians does not always equate to patient satisfaction as the difference between patients' and clinicians' perception of good outcomes is well known (15). This has led to the development and validation of patient-reported outcome measures (PROMs) or otherwise known as patient satisfaction scores in orthopaedic surgery. While there are numerous tools to measure patient satisfaction after these procedures, it is the long-term satisfaction that is the most important goal of surgery in patients with OA (11). This editorial will evaluate patient satisfaction following TKA as well as the factors that have a profound influence on satisfaction.

What is patient satisfaction?

The concept of patient satisfaction has been around for at least three decades. In 1983, Ware *et al.* (16) wrote on the theory of patient satisfaction. In their paper, they explained the difference between objective and subjective outcomes. They further described patient satisfaction as being composed of satisfaction determinants and satisfaction components. Satisfaction determinants are patient-dependent variables that affect the degree of satisfaction the patient experiences. Satisfaction components refer to a measure of care that is actually received. In a more recent review by Chow *et al.* (17), it is explained that patient satisfaction provides the ultimate end point of the patient's

perspective. Satisfaction can also be thought of as giving an end point to the assessment of the quality of health care. Patient satisfaction is affected jointly by current health state as well as quality of life and gives us an important balance against the normally dominant perspective of the health care provider. Thus, measurement of satisfaction is an essential part of quality assessment after TKA.

How is patient satisfaction measured?

Surveys and questionnaires are tools that measure patient satisfaction. Of the numerous surveys and questionnaires that are available, only a few are specific to TKA. Tools that measure patient satisfaction must be tested and validated through psychometric analysis (18). This implies application of scientific methodology to the measurement of patient satisfaction. Validation generally consists of three components—validity, reliability and responsiveness. In the past, patient satisfaction questionnaires and surveys have been off the mark when validated using psychometric analysis. Sitzia and Wood (19) evaluated patient satisfaction studies and found that only 6% of the 181 studies reviewed utilized principles of psychometric analysis to validate the tools utilized to measure patient satisfaction. Of these studies, none were specific to arthroplasty. To date, we are only aware of two patient satisfaction scales specific to arthroplasty that have been demonstrated to have validity and reliability. One is the patient satisfaction scale developed by Mahomed *et al*. (20) and the other by Dunbar *et al*. (18). Most institutions today measure patient satisfaction via the use of WOMAC, SF-36, SF-12, the Oxford Knee Score and the Knee Society Score (21-25).

Patient satisfaction in total knee arthroplasty (TKA)

Most studies to date have reported that satisfaction following TKA is high. However, there is always that population of patients that are dissatisfied after surgery. Mahomed *et al*. (20) evaluated 857 patients 1 year following TKA and reported an overall satisfaction score of 88%. A study on 25,275 patients from the Swedish Joint Arthroplasty Registry showed a satisfaction score of 81% (18). As mentioned previously, both these studies utilized a validated scale. These results are comparable to those studies that have utilized non-validated questionnaires. Bourne *et al*. (13) reported an overall satisfaction rate of 81% in his study that evaluated 1,375 patients 1 year following TKA. Similarly Scott *et al*. (26) reported a satisfaction rate of 81.4% in his study of 1,290 TKAs. While we have these figures to quote from studies performed on a predominantly Western population, there are no large-scale studies that have evaluated satisfaction rates on Asian patients undergoing TKA. With a different set of expectations, one might expect a slightly different satisfaction rate.

Determinants of satisfaction in total knee arthroplasty (TKA)

Age

Age of the patient undergoing TKA has always been implicated in patient satisfaction. Bourne *et al*. (13) suggested that increasing age was associated with a greater degree of dissatisfaction. This was also reported by Noble *et al*. (10), who concluded that patient satisfaction correlated significantly with age less than 60. However, Merle-Vincent *et al*. (14) found that an age of more than 70 correlated positively with patient satisfaction. To make the literature even more dubious, Scott *et al*. (26) and Gandhi *et al*. (27) found that there was no meaningful relationship between patient age and satisfaction. To date, the effect of age on patient satisfaction is still not clearly understood. Suffice to say, a fitter older person may tend to be more satisfied than a younger person with lesser reserves.

Gender

In a study by Kennedy *et al*. (28), it is reported that women showed greater disability than men in the physical performance and self-report measures. However, they utilized a non-validated measurement tool, the Lower Extremity Activity Profile. By and large, there are no other studies that have proven that the gender of the patient has an influence on patient satisfaction. In fact, it has been shown that gender does not seem to have an impact on patient satisfaction (10,27).

Expectations

Patients' expectations are fast emerging as an important parameter of assessment when studying patient satisfaction. The fulfillment of patients' expectations has been found to be highly correlated with patient satisfaction, as reported

by Scott *et al*. (29). In his study, 323 post-TKA patients completed an expectation questionnaire, Oxford score and SF-12 score pre-operatively. At 1 year post-operatively, the Oxford score, SF-12, patient satisfaction and expectation fulfillment were assessed. High fulfillment of expectation was significantly predicted by young age, greater improvements in Oxford score and high pre-operative mental health scores. Bourne *et al*. (13) reported that the most important contributing factor to dissatisfaction following TKA was not meeting patients' expectations. From these studies, it is apparent that patients' expectations of the outcomes of TKA have a significant bearing on patient satisfaction. The importance of managing patients' ideas, concerns and expectations pre-operatively at the clinic setting by the surgeon cannot be over-emphasized. The arthroplasty surgeon must be well versed with the cultural and social aspects of the patient care so that the expectations of the patients are better dealt with. Vissers *et al*. (30) conducted a systematic review of 35 studies which examined the impact of psychopathology and found that lower preoperative mental health was associated with lower self-reported patient outcomes.

Comorbidities

Comorbidities can be dichotomized further into psychological and medical comorbidities. The mental health of the patient undergoing TKA has been found to have an impact on patient satisfaction. In a recent study by Clement *et al*. (31), it is reported that poor mental health was associated with a diminished improvement in the Oxford knee score and increased the rate of dissatisfaction following TKA. This is also echoed by Ellis *et al*. (32) who conducted a study within an indigent population. He reported that psychopathology may result in lower satisfaction scores at 1 year following TKA. While it is very clear that mental comorbidities have a deleterious effect on patient satisfaction, the same cannot be said for the impact of medical comorbidities. Gandhi *et al*. (33) reported that there was medical comorbidities had no significant impact on patient satisfaction. Only Scott *et al*. (26) found that there as a minimal but statistically significant increase in dissatisfaction in patients with a higher mean number of medical comorbidities.

Primary diagnosis

Interestingly, Robertsson *et al*. (11) found that patients with a primary diagnosis of rheumatoid arthritis had a higher satisfaction rate as compared to patients with OA. He postulated this may be due to the fact that patients with rheumatoid arthritis may experience a greater amount of pain relief as compared to those with OA. This was also found by Bullens *et al*. (4) who cited the lower preoperative expectations of rheumatoid patients as the main reason for the higher satisfaction rate.

Range of motion

As mentioned previously, one would expect the Asian patient to be concerned with the amount of post operative range of motion and thereby affecting patient satisfaction. A study by Miner *et al*. (34) on Western patients found that post operative range of motion after 1 year was not associated with patient satisfaction. However, Seng *et al*. (35) reported improved patient satisfaction scores 5 years following high-flexion TKA on Asian patients. Indeed, this may be unique to the Asian TKA given the higher demands for flexion.

Symptoms

Unresolved pain following TKA has been consistently found to be a significant factor leading to patient dissatisfaction. Scott *et al*. (26) cited unresolved pain as the most important predictor of patient dissatisfaction following TKA. Similarly, Franklin *et al*. (36) also concluded that unresolved pain up to 1 year following TKA was associated with a higher dissatisfaction rate.

Components of satisfaction in total knee arthroplasty (TKA)

Type of anaesthesia

There is a lack of evidence with respect to anaesthetic techniques and their impact on patient satisfaction, mainly because most of these studies did not assess satisfaction scores. However, Thorsell *et al*. (37) did report that there were higher rates of satisfaction when comparing local infiltration with continuous epidural anaesthesia.

Minimally-invasive surgery (MIS)

A meta-analysis by Smith *et al*. (38) suggests that whilst incision length was significantly smaller in MIS and range of motion was significantly greater following MIS, there were

no statistically significant differences in all other clinical or radiological outcomes between MIS or conventional TKA. In another study, Hernandez-Vaquero *et al*. (39) found no statistically significant differences between MIS and conventional TKA with regards to the radiological alignment of the implant, range of motion, KSS scores, the SF-12 scores, patient's pain perception, satisfaction or subjective improvement. However, in an Asian study, Seon *et al*. (40) reported better WOMAC scores in patients who received a MIS TKA up to 9 months following surgery. In his study, he compared the clinical and radiological results achieved using MIS and conventional techniques in 42 bilateral TKA patients. This again adds strength to the argument that the Asian TKA may have to be approached differently.

Use of navigation

To date, the use of navigation does not seem to affect clinical outcomes and patient satisfaction. Burnett *et al*. (41) concluded that longer-term studies demonstrating improved function, lower revision rates, and acceptable costs are required before navigated TKA may be widely adopted as current literature is largely inconclusive. Even in the Asian literature, Venkatesan *et al*. (42) concluded that computer-assisted navigated knee arthroplasty provides some advantages over conventional surgery, but its clinical benefits to date are unclear and remain to be defined on a larger scale. In light of the current literature, we would think that the use of navigation does not affect patient satisfaction scores.

The way forward

Patient satisfaction without a doubt is an important outcome measure of TKA that has to be taken into consideration by all arthroplasty surgeons. TKA in the Asian population involves a few unique challenges especially with higher demands of post-operative flexion. Improving patient satisfaction following TKA is certainly a challenge, given the already high satisfaction rates. However, there is still that small population that remains dissatisfied. We need to channel our efforts to improve the satisfaction rates in these patients. The factors that we have discussed above all play very important roles in determining patient satisfaction. However, it is of utmost importance that the surgeon fully understands the patient's ideas, concerns and expectations pre-operatively. Proper per-operative education is essential in achieving good results post-TKA.

Summary

Patient satisfaction should be approached from two prongs—determinants of satisfaction and components of satisfaction. Patient satisfaction can be improved by modifying the elements from these two categories. Patient satisfaction is one of the PROMs used widely in orthopaedic surgery and is fast becoming an important tool to measure surgical outcomes. It is an essential modality of the patient-centred care that we all aim to provide.

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Footnote

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Editorial

Comparison of self-reported and measured range of motion in total knee arthroplasty patients

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Abstract: Total knee arthroplasty (TKA) is an established method used in the treatment of end-stage knee osteoarthritis. Range of motion (ROM) and relief from pain show success of TKA. One of the most important aims of this treatment is to achieve an adequate ROM. Numerous outcome instruments and patient-reported questionnaires are in use to evaluate of TKA patients. For this purpose, disease-specific questionnaires and self-reported ROM and function evaluation tools are also being developed. The most important criteria in musculoskeletal care is assessing the joint mobility of the patient's. Joint mobility can be measured with visual estimates, universal goniometer, X-ray radiography, digital gravity goniometers and applications found in smart phones. Apart from the reliability and validity of the method, obtaining the same results from different examiners is very important. The clinical follow-up of patients is an important part of postoperative care after TKA. The follow-up interval and duration remain dependent on the physician's anticipation of the clinical progress of the individual patient. Long-term surveillance of joint arthroplasty is necessary, but it has also become increasingly burdensome as greater numbers of TKAs are performed, and in younger populations. Patient self-reported questionnaires and self-goniometric measurement are used by many investigators to decrease this burden on the surgeon or staff, and in combination with telemedicine radiographs might be a reasonable option to routine clinic visits. They could reasonably be expected to lower the burden on both the patient and the clinician without eliminating contact and thus sacrificing quality of care. At the same time, it would reduce the financial burden too. Self-reported measured ROM can use in the routine follow-ups to reduce surgeons, physiotherapist and other staff.

Keywords: Total knee arthroplasty (TKA); goniometric measurement; range of motion (ROM); self-reported

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Total knee arthroplasty (TKA) is an established method used in the treatment of end-stage knee osteoarthritis. Range of motion (ROM) and relief from pain show success of TKA. One of the most important aim of this treatment is to achieve an adequate ROM (1,2). The postoperative flexion is an important factor that affecting patient satisfaction after TKA. Normal activities of daily living require a minimum of 105° and 110° of flexion, patients from non-Western cultures often engage in activities such as kneeling and squating that require higher flexion. ROM affects individuals' activities carried out during the day (3).

Knee flexion and extension ROMs are incorporated into orthopaedic knee scoring systems to assess disease severity, are frequently used to track recovery after various knee surgeries, and are also used as clinical indicators by which to monitor and benchmark physiotherapy or rehabilitative performance (4).

Numerous outcome instruments and patient-reported questionnaires are in use to evaluate of TKA patients. For this purpose, disease-specific questionnaires and self-reported ROM and function evaluation tools are also being developed (5). These evaluation tools are used by surgeons, research assistants, physiotherapist and patients.

American Knee Society (AKS) questionnaire consistently reported significantly less pain to the physician during the clinic visit than they did when self-reporting. The fact that

the patient-reported pain and function after TKA differed significantly from those recorded in the clinician's office may have important implications for the use of these scoring instruments. However, a significant difference between patient-reported and clinician-recorded values was observed for the AKS pain and function subscores but not for the Oxford Knee Score. But, there is a need to more studies on this issue (5).

The AKS functional score records only walking distance, assistive devices used and how stairs are climbed. Patients may overstate the distance walked, exaggerate their stair-climbing ability or minimize their need for assistive devices in an attempt to please their surgeon when asked these questions in his/her presence (5).

The most important criteria in musculoskeletal care is assessing the joint mobility of the patient's. Joint mobility can be measured with visual estimates, universal goniometer, X-ray radiography, digital gravity goniometers and applications found in smart phones. Apart from the reliability and validity of the method, obtaining the same results from different examiners is very important.

Goniometry is an essential assessment skill in musculoskeletal practice, with the resultant measures used to determine the presence or absence of dysfunction, guide treatment interventions and generate evidence of treatment effectiveness. Universal goniometers (UG) are the most common form of goniometer used in clinical practice. They are easily accessible, relatively inexpensive, portable and easy to use. Reliability studies have shown that on repeated measures the UG demonstrated good overall intra- and inter-tester reliability. The validity of UG measures for knee range of motion have been reported, using measures taken from radiographs as a reference standard. The correlation between universal goniometer measures and radiographs were reportedly higher for larger degrees of knee flexion than for smaller degrees of knee flexion. The reliability and validity of UG measures can be affected by incorrect application of the goniometer (6).

Older people tend to make errors and a statistical trend that less educated people are more likely to make errors. Use of patient self-assessment of ROM is suitable for young and educated populations (7).

The major advantage of digital photographs is that one clinician can measure and re-measure the standardized image at each time. This could be useful in a setting where different clinicians measure the ROM. It is better than goniometric measurement (4,8).

Although radiographic measurements give the most accurate information in clinical practice, many surgeons prefer to goniometric measurement. Use of radiographs to reliably measure range of motion following knee arthroplasty has allowed us to set up a 'virtual knee clinic' (9).

In recent years the advent of smartphones has brought a range of new technological applications within the reach of most consumers. Number of smartphone based goniometry apps are now available. Universal goniometer has been demonstrated in repeated measurements better results than apps. The Smartphone application used may be considered as precise and accurate in clinical practice (10,11). Navigation, inclinometer and camera measurements can be performed in smartphones. Camera-based smartphone measurement of the knee range of motion is fit for purpose in a routine clinical setting (12).

The clinical follow-up of patients is an important part of postoperative care after TKA. The follow-up interval and duration remain dependent on the physician's anticipation of the clinical progress of the individual patient. Long-term surveillance of joint arthroplasty is necessary, but it has also become increasingly burdensome as greater numbers of TKAs are performed, and in younger populations. Patient self-reported questionnaires and self-goniometric measurement are used by many investigators to decrease this burden on the surgeon or staff, and in combination with telemedicine radiographs might be a reasonable option to routine clinic visits. They could reasonably be expected to lower the burden on both the patient and the clinician without eliminating contact and thus sacrificing quality of care. At the same time, it would reduce the financial burden too (13).

"A Comparison of Patient-Reported and Measured Range of Motion in a Cohort of Total Knee Arthroplasty Patients" is written by Drs. Jamie E. Collins, Benjamin N. Rome, Meghan E. Daigle, *et al*. and was published on *The Journal of Arthroplasty* on February 2014 (14).

At this study, subjects were assessed pre-operatively at baseline and at 3 and 6 months post-operatively. Knee extension was measured in standing; knee flexion measurements were performed using a wheelchair. They reported that the height of the chair is not important but there is no citation about it. Considering the difference between the height of the patient, we believe that this type of measurement would affect the results. There is no information and education about how to make measurements of patients who were attended the survey by mail.

There is not blind the person who made the assessment. This situation may have influenced the results of the study

and it can lead to bias.

A total of 112 patients were included in the analysis. But, only follow-up patients were focused in the analysis (Patients with both self-rated and objectively measured ROM: n=100 at baseline, n=62 at month 3 and n=53 at month 6). Patients who come to the clinic for evaluation were included in that study. However, patients who were followed by the mail, initially given the impression that they were also included in the study. There is no relationship with these patients and that study. There is a table and information about who were followed by mail and those patients' information didn't use in anywhere or any statistical analysis. The presence of this information is senseless and unnecessary. Although written like that "*Patients were given the option to complete the post-operative visits in person or to mail in a study survey*" in method section, "*Patients were given the option to complete follow-up visits in the clinic or over the phone*" were written in discussion.

In general, it is not a study that can easily be understood by another researcher. Everything is not expressly mentioned in that study. But, self-reported measured ROM can use in the routine follow-ups to reduce surgeons, physiotherapist and other staff.

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Footnote

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Editorial

The potential utility of patient-reported range of motion after total knee arthroplasty

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Total knee arthroplasty (TKA) is a safe, cost-effective treatment for pain relief and improvement of knee function in patients with knee arthritis (1-3). The procedure has become extremely common in the United States: in 2008 alone, over 615,000 TKAs were performed (4) mainly driven by the high prevalence of symptomatic osteoarthritis (OA) (5). Candidates for the procedure typically have diminished quality of life due to persistent knee pain and significant functional limitation (1). OA is the main clinical indication for TKA (approximately 97% of cases) (6). Advanced OA is associated with reduced knee range of motion (ROM), which leads to increased disability (7,8): an individual requires 67° of knee flexion to walk normally, 83° of flexion to climb stairs, 90° to walk down stairs, 105° to get up from a chair, and 115° to rise from a sofa (9,10).

A variety of measures exist to assess the outcome after TKA, however, there is no universal standard (11). The American Knee Society Score (AKSS) is one of the most widely used scoring systems to assess knee functionality. It consists of both a clinical score and a functional score and is typically administered in office visits (12,13). ROM measurements are an integral component of the AKSS score. Final ROM achieved after TKA is an important determinant of both patient satisfaction and function (14,15). ROM is traditionally measured by clinicians or trained researchers using a goniometer to assess angle of flexion and extension. Goniometer measurements have been found to be highly reproducible between trained measurers when the same technique is used (16).

ROM after TKA is influenced by numerous factors including pre-operative ROM, age, body mass index, comorbidities (particularly diabetes mellitus), and intraoperative variables such as implant type and anesthesia modalities (17-22). Patients with stiffness and poor ROM post-TKA are typically managed first with aggressive physical therapy. If stiffness persists, patients may require more invasive measures such as manipulation under anesthesia (MUA) or arthroscopic lysis of adhesions. MUA is typically performed under general or regional anesthesia to allow complete muscle relaxation. The hip is flexed to 90° and the knee is bent until a firm end point is encountered. Although most patients experience improvements in ROM after MUA, patients with diabetes mellitus or patients who received a cruciate-retaining prosthesis have been found to be at risk for lower final ROM (23).

Long-term follow-up of patients after TKA is necessary. However, with the rapidly increasing population of patients undergoing TKA and its more prevalent use in younger patients, in-office follow-up can become burdensome and expensive (4,24). The necessity of using trained clinicians or technicians to measure ROM with a goniometer only amplifies the time and cost of in-office long-term follow-up visits. Questionnaires such as the Oxford Knee Score (25) attempt to assess patients' evaluation of knee function and impact on quality of life. These questionnaires can be administered by phone, mail, or online thereby potentially reducing the need for an office visit, thus potentially reducing the burden on the healthcare system of long-term follow-up post-TKA. Although previous studies have shown a correlation between patient-reported questionnaires such as the Oxford Knee Score and more thorough knee evaluations such as the AKSS 2 years after TKA, no long-term (5 and 10 years post-TKA) correlation is observed (26). Furthermore, patient-reported questionnaires such as the

Oxford Knee Score do not properly assess ROM, a vital component to evaluating knee functionality. Though the idea of self-reported outcomes such as the Oxford Knee Score present a potential way of reducing the burden of long-term post-operative follow-up, these simple at home questionnaires miss vital components of a more thorough clinical assessment.

A recent study by Collins *et al.* in the *Journal of Arthroplasty* proposed a new solution (27). This study utilized a method of patient-reported outcomes initially developed by Gioe *et al.* in which post-operative TKA patients were mailed surveys with lateral knee photographs that showed knee ROM in small increments to compare to their knee ROM (28). This method was further validated by Khanna *et al.* in 2011 (29). Khanna and colleagues compared patient-reported ROM using similar methods developed by Gioe *et al.* with clinically measured ROM using a goniometer. They stated that patient-reported ROM using photographs could be considered accurate for the purposes of long-term follow-up of patients after TKA. Patient recorded flexion assessed by the use of photographs was not significantly different than clinician-measured flexion as determined by goniometer measurements—a difference of just 0.7° (P=0.48). Although the assessment of extension was significantly different between the self-reported method and the clinician measurements (difference of 1.7°, P<0.001), the small absolute measurements of extension (often 1-4°) makes the comparison more difficult. Additionally, previous studies have shown a correlation between patient-report extension using photographs and physician-measure extension using a goniometer (28). These studies using patient-reported ROM with photographs only looked at patients after TKA. Understanding the ROM before TKA is important, as pre-operative ROM is the key determinant of post-operative ROM (17). Neither study evaluated change in patient-reported ROM over time or compared patient-reported ROM at baseline before surgery and after TKA.

To address these gaps in the data and further validate this patient-reported ROM methodology, Collins *et al.* enrolled 112 TKA patients. Subjects were assessed at baseline (pre-TKA), 3 months post-operatively, and 6 months post-operatively. ROM (both flexion and extension) were assessed either in office by goniometer measurement from a trained research assistant or at home using photographs depicting varying ranges of flexion and extension and asking the patients to select the photograph closest to their current ability to flex or extend. The authors found a statistically significant association between the objective measurements using the goniometer and self-reported ROM using the photograph method for both flexion and extension, thus further validating this method as a way of assessing ROM.

Collins and colleagues were also able to show that self-reporting of ROM using this method was valid over time: reports of improvement, worsening, or stable ROM was associated with clinical goniometer measured changes over time. This has important implications in long-term follow-up of TKA patients post-operatively. Younger patients generally have greater rates of revision of TKA than older patients likely due to longer required lifespan of the prosthesis as well as better post-operative health and mobility resulting in increased wear-and-tear (30). Additionally, as the lifespan of the population as a whole increases and the popularity of TKAs continue to rise, the number of knee arthroplasties that become functionally compromised years after the operation will continue to increase as well. Although the follow-up time used by Collins *et al.* was limited to 3 and 6 months, the accuracy of the changes in measurement over time suggest that this method may be valid for not only short term, but longer follow-up intervals as well.

As Collins demonstrated, the patient-reported ROM using photographs was sensitive to change—both increasing ROM and decreasing ROM. The ability to accurately detect changes in ROM over time is vital. Early detection of a change in ROM and instability can indicate early failure and therefore allow earlier intervention. Polyethylene wear can lead to osteolysis, deterioration of bone, and eventual loosening. This process can begin before a patient is symptomatic and may only be evident on radiographs (31). Often, patients do not present with a prosthesis in which function has become compromised until there is pain, sensation of instability, recurrent joint effusions, or dramatic decrease in functionality. Delayed detection can lead to a more technically challenging revision procedure because of decreased bone stock. However, with accurate patient-reported ROM in small, 5° increments as used by Collins and Khanna, it is possible that a potential impending failure can be detected earlier, before significant polyethylene wear and osteolysis occurs. Consequently, a partial or complete revision would likely have greater rates of success with early detection. In the immediate post-operative period evaluation of ROM patient progress can be recorded and intervention can be performed sooner if patients are not achieving an adequate arc of motion. Aggressive physical therapy is typically the first line intervention however if

patients do not make adequate improvements with therapy alone then and MUA is indicated. Shorter intervals between TKA and any intervention allow greater success than if therapy or MUA are delayed and significant functional limitations have already been realized (23).

This study validated this patient-reported method and was able to show accurate measurements over time and changing ROM. The short-term follow-up time points used by Collins *et al.* (3 and 6 months post-operatively) are important as they can play a role in determining whether there is stiffness and poor ROM that needs treatment with physical therapy or MUA. Evidence suggests MUA within 90-day results in greater ROM compared to longer intervals (32,33). Although survival of TKAs is high years after the operation (10-year survival, 85-97%) (34,35), long-term follow-up on patients with TKA is needed as there are still a considerable number of patients requiring therapy or revision years after the operation. The results from Collins and colleagues suggest that this method may be valid with longer follow-up; however, future work confirming the ability of this method to detect changes in ROM and stability over a long time period post-operatively (5, 10, 15 years) would be ideal. Now that this methodology has been validated in several studies, there is a need for determination of the appropriate way to incorporate this patient-reported ROM into clinical practice. Clearly, this could reduce the number of in-office follow-up visits after TKA. However, the proper balance of patient-reported outcomes and evaluation by a clinician must be maintained to ensure proper long-term care for patients with a knee replacement. Additionally, cost-effective analysis of widespread, long-term employment of this technique is necessary to determine if this does truly benefit the healthcare system.

With the increasing prevalence of TKAs, validated patient-reported outcomes such as self-reported ROM using photographs as described above could help relieve some of the burden that is placed on both patients and the healthcare system with the necessary follow-up of patients with TKA. The cost and resource savings that could result from implementation of this technique could help make TKAs—which are already considered highly cost-effective (2)—even more efficient long-term result in significant savings in cost and resources.

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Footnote

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Editorial

The effect of obesity on mechanical failure after total knee arthroplasty

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Abstract: "Increased aseptic tibial failures in patients with a BMI ≥35 and well-aligned total knee arthroplasties" published in *The Journal of Arthroplasty* on July 2, 2015 draws the conclusion that the risk of revision total knee arthroplasties (TKA) due to aseptic tibial component loosening is two times greater in patients with a BMI ≥35 kg/m^2, independent of age or limb alignment. This result confirms that obese patients are at a higher risk of mechanical complications after performing TKA, independently from the risk of infection. This study suggests that the management of obese patients for TKA must be meticulous, careful, and should inspire from great bone deformations in valgus of varus when choosing implants.

Keywords: Obesity; total knee arthroplasty (TKA); tibial failures; aseptic loosening

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Knee-replacement surgery is a very frequent and highly successful procedure, with more than 600,000 arthroplasties in 2008 in the US. It relieves pain and improves knee function in people with advanced arthritis of the joint. Total knee replacement (TKR) is a successful gold standard in the treatment of end-stage degenerative joint disease or deformity of the knee. A couple long-term follow-up studies of standard total knee arthroplasty (TKA) have shown excellent results for pain reduction, functional improvement, and survivorship of 90-95% at 15 years (1,2). The prevalence of total knee arthroplasties has increased in the past 2 decades and the demand is expected to dramatically grow in the future. In the same period, the prevalence of obesity of adults also grew in occidental countries. By 2030, more than 80% of the adults are expected to be obese in the US. There are several causes of failure in TKR, and the literature is divided over the influence of obesity on outcome in these arthroplasties. Some authors found similar results for obese and non-obese patients (3-7) whereas others describe obesity as having a negative influence on outcome (7-9). Aseptic loosening of the tibial component is the most frequent cause of failure in TKR (10). Implant-bone stress levels, particularly on rather weak cancellous bone, have been implicated as the predominant cause for aseptic tibial component loosening (11). A high body weight increases the stress transferred through a TKR to the surrounding bone (12), suggesting TKR to be associated with a poor outcome and a higher failure rate in obese patients, owing to higher peak stresses and cycle loading across the replaced joint.

In this study, based on patients undergoing primary unilateral TKR for osteoarthritis in an American institution, the team focused on risk factors for aseptic loosening of the tibia, particularly related to body mass index. Patients who underwent revision due to aseptic loosening, polyethylene wear, instability, or arthrofibrosis were excluded. Patients were stratified into six categories according to the World Health Organization: "underweight" (<18.50 kg/m^2), "normal" (18.50-24.99 kg/m^2), "overweight" (25.00-29.99 kg/m^2), "obese class I" (30.00-34.99 kg/m^2), "obese class II" (35.00-39.99 kg/m^2) and "obese class III" (≥40 kg/m^2). The overall revision rate due to aseptic tibial component loosening was 1%. Patients experiencing aseptic loosening were younger and had a higher BMI, with a risk for revision almost two times greater in those with a BMI ≥35 kg/m^2. Another study showed that focal osteolysis rates were five times higher in patients with a BMI >40 kg/m^2 (5). The cutoff for outcome measures in TKA is not perfectly determined yet, with studies finding differences at 30 kg/m^2 (9,13-16),

and others at 35 kg/m^2 (17,18). Ries *et al.* (19) found a greater rate of loosening of the tibia with short keels when implanted in obese patients compared to standard keels. A greater contact area between bone and implant would lead to a better repartition of stress, like in great bone deformations in valgus or varus. Surgeons should be careful when performing TKR in grade II or III obese patients, particularly concerning tibial loosening. Technical features, like the systematic use of long keels or stems might be examined in the future.

Performing TKR requires a team of medical experts, including surgeons, anesthesiologists, endocrinologists and experts from various departments. Prospective randomized trials will be needed to further demonstrate the outcome after TKR in obese patients. Meanwhile surgeons must be careful and meticulous when performing TKR, in particular concerning the choice of implants, alignment of the limb, and the risk of infection.

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Editorial

Results of sleeves in revision total knee arthroplasty: an editorial comment on recently published in the *Journal of Arthroplasty*

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Abstract: The paper entitled "Direct, cementless, metaphyseal fixation in knee revision arthroplasty with sleeves-short-term results" published in the *Journal of Arthroplasty* to analyze the short- and mid-term results in revision total knee arthroplasty (TKA) in a largest series so far. This article shown that cementless metaphyseal fixation with sleeves is a promising option for revision TKA implant fixation. The clinical outcomes regarding the range of motion and the KSS are also promising. Based on this article and related literatures about sleeves, we assess the short to mid-term outcomes and the clinical perspectives in revision TKAs.

Keywords: Sleeves; knee revision arthroplasty; bone defect; metaphyseal fixation; cementless

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The number of revision total knee arthroplasty (TKA) is increasing as the primary TKA becomes widespread (1). This is predicted to continue with an estimated 601% increase from 38,300 to 268,300 between 2005 and 2030 in the United States (2). The annual report of the National Joint Registry (NJR) for England, Wales and Northern Ireland founded that the revision arthroplasty comprised 6.1% of all TKA in 2011 (3), while the revision arthroplasty increased rapidly with a 17% increase in the United Kingdom from 2011 to 2012 (4). Different methods of reconstruction depend on the factors such as the remaining bone stock, integrity of the remaining ligaments and so on. The Anderson Orthopaedic Research Institute (AORI) classification for bone defect provides a useful tool for classifying and scientific guidance for method of reconstruction in revision TKA (5). Bone graft (6), cement and screws (7), block augments (8), tumor mega-prostheses (9) and custom-made prostheses (10) have been used with some success.

Unlike primary TKA which mainly acquired fixation at the solid bone cuts on the joint surface (zone 1), this zone is mostly compromised and cannot be reliably used in revision TKA, so additional fixation in the diaphysis (zone 3) and/or metaphysis (zone 2) is recommended (11). An alternative option for filling bony defects is the use of porous coated metaphyseal filling implants, which also achieve stable fixation in metaphysis to avoid excess bone resection. There are two distinct technologies implants that have different implantation techniques and philosophies (12): tantalum cones and metaphyseal sleeves. Metaphyseal sleeves have a long history more than 30 years which were used with rotating hinge knee system, while it was until 2005 the metaphyseal sleeves were introduced with posterior stabilized and VVC constraint implants (13). The base component of the sleeve is made of titanium alloy and the porous surface is sintered by titanium with the porosity from 50% to 80%. Biological fixation metaphyseal sleeves of osseous integration not only provide a stabile scaffold of joint reconstruction, but also avoid potential complications of cemented block and wedge augments and the potential disease transmission of allografts (14,15).

On Jun 20, 2015, a paper entitled "Direct, cementless, metaphyseal fixation in knee revision arthroplasty with sleeves-short-term results" published in the *Journal of Arthroplasty* to analyze the short- and mid-term results in a larger revision TKA series. Compared with previously

published smaller series studies (16-18), the 156 patients been analyzed was the largest sample size so far. All the cases were aseptic knee revisions with complete exchange of the implant in a single institution from February 2007 to October 2011. As 18 patients died and 17 patients could not be reached, finally 121 patients were included for re-evaluation. Mean follow-up was 3.6 years (range, 2-6.1 years). The results in 121 patients with 193 sleeves (119 tibial and 74 femoral) were analyzed. Analysis included clinical and radiographic assessments, and a special focus was paid to the analysis of the revision failure reasons and the re-revision surgeries. In all cases, the AORI classification of the tibial side was 114 cases type II defect (77 type IIa and 37 type IIb) and the rest were type III. And the proportion of type III was higher on the femoral side (28 cases), and the rest were type II (46 cases). All surgeries were done by Heiko Graichen or Marco Strauch using the same tibia first, gap balanced technique. In 117 of the 119 tibial sleeves and in 25 patients out of 74 femoral sleeves additional stem were applied.

Sleeves with Morse taper not only provide axial support, but also have excellent rotational stability. The stem provides the immediate support, while the porous coated sleeve with osseous integration provides long-term support. Because of the above theoretical basis, the authors reported promising results of clinical and radiological assessments. The clinical results showed that the ROM, KSS and Function Score improved significantly, with the similar results with the previously published articles. Radiological analysis showed the mean leg axis was changed from 2.1±2.2° varus preoperatively to 0.6±0.3° postoperatively. Most (96.4%) of the sleeves showed good osseous integration. Radiolucent lines could be found in seven sleeves, and three of them have no clinical symptoms.

Although the proportion of radiolucent lines is relative low, special attention should be taken for this problem. It might affect the long term stability, and might be related with loosening if the radiolucent lines progress during the follow-up. Huang *et al.* (12) reported two loosening cases in 119 sleeves (1.7%) and Agarwal *et al.* (16) reported one progressive radiolucent lines in 104 knees. In Alexander's study (17), all implants showed radiographic evidence of osseous ingrowth, and no components had sighs of loosening, and Bugler *et al.* (18) came the same results with no loosening. Barnett *et al.* (19) reported four patients with radiolucent lines which were all limited to the tibial plateau adjacent to the tray and did not extend to the sleeve ingrowth surface, and two other patients showed signs of distal osteolysis, the follow-up results suggested that the osteolysis were focal and quiescent, as a result, none of the patients had sign of loosening. From the above results, many radiolucent lines and osteolysis were limited to the tibial plateau and distal of the stem. The presence of osseous integration to the porous coated surface still provides the stability for the implants.

End-of-stem pain is another complaint usually happened to this reconstruction method. In this study, stem pain on the tibia side was found in two patients (1.7%, one was found a loosening of the tibia implant in a later revision) and in one patient on the femoral stem tip (1.4%). Agarwal *et al.* (16) reports a study with one knee used intramedullary stem on the femoral side, 20 knees used on the tibial side, 78 knees on both sides and 5 knees not used. The results showed no patients had implant stem tip pain on either side. While Alexander *et al.* reported a higher proportion of patients complained of end-of-stem pain (7 patients, 23.3%) in 30 revision TKAs. For more than 2 years conservative treatment, three of the seven patients (10%) remained chronic mild to moderate end-of-stem pain. All the three patients had used the longest diaphyseal stems [up to 150 mm, not statistically significant (P=0.139)] and small diameter stems [10-16 mm statistically significant (P=0.05)]. The result showed small stem diameter might be a cause. As the limited sample size, it could not to get conclusion that the end-of stem pain was related to slotted versus non-slotted stems (17). Given the different reported results, it may be the different ways of fixation which were applied in different studies. There was no clear explanation for the reason of the end-of-stem pain, so more exploration should be taken into this field.

Fourteen re-revision surgeries (11.4%) have been performed until the follow-up (mean 3.6 years). The reasons for revision were four infections, three instabilities, one malalignment, one extensor mechanism failure, four aseptic loosening and two fractures at the junction between stem and sleeve. All the aseptic loosening happened in rotating hinge implants, and there was no significant difference between stemless and stemmed augmentation. While the two loosen sleeves in Agarwal's study did not have any stems used with them (16). So we should pay special attention handling sleeves with rotating hinge implants or stemless implants. Other complications such as intraoperatively tibial fracture (18,19) and patellofemoral symptoms (18) are recorded in related literatures about sleeves

Despite the advantages of easy surgical technique, the reserve of the limited remaining bone and the promising

results, there are some challenges of the sleeve surgery. The first challenge is the correct placement of the sleeve, and it is difficult to put a proper angle in the coronal and sagittal plane using a metaphyseal sleeve only. Therefore guidance with stem is helpful to solve this problem. The second challenge is how to remove the well-fixed sleeve with the well bone ingrowth in revision surgery.

Although this is so far the largest sample size study in this field, there are some limits for this article. Firstly, it is a relatively short follow-up time. As the re-revision surgery would be much more difficult, good result for long follow-up time results to avoid re-revision surgery would be important. Secondly, the implants were fixed by different ways such as stem or stemless, it might bring confounding factor. Thirdly, the lack of a control group as well as non-randomized patient selection reduces the level of evidence of the study.

In conclusion, recent studies had shown easy surgical technique, excellent bone ingrowth and promising short to mid-term results. Sleeves could be a promising option to deal with large bone defect (AORI II and III) in revision TKAs both tibia side and femoral side. Meanwhile, we should pay attention to the end-of-stem pain and failure in revision, and we should handle these problems properly.

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Editorial

Is there a rationale to use highly cross-linked polyethylene in posterior—stabilized total knee arthroplasty?

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The use of highly cross-linked polyethylene (HXLPE) in total knee arthroplasty (TKA) is controversial (1).

The concept behind the development of HXPLE in total hip arthroplasty was to reduce wear and to prolong the implant survival. While plastic wear and secondary osteolysis is a main concern in total hip arthroplasty its impact on longevity of total knee arthroplasties is less clear. Aseptic loosening is the main reason for failure of total knee replacement and accounts for around one-third of all revisions (2,3). Other early failure mechanisms are infection, instability and stiffness (2). Wear induced osteolysis is not encountered until more than 15 years after the initial surgery and is not considered a main cause for revision TKA (2).

HXLPE is a modification of standard polyethylene (PE) (4). Irradiation initiates free radicals that promote cross-linking and results in a higher density PE. In a further melting step attempts are made to eliminate remaining free radicals to improve the resistance to oxidation. HXPLE is more resistant to adhesive and abrasive wear (1). However, HXPLE has decreased toughness, ductility and resistance to fatigue and fractures. If residual free radicals are not destroyed by post radiation treatment, HXPLE has an increased propensity to oxidative breakdown (1). Especially the first generation of HXPLE is at increased risk. Therefore manufacturers tried to improve the characteristics of the second-generation HXPLE by sequential irradiation and annealing or by utilizing anti-oxidants like vitamin E.

The benefit of HXLPE has been confirmed for total hip arthroplasty (5). However the PE bearing in hip and knee arthroplasty is exposed to different biomechanical loads. The hip suffers from abrasive and adhesive wear in a highly conformed ball in socket articulation, while, the knee is exposed to shear forces and point contact loads because of its round (femoral condyle) on flat (tibial insert) design. Beside the point loading of the bearing surface there are additional areas with increased mechanical stresses including the tibial post and the insert locking mechanism (6).

Most supporting evidence for HXPLE in knee arthroplasty is derived from *in vitro* wear simulator studies that are showing a reduction of wear up to 60% (7). Although laboratory tests are essential for the development of new materials, *in vitro* studies should only be applied with caution. *In vitro* studies assume an optimal alignment and ligament balance, and primarily test for abrasive and adhesive wear. In addition *in vitro* studies don't include third body wear (cement particle) and wear simulators do not perfectly reflect the kinematics of the normal knee. In the past catastrophic failures of PE that tested well *in vitro* have been encountered and should increase our caution when implementing new materials based on *in vivo* test results alone (8).

Is there any *in vivo* evidence supporting the use of HXPLE? A clinical study about particles in the synovial fluid one year after surgery could not find any difference in number, size and shape of the PE particles between standard PE and HXPLE (9). Kim *et al.* investigated the clinical and radiographic differences between highly cross-linked (XLPE) and conventional PE in 308 patients 5 years after bilateral posterior cruciate substituting TKA—and did not report a difference in outcome nor revision rate (10). There are other short and mid term studies that show no difference in outcome between the two materials (6,11,12).

Since HXPLE reduces the fracture toughness tibial

post fracture has been a main concern in posterior stabilized knee arthroplasty. Tibial post fractures have been documented in several studies with standard PE and HXPLE (13-16). Ansari *et al*. (15) reported on two cases of post fractures with inserts made of moderate cross-linked PE. Two failure mechanisms have been suggested: reduced mechanical properties of HXPLE increase the risk of tibial post fracture and oxidation of the HXPLE over time can increase the fracture risk.

Beside the problems of using *in vivo* studies to predict *in vitro* performance there are a number of concerns with the current clinical studies. All reports lack long term follow up beyond 10 years (2). In addition the sample size is rather small suggesting that they might be underpowered to detect certain failure modes like tibial post fracture. Furthermore most studies include a high percentage of normal weight women. Kim *et al*. (10) report on 288 women and only 20 men and did not include patients with a BMI above 40 kg/m^2.

Is there a good reason to consider HXPLE in primary total knee arthroplasty? There is little doubt that today's patients are younger and request a more active life style and it can be argued that conventional PE might not be the optimal bearing for these patients. However, the history of orthopedics has its fair share of disastrous failures of well-meant implant "improvements". Especially considering our recent experience with metal on metal bearings in total hip arthroplasty I recommend applying caution when using HXPLE in knee arthroplasty. HXPLE has not shown any clinical benefits, is more expensive and has not been adequately tested in obese and young active male patients (1,17). Its unrestricted use cannot be encouraged.

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Editorial

Hospital readmission rates following primary total hip arthroplasty: present and future in sight

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The number of total hip arthroplasties has been rising last decades, and it's going to be more for futures decades. Coxarthrosis is the most common diagnosis that led this procedure and it is well known that it is growing in prevalence with the progressive aging population. In 2020 it was estimated that 18.2% of US Americans will be diagnosed with arthritis (1). About 10% of patients, who were undergoing total hip arthroplasty, will require the same procedure in the contralateral hip the following year. This percentage rises to 20% in the next 5 years, making a total of 42% of the patients who were undergone bilateral total hip arthroplasty (2). In view of the data, we are faced with a common procedure with growing interest. The readmission rate published to date is around 3.65% (3).

Economic difficulties of nowadays, give more value to efficient interventions, and a frequent procedure such as total hip replacement should not be excluded from that aim. Since the first total hip replacement was performed, some things have progressed in the development of the technique, which have resulted in a small risk derived from intervention. Early mobilization to 24 h after surgery, the recent use of tranexamic acid for bleeding control (4), and standardization of the procedure (5) are involved in the successful global results. Furthermore, the fact that it has become a relatively common procedure in many hospitals, even in those considered secondary ones, has made surgeons experience could be high (6).

Thanks to set up National Registers of knee and hip replacements, we can better assess these procedures and their complications. But few are the studies in the field of orthopedics that we can considered as level one of evidence, and conclusions are hardly generalizable. In addition, certain limitations are inherent to the national registers database such as the hospitals included, the no evaluated conditions and they may suggest various confounding factors. Therefore, if we think of national records as diagnostic tests, we can say that the records have high sensitivity, but require more specific studies to reach valid conclusions.

The mean age of hip prothesis replacement, is between 68 and 79 years (7). An elderly age makes the number of comorbidities presumably be higher, and therefore we should not treat the patient only as a part, if not as a whole. In an interesting article recently published by Mednick *et al.*, regarding prognostic factors of hospital readmission in patients with total hip replacement, the greatest number of readmissions were secondary to comorbidities of these patients and not just for the complications of the own intervention (3). Mednick *et al.* uses the current procedural terminology (CPT) to include the patients in study. Despite not taking into account the previous diagnosis that led to the intervention, which affects the number of complications and hospital readmissions (8,9), confirms that a high percentage of readmissions after hip arthroplasty due problems, are not directly related to the surgery itself. Therefore it is on that topic where it seems we have to improve and focus the vision near future. For an orthopedic surgeon, the management of these comorbidities is, in many cases, a challenge that is difficult to handle, and where the evaluation of a multidisciplinary team seems necessary. The group of hospitalists professionals (geriatricians, internists or general practitioner doctors) seems increasingly in importance in recent years. Berend reported after 1992 no mortality after the inclusion of internal medicine team in the perioperative time of bilateral single time hip arthroplasty (10). One of the

main differences between the two moments was the decline in morbidity and mortality of its first patients compared to the second ones. This difference may be related with the multidisciplinary hospitalist team in the perioperative team. In a sample published of 339,319 total hip replacements, the orthopedic surgeon requested in 63% of cases medical consultation, being much higher in patients with more than two comorbidities, which as it is known are the more frequent situation in total hip arthroplasty (11). These results agree essentially with the statement made by Manning in his series of subsequent readmissions. Therefore, the idea of controlling perioperative morbidities, seem more important than we could think in a first time and it does not mean a greater number of days of hospitalization (11). In our institution since year 2011, perioperative medical care is assumed by internal medicine team in selected patient (elderly patient with more than two comorbidities), whose presence has been shown to improve the comorbidities control, adjust up to 62% of cases, the oral medication of previous diagnoses, and increase patient satisfaction. It may be tempting to think that treating patients is cheaper than prevent complications. In modern medicine is well known that to make a good prevention is more efficient than complication treatment.

The obesity epidemic continues increasing. It is estimated that the risk of requiring a total hip replacement is 8.5 times higher in patients with a BMI of 40 or more (12). One of the reasons we could give, following this fact, is that obesity has been associated as a risk factor for developing osteoarthritis (13). The reality is that the majority of patients with coxarthrosis are obese, and therefore, these are the kind of patients more common in these interventions. His influence on the outcome and complications of the surgery, has been the subject of several studies last decade. Although for years, some authors found no major problem in intervention of obese patient (14,15), the current tendency is to think that actually, it is. Haverkamp in 2011 published a meta-analysis showing a greater tendency to postoperative complications in obese patients (16), however, it was not clear that these complications, were following a greater number of hospital readmissions. The new concept reported by Mednick *et al.* associate obesity as an independent prognostic factor for hospital readmission, objectified by a high BMI (greater than 40), with twice risk of readmissions in obese patients than in those with normal weight (3). We should note that technically, the procedure of total hip arthroplasty in a patient with a BMI above 40, is more demanding for the surgeon, with more difficulties to avoid soft tissue damage, more surgical time and bleeding and increased risk of thromboembolism (17-19). Besides this, we must add the higher frequency of diabetes and cardiovascular disease in obese patients. Therefore, the attentions to obese patients are particularly important in our procedures and the multidisciplinary approach is essential, and should be taken into account from the preoperative.

Thinking that primary hip replacement is an elective surgery, whose successful results are compromised in patients with a BMI greater than 40, or those called "super obese" by Schwarzkopf *et al.* (20), and considering that as load joint, a lower weight can lead to symptomatic improvement, the obesity surgery should be a first choice in obese patients (BMI over 40), especially if a poly articular load joint pain is present. If we are in front of a young patient with these characteristic, with more reason we should start focusing on that side. It is difficult to determine the value of BMI in which we must think of a previous surgical or medical treatment of obesity. But the cited ideas should aid us to make the best option.

To determine the risk factors for hospital readmission is an important task, and should be a challenge for the future. Efforts to improve the technique and technology of implants help us improve a part of the process. We must to ensure comprehensive care of the patient in his globality, to improve hospital readmission rates.

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Editorial

SNPping away at the genetic basis of adolescent idiopathic scoliosis

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Abstract: Adolescent idiopathic scoliosis (AIS) is a genetically complex disorder of spine development, defined by a lateral curvature of the spine of 10° or greater which affects children during their pubertal growth spurt. Prior linkage and candidate gene approaches to elucidating the genetic basis of AIS have been of limited use for identification of candidate genes for this condition. Genome wide association studies (GWAS) have recently identified single nucleotide polymorphisms (SNPs) in *LBX1* and G protein-coupled receptor 126 (*GPR126*) that contribute to AIS occurrence. These discoveries support prior etiologic hypotheses regarding altered somatosensory function and skeletal growth in AIS. However, these loci account for a small percentage of the phenotypic variance associated with AIS, indicating the vast majority of the genetic causes of AIS remain to be delineated. A major translational application regarding understanding the genetic contributions to AIS relates to bracing efficacy.

Keywords: Adolescent idiopathic scoliosis (AIS); bracing; genome wide association study; single nucleotide polymorphism (SNP); skeletal growth; somatosensory function

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Adolescent idiopathic scoliosis (AIS) is defined as a lateral curvature of the spine of 10° or greater which affects children during their pubertal growth spurt for which no cause can be determined (www.srs.org). Although there is evidence that genetic and environmental factors are likely to play a role in its occurrence the mechanisms responsible for AIS remain uncertain at the present time. Rotational deformity is measured by an inclinometer in the forward bending position, and the scoliometer as an angle of trunk rotation (ATR). Confirmation of scoliosis is obtained by obtaining a lateral spine film and measuring the degree of curvature or Cobb angle.

The incidence of idiopathic scoliosis (IS), encompassing all age groups in the general population ranges from 2-3%, varying with the definition of the magnitude of the curve. Older IS subclassification is based on the age of presentation categorized as: (I) infantile (birth to age 3 years); (II) juvenile (age 3 to 11 years); and (III) adolescent (11 years and older). The incidence of AIS has ranged from 0.47% to 5.2% (1).

Population studies indicate that 11.1% of 1st degree relatives are affected with significant spinal curvature, in contrast to 2.4% of 2nd degree, and 1.1% of 3rd degree relatives (2). By the age of 16 years, 0.6% of affected people will have required intervention through active treatment with a full-time thoraco-lumbar-sacral orthosis (TLSO) or surgical correction with instrumentation (3,4).

These late consequences associated with IS are not surprising in light of the pathological consequences associated with the disorder. Significant health problems reported in association with IS, include chronic back and neck pain, disc herniations flatback syndrome, osteoporosis, kyphosis, cosmetic dissatisfaction, disability and psychologic distress (5). Patients with curves >70° (severe scoliosis) are 3 times more likely to die from cardiopulmonary disease than unaffected individuals (6).

Hypotheses put forth to explain pathogenesis of IS include abnormalities in the composition of the connective tissue matrix, alteration in body axis, calmodulin, melatonin, neuromuscular imbalance and altered vestibular function.

The mode of inheritance of IS has not been solidly established and is under debate (2,5,7-11). Inheritance patterns reported include autosomal dominant with variable penetrance, autosomal recessive, multifactorial and X-linked dominant modes. Previous studies reviewed in (12) demonstrated genetic heterogeneity for IS. Family based linkage studies have been used to identify genomic regions associated with IS (13,14). While these studies are of some use, they have a disadvantage because of their low power to detect genes associated with more complex disorders and identify relative large chromosome segments with a large number of candidate genes for a particular condition (15).

Association studies such as the finding of over transmission of the *CHD*7 associated polymorphism, rs4738824 in patients with IS have helped to elucidate genetic contributions to IS. Substitution of the A allele of this polymorphism with the G allele is predicted to disrupt a possible binding site for caudal-type (cdx) homeodomain-containing transcription factors. Mutations in *CHD*7, a chromeodomain helicase DNA binding protein are associated with CHARGE syndrome (coloboma of the eye, heart defects, atresia of the choanae, retardation of growth and/or development, genital and/or urinary abnormalities, and ear abnormalities and deafness) (16). A hypothesis for the development of IS is *CHD*7 may act postnatally to alter spinal growth during the adolescent growth spurt. *CHD*7 in zebrafish is expressed in somites, brain, eye and otic vesicle. *CHD*7 enables proper symmetric expression of critically important somitogenesis associated genes located downstream from Wnt including *her*7, *cdx1a*, *dlc*, *mespa* and *ripply*. Zebrafish morpholinos in which *CHD*7 was knocked down were noted to have tail kinks and a progressively shortened axis, thus providing supporting evidence for an important role for *CHD*7 in body axis formation (17).

Genome wide association studies (GWAS) have circumvented challenges associated with linkage and candidate gene approaches because they measure association between common variation across the entire human genome in the form of single nucleotide polymorphisms (SNPs) and identify genetic associations with observable traits (15). Two recent GWAS studies performed by the same group of investigators highlight their discovery potential (18,19). In the first study a GWAS was performed using the Illumina Human610 Genotyping BeadChip and the Illumina HumanHap550v3 Genotyping BeadChip for 1,050 Japanese females with AIS and 1,474 control subjects respectively. Three SNPs on chromosome 10q24.31, located within the same linkage disequilibrium block, which is defined by the association of inheritance between two closely linked alleles, reached genome-wide significance of $P<1.0\times10^{-7}$ with rs11190870 demonstrating the strongest association in both the initial GWAS and replication study ($P=1.27\times10^{-10}$). Through the use of imputation or statistical inference using MACH (Markov Chain framework for genotype imputation and haplotyping) the imputed SNPs and the three original SNPs on 10q24.3 were all localized to the 3' flanking region of *LBX1*.

In GWAS studies it is necessary to control for population stratification. This refers to the presence of genetic differences between cases and controls that represent discongruity in sampling from the respective populations and are not related to the underlying disease process. Nearly all subjects fell into the main cluster of the Japanese population. Additionally, using logistic regression, the principal components were not associated with disease status, arguing against population stratification.

LBX1 is a homeobox gene with homology to the drosophila ladybird late (*lbl*) gene (20). It is expressed in the dorsal part of the spinal cord, hindbrain, a subpopulation of cardiac neural crest cells and muscle precursor cells. *Lbx1* in mice is an important determinant of dorsal spinal neurons and hindbrain somatosensory neurons (21). Somatosensory information from the periphery to higher brain centers is mediated by the dorsal spinal cord. The observation of somatosensory dysfunction in some individuals with AIS, in addition to *lbl* expression data support a hypothesis for *LBX1* having some type of somatosensory role (22). The exact genetic mechanism of *LBX1* action is not precisely understood.

In a second GWAS study performed by the same research group (18) 10,641 X-chromosome SNPs were added to the initial study sample, with six SNPs suggestive of AIS association ($P<1\times10^{-5}$). One SNP, rs6570507 on chromosome 6q24.1 reached was associated with AIS ($P=3.02\times10^{-5}$). This finding was significant when Bonferroni-corrected (adjustment for error due to false negative test results; $P<1.67\times10^{-2}$) and when replicated in an independent set of Japanese patients consisting of 786 cases and 24,466 controls with a combined P value of 2.25×10^{-10} [OR 1.28; 95% confidence interval (CI), 1.18-1.38]. Further association of rs6570507 was observed in a replicate set derived from a Chinese Han population of 743 cases and 1,209 controls and a population of European ancestry which consisted of 447 cases and 737 controls resulting in a combined P value of 1.27×10^{-14}. Using genome wide imputation, suggestive association was observed in

12 loci ($P<1\times10^{-5}$) with rs11190870 located on chromosome 10q24.31 reaching genome wide significance ($P<5\times10^{-8}$). Nineteen additional SNPs yielded evidence for association and were strongly correlated ($r^2>0.9$) with rs6570507, all localized in intronic regions of G protein-coupled receptor 126 (*GPR126*). Two SNPs, (rs7774095 and rs9403380) were evaluated by using Encyclopedia of DNA Elements (ENCODE) (23) annotated elements and hypothesized to have a regulatory role of transcriptional activation of *GPR126*. Zebrafish knockdown morpholino experiments blocking translation and messenger RNA splicing, demonstrated *GPR126* morphants had a significantly less mean body length and delayed ossification of vertebrae.

The observed *GPR126* results validate a prior hypothesis which postulates that scoliosis can be mediated by abnormal skeletal growth (24). Several other experimental lines of evidence are consistent with this hypothesis. Limb posture abnormalities and growth failure are observed in *GPR126*-null mice in addition to a hypomyelinating neuropathy (25). Zebrafish *GPR126* morphants display a slower escape time (triggered by impulsive hydrodynamic or visual stimulus) which may be related to myelination defect. Prior GWAS studies have demonstrated association between common SNPs in *GPR126* and stature in children and adults (26).

The irony of these thorough and meticulous analyses is that *LBX1* and *GPR126* account for only a modest 1% of the total phenotypic variance associated with AIS. This indicates multiple layers of complexity associated with AIS that can be hypothetically attributed to multiple gene and other environmentally mediated factors. In a recent comprehensive review, this complexity is underscored by the citation of 50 genetic studies related to IS in which genes associated with connective tissue metabolism, bone growth and metabolism, melatonin signaling and pubertal growth were identified by various researchers (27).

The translational value of identifying genes contributing to the development of AIS relates to possible benefit in the utilization of genetics to help predict which scoliosis curves will fail bracing. While the results of the Bracing in Adolescent Idiopathic Scoliosis Trial (BrAIST) indicate that bracing significantly increases the likelihood of reaching skeletal maturity with a curve of less than 50 degrees as compared to observation alone, bracing treatment fails in approximately 15% of patients with AIS (28).

Attempts to use modeling derived from Cobb angle, Lenke classification of curve type, Risser score, menarchal status and 53 SNPs involved with calcium metabolism, neurodevelopment and signal transduction resulted in a negative predictive value nearing 100% for low risk scores less than 41. While 99% of high risk scores greater than 190 or greater resulted in severe curve progression it was not possible to predict outcome for scores in between 41 and 190 (29). These patients with intermediate risk scores would require close follow up for curve progression by an orthopedic surgeon.

The promoter polymorphism (rs11063714) in the neurotrophin 3 (*NTF3*) gene is associated with curve severity for IS in the Chinese Han population. Individuals affected with IS having an AA genotype had lower mean maximum Cobb angle as compared to patients with AG and GG genotypes (30). Patients who were skeletally immature with an AA genotype had greater success for treatment with bracing as compared to patients with GG genotype. In the corresponding mouse model, Egr $3^{-/-}$, affected mice fail to express *NTF3* and have proprioceptive dysfunction due to muscle spindle agenesis, apoptosis of proprioceptive neurons, proprioceptive neuron apoptosis and disruption of synaptic connectivity between muscle sensory and motor neurons. Moreover, a reduction in the number of muscle spindles and malfunction has been demonstrated in spinal muscle obtained from patients with IS, examined histologically and histochemically, suggesting that abnormalities in proprioception may contribute to IS pathogenesis (31).

In summary two recent GWAS studies highlight association between AIS and SNPs in *LBX1* and *GPR126*. The hypothetical effect that SNPs in these genes can have on spine development in utero and after birth is consistent with prior hypotheses related to altered somatosensory function and skeletal growth. There is much more work that needs to be done before genetic analyses can be used to predict clinical course in scoliosis. Further research to elucidate the complexity of genetic and possibly epigenetic contributions will likely require the collaboration of larger numbers of patient centers and functional analysis of genetic variants.

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Editorial

Current progress in genetic research of adolescent idiopathic scoliosis

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Abstract: Previous genetic linkage analysis and candidate gene association analysis have unveiled dozens of variants associated with the development of adolescent idiopathic scoliosis (AIS), which however can seldom be replicated in different ethnics. Recently, two genome-wide association studies of AIS performed in Japan revealed that *ladybird homeobox 1* (*LBX1*) gene and *G protein–coupled receptor 126* (*GPR126*) gene could play a role in the etiopathogenesis of the disease. Since the association between these two genes and AIS were successfully validated in the Caucasian and the Chinese population, *LBX1* gene and *GPR126* gene were the most reliable genetic variants underling the development of AIS.

Keywords: Adolescent idiopathic scoliosis; genome-wide association study; *ladybird homeobox 1* (*LBX1*); *G protein–coupled receptor 126* (*GPR126*)

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Adolescent idiopathic scoliosis (AIS) is a structural deformity of the spine estimated to affect millions of children with a prevalence of 2-4% (1-3). Commonly understood as a complex disease, AIS is believed to be resulted from the interaction among multiple genetic loci as well as certain environmental factors (4-6). It is possible that genetic factors may be involved in specific aspects of scoliosis including the shape of a scoliosis curve and the risk for curve progression. A number of population studies have documented that scoliosis runs within families and that there is a higher prevalence of scoliosis among relatives of patients with scoliosis than within the general population (7).

In the past decades, genetic linkage analysis and candidate gene association analysis were utilized broadly to reveal the genetic basis underling AIS (7-14). Since year 2000, several genes have been reported to be involved in the etiopathogenesis of AIS, including estrogen receptor estrogen receptor 1 (ESR1) (14), estrogen receptor 2 (ESR2) (9), matrilin 1 (MATN1) (10), melatonin receptor 1B (MTNR1B) (13), tryptophan hydroxylase 1 (TPH1) (11), DOT1L (15), TGFB1 (16) and so on. Seemingly great progress being made to clarify the aetiology of AIS, it should be noted that validation of these genes in different populations is always challenging. Replication of the associations in other studies with larger sample sizes or different populations is of great importance to validate the results of genetic association studies. Tang *et al.* (17) reported that ESR1 was not associated with the risk of AIS in HongKong. Similarly, Takahashi *et al.* (18) also found no association between polymorphisms of ESR1 and occurrence of AIS in Japan. As for *ESR2*, *TPH1*, *MATN1*, and *MTNR1B* gene, none of them can be successfully validated (19). Recently, we analysed the genotype of TGFB1 in a large cohort of AIS patients and healthy controls from Chinese population, whereas no significant association was found (under submission).

As a powerful tool for the investigation of complex disease, genome-wide association studies (GWAS) was recently applied to the genetic research of AIS (20,21). In 2011, Ikegawa and his fellows performed the first GWAS in Japanese AIS population, and reported that *ladybird homeobox 1* (*LBX1*) gene were significantly associated with the occurrence of AIS (21). Two years later, on the basis of previous GWAS data, the group of Ikegawa *et al.* reported another gene, *G protein–coupled receptor 126* (*GPR126*), could

be implicated in the development of AIS (22). Compared with previously reported genetic locus of AIS, variants of LBX1 and GPR126 seemed far more promising with regard to their contributions to the development of AIS. The sample size of the GWAS performed by Ikegawa was several times larger than earlier association studies. In the stage of chips experiment, they included a cohort of more than 2,000 patients and controls. And in the validation stage, over 10,000 normal controls were recruited (21). In addition to the large sample size, it is noteworthy that both genes were successfully replicated in other ethnics including southern and northern Chinese Han population and European ancestry (22-24). More importantly, high expression level of LBX1 was detectable and specific to skeletal muscle and spinal cord of both adult and fetal (21). And GPR126 was highly expressed in the cartilage of human and the proliferating chondrocytes of the vertebral body of the embryonic mouse (22). Moreover, the functional consequence of GPR126 was also confirmed by the studies of Ikegawa *et al.* (22). They found that GPR126 knockdown zebrafish had shorter body lengths and delayed ossification of the vertebrae, as well as slower escape responses, indicating possible neurological defects (22). Taken together, these findings greatly extended the genetic research of AIS, and expanded our understanding on the possible etiology.

It is widely hypothesized that AIS could be induced by abnormal skeletal growth, abnormal somatosensory function and abnormal development of neural system (4). The function of the two AIS-related genes reported by Ikegawa *et al.* appears well coincided with the classical hypothesis of the aetiology of AIS. In mouse, LBX1 is an important determinant of dorsal spinal neurons and hindbrain somatosensory neurons (25). A recent study reported that GPR126-null mice have limb posture abnormalities and growth failure (26). The most significantly associated SNP rs6570507 of *GPR126* gene was also associated with trunk length in a GWAS meta-analysis of height in European populations (27). GPR126 also functions in nervous system control, and this process may contribute to AIS susceptibility. Several studies have indicated that GPR126 is essential for myelination, a process necessary for proper nerve conduction velocity (28). To conclude, these observations extraordinarily suggest the possibility that *LBX1* and *GPR126* gene may be involved in the susceptibility of AIS through abnormal spinal development or neural system growth.

Prior to the GWAS performed by Ikegawa *et al.*, Sharma *et al.* performed GWAS of approximately 327,000 SNPs in 419 white AIS families. They found the rs1400180 of the *CHL1* gene was strongly associated with AIS. It was an interesting finding since CHL1 encodes an axon guidance protein related to Robo3, the mutations of which can lead horizontal gaze palsy with progressive scoliosis (20). As a well-established AIS susceptibility gene in Caucasian population, however, *CHL1* gene failed to be replicated in Chinese Han population (29). In another GWAS consisted of 196 cases and 401 controls from southern Chinese population, Fan *et al.* (from personal communication) reported two SNPs on one particular chromosome showed marginal significant association (snp1: $P=1.32\times10^{-6}$, odds ratio =0.52; snp2: $P=1.23\times10^{-5}$, odds ratio =0.55), both lack of further validation in an enlarged sample of cases and controls. Therefore, for the genetic research of AIS, the following points should be kept in mind to have a sound and reliable result. First, there exists a significant divergence between different populations regarding the association of susceptible genes with pathogenesis of AIS. Second, independent replication study with enlarged sample size is always warranted for the determination of the susceptible gene. Third, population stratification should be well controlled when recruiting the subjects.

Conclusions

As estimated by Ikegawa *et al.*, variants of LBX1 and GPR126 can explain approximately 1% of the trait variance in AIS (22). It is obvious that additional AIS risk factors wait to be discovered. A global meta-analysis of published GWAS data should be helpful for the elucidation of the veiled genetic locus related to AIS. Further functional studies are also necessary to elucidate how the variants in LBX1 and GPR126 alter the risk of AIS in humans.

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Footnote

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Editorial

Genetics of adolescent idiopathic scoliosis in the post-genome-wide association study era

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Recently, analyses of a genome-wide association study (GWAS) conducted in a Japanese population found several common susceptibility variants associated with adolescent idiopathic scoliosis (AIS) (1-3). The top variants identified from this GWAS reside in genomic regions with potentially etiologically relevant genes and have been replicated across multiple populations and ethnicities. As a result, genes involved in biological pathways that are now viewed as promising targets for downstream functional investigation include abnormal somatosensory function (*LBX1*) (1), delayed ossification of the developing spine (*GPR126*) (2), skeletal dysplasia (*SOX9*) (3) and scoliosis associated with syndromic disease (*KCNJ2*) (3), One of these variants, a single nucleotide polymorphism (SNP) in the 3'-flanking region of the *LBX1* gene (rs11190878) (1), has been consistently replicated in several independent populations (4). Other GWASes have also identified novel AIS-associated variants, with some overlap among the top ranked SNPs, including rs11190878 (Albertsen *et al.*, 2014, ASHG conference abstract) (5).

Despite the successes of the AIS GWASes, no causal variants have been definitively linked to any of the top gene candidates. The GWAS design, with its focus on common SNPs, is limited in its ability to uncover genetic variants contributing to a disease phenotype, leading to the "missing heritability" problem. Furthermore, the clinical utility of GWAS-identified markers is presently limited. The 53 significantly associated SNPs from a GWAS used in a DNA-based test for the prediction of the risk of curve progression in Caucasians (ScoliScore, Transgenomic, Inc., New Haven, CT) were not replicated in other studies (5,6). The clinical validity of the ScoliScore is also currently unclear (7,8).

Given the apparent genetic heterogeneity of AIS, other approaches to identifying susceptibility variants need to be applied. Copy-number variants (CNVs) comprise another type of genetic variation that may contribute to the missing heritability of etiologically complex diseases such as AIS. Accounting for approximately 13% of the human genome, functionally relevant CNVs can alter gene function or regulation and may consequently induce phenotypic changes (9). An exploratory whole-genome study found several CNVs enriched in AIS patients (10). Fortunately, CNVs can be readily detected using existing GWAS SNP microarray data (11).

The lack of functional variant identification may also be due to the presence of rare family-specific mutations with large effects (12). Such family-specific variants may be necessary, but not sufficient, for disease development within individuals in a family; that is, individuals within the family develop AIS when at least one family-specific variant is present in the context of more common variants associated with AIS. This genetic effect has been shown in other diseases, such as asthma (12). With the increasing affordability of next-generation sequencing, whole-exome or whole-genome sequencing strategies should be used to pinpoint these rare variants that segregate within families.

These strategies are but two of many approaches that can be utilized in the search for susceptibility variants and, importantly, precise causal variants to better understand the genetic basis of AIS. The ultimate goal is to translate these genetic findings into clinical practice.

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Footnote

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Editorial

What is the best way to determine the cause of adolescent idiopathic scoliosis?

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Adolescent idiopathic scoliosis (AIS) is defined as a lateral deviation of the spine associated with rotation that is found in healthy individuals and has no known cause. These subjects do not exhibit neuromuscular conditions or other disorders until the onset of sexual maturation at approximately 10 years of age (1). Diagnosis is challenging; radiography reveals curves of more than 10 degrees by Cobb method (2) without vertebral abnormalities. Additionally, the angular deviation required for diagnosis is controversial, which further complicates diagnosis. In 1995, Winter questioned the accepted diagnostic value used to characterize the disease and proposed that a curve of 5 degrees should be considered pathological or a variation from a normal spine (3). Furthermore, it is important to observe how rotation impacts the condition, as this feature may be more characteristic of the disease than the curvature itself.

Since 1875, studies have been performed on twins to ascertain the influences of genetic and environmental factors on the manifestation of certain diseases (4). Fisher and George studied pairs of monozygotic and dizygotic twins with idiopathic scoliosis and compared their deformities. These studies revealed that environmental factors were able to modify the features and severity of the disease, especially among dizygotic twins (5). In a systematic review, Kesling and Reinker reported an agreement rate of 73% in 37 pairs of monozygotic twins and 36% in 31 pairs of dizygotic twins, thus revealing a stronger similarity between monozygotic twins (6).

Del Curto *et al*. presented a pair of monozygotic twins with AIS and curves that differed in type, direction and severity, suggesting that these differences could be attributed to environmental influences or epigenetic factors (7). Epigenetic factors regulate gene expression by mechanisms that are not directly related to the primary sequence of DNA. Three examples of mechanisms of epigenetic factors include: DNA methylation, histone modification and the action of non-coding RNAs (7).

Since 2000, linkage studies in families with multiple affected members have revealed several regions of chromosomes that may be related to the etiology of AIS. Linkage studies have been successfully used to determine the regions of DNA responsible for other diseases that are caused by one or a few genes. Linkage studies also allow facile differentiation between affected and unaffected individuals, preferably within the same family, by identifying certain molecular markers in specific regions within the human genome.

Using this technique, Wise *et al*. in 2000, described the first regions of DNA related to AIS on chromosomes 6p, 10q and 18q by studying an extended family with seven members affected by this disease (8).

In subsequent years, other family studies have suggested that AIS is related to chromosomes 6, 9, 16 and 17 (9) and to the chromosomal regions 17p11 (10), 19p13.3 (11), 8q12 (12), 9q31-q34.2, 17q25.3-qtel (1), and 12p (13) 18q12.1-12.2 (14). In 2010, Wajchenberg *et al*. found no association while studying a family with nine affected members from central Brazil and cast doubt on the use of linkage analysis to study AIS. This report criticized the Cobb method, which is used to measure the curvature of the spine. First described in 1948, the Cobb method is dependent on the examiner, and small variations may interfere with the classification of an individual as affected or normal. Thus, patients with a difference of only two degrees (nine or 11 degrees of curvature) are classified in different ways (15).

In 2011, Takahashi *et al*. performed an important multi-center study (16). In this study, 1,050 Japanese women with

AIS and 1,474 control women without AIS were evaluated using of curves greater than or equal to 15 degrees as the criterion for affected patients, which was the same as in Wise *et al.* (8) and Wajchenberg *et al.* (15). Using a genome-wide association study (GWAS), this report successfully correlated the chromosome region 10q24.31 with the disease by locating the single nucleotide polymorphism (SNP) 11190870 (odds ratio =1:56). This region is within the region 10q described by Wise *et al.* in 2000 and contains the *LBX1* gene. This gene is expressed in the dorsal region of the spinal cord and skeletal muscle, and also operates in somatosensory neurons. LBX1 may be related to the etiology of the disease due to somatosensitive dysfunction. In addition to LBX1, this DNA region contains regulators of gene expression, which could influence the manifestation of the disease depending on the polymorphism (TT, TC and CC) that is present. The authors analyzed the expression of LBX1 and detected high levels of expression in the skeletal muscle and spinal cords of adult and fetal humans.

However, as observed in a recent systematic review and meta-analysis by Chen *et al.* (17), the control group presented in the study by Takahashi *et al.*, though numerous, was not subjected to the appropriate evaluation for diagnosis of idiopathic scoliosis. The authors presumed that within this group, the rate of affected patients matched that of the Japanese population.

Other authors in Asian eastern populations have also reproduced the data reported by Takahashi *et al.*, but GWAS of 491 families conducted in the US detected the unrelated SNP rs11190870 among the 100 SNPs most linked to the disease (18).

In 2013, Kou *et al.* extended the Takahashi *et al.* study. Not only did this extension confirm the relationship of 10q24.31 region with AIS, but it also identified a new correlated DNA region, region 6q24.1, and related a Han Chinese population to another population of European ancestry (19). The authors also reported a relationship between the disease and the *GPR 126* gene (rs6570507 SNP—odds ratio =1.27) within the same region studied. According to the authors, neither the expression of this gene in the skeletal tissue of humans nor its relationship to scoliosis has been explored. Thus, they attempted to study its expression in various tissues, such as bone, cartilage and intervertebral disks, and they found high expression in cartilage.

AIS is a disease that is influenced by genetic factors and the environment and has a complex inheritance pattern. However, despite many studies and technological advances, it is still not possible to fully describe the genes responsible for the disease. The family studies may assist in our understanding of the disease, but great difficulty lies in labelling the affected individuals due to the high degree of phenotypic variability. This variability is largely due to doubt in the deformity measurements by the Cobb method. Still, Wise *et al.* [2000] claimed that their analyses were made in affected members of the family because the individuals who were considered normal could be carriers of the genetic alterations. However, the frequently low penetrance associated with AIS confounds their analysis.

In general, the low success rate of GWAS in identifying the genetic variants with significant effects and in accounting for the relevant contributors to the heritability of the trait of interest suggests that some common diseases may be caused by rare variants (as well as monogenic disorders of Mendelian inheritance) that cannot be identified by this approach. According to this model, the rare variants, so named because of their low population frequency, would be numerous in each affected individual and would be jointly responsible for the manifestation of the phenotype. In this way, the effect of each of the variants associated to the studied trait would be expected to be modest, and each individual contribution would not be large enough to be identified by binding studies. Additionally, according to this hypothesis, common variants cannot be ruled out as possible regulators of expression of genes pertinent to the disease, which may contribute, for example, to the clinical heterogeneity observed in AIS (20,21).

We believe that the polymorphisms identified in the studies of patients known to be affected, as performed by Aulisa *et al.* (22) (*IL-6* and *MMP-3* gene), Qiu *et al.* (23) (*DPP9* gene) Chen *et al.* (24) (*Matrilin-1* gene), Wajchenberg *et al.* (25) (*ACE* gene), Jiang *et al.* (26) (*LBX1* gene) aid in detecting regions that may influence AIS. Mostly likely, AIS is caused by genes that are responsible for the synthesis of proteins that are important for the composition of human spinal tissues. When evaluating only those patients who are affected with severe deformities (with surgical indication or, at least, bracing) the risk of underestimating the numbers of affected individuals with small curvatures related to the variable expression of the disease can be avoided. Based on these studies, the evaluation of tissue-specific gene expression using biopsies during surgical procedures may further our understanding of the disease.

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Footnote

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Editorial

Long term outcomes of Charnley THA in patients under the age of 50: an editorial comment on recently published article by Warth *et al*.

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Fifty three years have passed from 1962 when Sir John Charnley developed the procedure of total hip arthroplasty (THA) in UK (1). Since then the principles of total joint replacement remain very similar to those advocated by Charnley. Moreover, the Charnley low friction arthroplasty represents the most classical cemented arthroplasty that has been used and currently used in several orthopaedic centers with minor changes regarding the initial procedure and implant design and the only implant where long term outcomes exceeding 30 years have been reported. The published literature is dominated by a large amount of studies reporting on outcomes of Charnley THA (2-5). The vast majority of these studies report on outcomes not exceeding follow-up periods longer than 30 years and usually involve a wide range of ages among the included patients. Although THA was initially developed to treat end-stage arthritic conditions in older patients, the need for the procedure in younger, more active patients is increasing. However, despite the improvements in the design of the implants and the surgical techniques THA in younger patients has not showed comparable outcomes to those performed in older patients, rising from the increased biomechanical demand of patients under 50 due to the higher activity levels (2,6).

Warth *et al*. (7) recently published on long term outcomes regarding the most classical THA in patients under the age of 50. From the initial population of 69 patients (93 hips), 32 patients (41 hips) had available 35 years of follow up. The overall revision rate for any reason was 54% at 35 years (22 hips). The commonest reason for revision was aseptic loosening. Among these patients, 14 hips were revised due to aseptic loosening, 5 due to infection, 2 due to femoral fracture and 1 due to recurrent dislocation. The present study compared the outcomes of the 35-year follow-up periods with those reported at the 25 years of follow-up. The acetabular loosening had progressed over the additional period of 10 years (8 additional revisions). In contrast the durability of femoral cement fixation seems better, despite the early cement technique that was used, as only 18% of the femoral stems failed. The functional scores (Haris Hip Score, SF-36) and the 6-minute walking performance at the 35-year follow-up interval significantly decreased compared to the 25-year follow-up. The authors comment that this decrease in functional scores and walking distance was associated with the presence of co-morbid diseases. As far as the radiographic evidence of loosening is concerned (combined prevalence of definite or possible loosening and aseptic loosening) the values for acetabular loosening and femoral stem loosening were 49% (20 hips) and 24% (10 hips) respectively among patients with available 35 years of follow-up.

This cohort study, illustrates the importance of an exceptionally long term follow-up (35 years), in combination to the effectiveness and durability of Charnley THA in a young patient population. The most often criticism on cohort studies concerns matters such as, the length of follow-up required to determine outcomes and the absence of data on potential confounding factors if the data was not previously recorded. The magnitude of the 35 years follow-up and the comparison of the present data, to the data of the 25 years follow-up, diminishes the aforesaid disadvantages of the cohort study and documents long term durability and safety, as well as its functionality in the still living patients. The study grants its primary purpose, which

was the evaluation of the patients with Charnley THA, after 35 years. The survival of the implant is well documented by combining the rate of the revision of the primary THA and the radiographic evidence of loosening with regard to the radiolucency between the prosthesis and the cement in zone 1 of Gruen *et al.* (8), regardless of the width and the quantification of debonding, according to the Berry *et al.* system (2). The functional outcomes as they extracted from the Index (WOMAC) test, the Harris Hip Scores, the 6-minute walk test and the monitoring of the Step Watch Activity represent reliable tools for evaluating the durability of the implant and the quality of life of patients living at the time of the 35-year follow up.

To our knowledge, this is the largest study published up to date reporting on outcomes of THA after 35 years of follow-up. Callaghan *et al.* reported on long term outcomes as well of the Charnley THA, but only 15 patients had available 35 years of follow-up. Limited evidence exists in the published literature reporting on less than 35 years outcomes of the Charnley THA. Wroblewski *et al.* (9) has published the largest study up to date reporting on outcomes of the Charnley THA with a minimum follow-up of 30 years. The overall survival among the 110 hips included in the study was 88%. Goto *et al.* reported a survival of 54% and 75% of the acetabular cup and the femoral stem respectively at 30 years. Mullins *et al.* (10) reported a 30-year survivorship of the prosthesis of 73%. Particularly, in young patients under the age of 50 the Charnley THA was associated with high rate of acetabular loosening. Keener *et al.* (6) in a study of 69 hips reported a 34% rate of cup failure after a minimum of 25 years follow-up. These results resemble those of Berry *et al.*, who noted that the survivorship of the implant ranged from 68.7% for patients who were less than 40 years of age, to 100% for patients who were 80 years of age or older (2).

Despite the fact that several studies have reported on long term outcomes of the Charnley THA, the vast majority of the reported outcomes are not predictable and reproducible due to several reasons. Firstly, most studies do not include young patients at the time of index arthroplasty, so the follow-up does not exceed 25 years. Moreover, most of the studied groups are characterized by intragroup variability and the functional outcomes do not take into account individual agents (MBI, comorbidity and functional demands) (11) and they concern retrospective cohort studies, which are designed to use data, not available for long term analysis (12). Finally, the published evidence does not use a regular follow-up, which is essential after hip replacement surgery (3).

In conclusion, the durability and the function of the implant, after so many years, are well documented in this study as a large group of young population with Charnley THA was available for reevaluation. The study demonstrated satisfactory long term function and durability of the implant. The main value of the present well designed study is that the results should be considered a valuable index for the comparison with the outcomes of modern designs used in this particular group of patients. Since, the study of Warth *et al.* reports on the initially designed Charnley implant and the use of first generation cement, the remaining question regards the impact of stem surface texture on cement fixation, the nature or quality of the head, the quality and the hardness of the acetabular socket and the choice of newest cement techniques impaction. Will all the above improve the Charnley THA durability and function in young patients long-term? It is clear that a further long term research that will include the cited above parameters, as well as the influence of individual pathological characteristics or comorbidities could provide further evidence in the evaluation of THA.

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Editorial

Local infiltration anesthesia: does it really work?

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Postoperative pain control after major surgeries such as total hip arthroplasty (THA) is so important because leads to an increased mobilization, decreased opioids consumption and hospital stay, all of which are the major concerns after THA surgery. Perioperative local infiltration anesthesia (LIA) is one of the recent techniques for achieving these purposes (1-3). LIA to the operation site is a simple way and have demonstrated great impacts on abdominal, thoracic, and plastic surgical setting. Actually, it is a widely used analgesic technique in recent years. In this technique, a solution including long-acting local anesthetic combined with opioids, non-steroidal anti-inflammatory drug (NSAID) or steroids are used (3,4). It can be done anytime related to surgery and preemptive usage of this modality is encouraged as well. In one study conducted by Ong *et al.* (5), it was indicated that preemptive LIA improved analgesic consumption and time to first pain relieving request, but it did not result in any decrease in postoperative pain scores. However, it has been shown that patients who received infiltration with local anesthetics experience lower pain scores as well as lower analgesic requirement. The effects of LIA could differ according to the type of surgical procedures, type and dosage of the used local anesthetic, adding adjuvants to local anesthetic, injection only into incision site or the whole wound, flap or joint and the use of intraarticular catheters for postoperative infusion. Shin *et al.* showed that preoperative bilateral superficial cervical plexus block and ropivacaine wound infiltration were more effective for reducing pain scores than ropivacaine wound infiltration alone in patients undergoing robotic thyroidectomy, which shows the efficacy of performing multiple injections for pain control (6).

In 2008, LIA technique is first described by Kerr and Kohan to improve mobilization after THA and reduce pain and opioids consumption (7). The results of this study revealed that adding ketorolac to the ropivacaine and epinephrine via LIA technique decreased the postoperative pain score and opioids consumption; the addition of epinephrine helps to reduce the toxicity of the local anesthetic by keeping it localized to the area of injection. Hofstad *et al.* in their study have used perioperative LIA with ropivacaine in 116 patients under THA, and found no superiority for LIA regarding analgesic effect after THA compared with multimodal analgesic regimen. They did not report any pain reduction and opioid consumption (1). Interestingly similar controlled study by Dobie MPhil in 2012 on 96 patients showed parallel results. The case group in their study received levobupivacaine with adrenaline. They measured the level of pain and morphine consumption 24 after operation and reported that local anesthesia during THA did not decrease the level of pain, morphine consumption, hospitalization and did not impact on mobilization (8). In harmony with these findings another double-blind controlled trial by Lunn *et al.* in 2011 on 120 patients indicated that infiltration of high volume of ropivacaine did not reduce pain and consumption of oxycodone after THA. Hence, the authors concluded that intraoperative local infiltration analgesia is not effective and they did not recommend it in THA (9). However in contrast to these results three systemic reviews in 2012 by McCarthy *et al.*, in 2014 by Marques *et al.*, and in 2014 by Gupta *et al.* have indicated that the LIA significantly decreased the pain score, analgesic consumption and hospital stay in THA (10-12). On the other hand, several studies have evaluated the efficacy of intraarticular infiltration, both intraoperatively and postoperatively. Badner *et al.* found

that intraarticular injections of bupivacaine and adrenaline at wound closure reduced the postoperative need for opiates in total knee arthroplasty surgery (13). In a study done by Busch *et al*. in 2010 (14), they found that periarticular intraoperative injection with multimodal drugs can reduce postoperative patient-controlled analgesia requirements and pain on activity in patients undergoing THA with no apparent increase in risk. The rate of infection and delayed wound healing in patients with total hip replacement (THR) should be noted. Although if proper aseptic techniques are maintained for insertion and bolus administration the risk of infection can be minimized (11,12,14,15).

It is difficult to interpret these conflicting results in light of the potential relationship between LIA and its impact on pain, opioids consumption and hospital stay. Local anesthetic infiltration can decrease pain levels after THR, with less opioid consumption and a low incidence of vomiting and nausea. This could explain the early mobilization and earlier discharge of patients who received local anesthetic infiltration, irrespective of alternative pain management strategies (3). However, the reason for such a discrepancy might be related to the difference in patient's selection, study design and possibly using different kind of local anesthetics (long- or short-acting local anesthetics) in these studies. For example, ropivacaine has long block duration, a greater margin of safety, and reduced toxic potential compared to bupivacaine. Hofstad *et al*. confirmed the result of previous controlled trial by Lunn *et al.*, but relatively small sample size (in both studies) limit the ability to generalize the results of this study and certainty of its conclusions (9). We recommend to the authors conduct a study with similar methodology and larger sample size to validate findings reported here.

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Footnote

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Editorial

Editorial on "Comprehensive geriatric care for patients with hip fractures: a prospective, randomized, controlled trial" published in *The Lancet* on April 25th, 2015

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Abstract: A third of elderly adults fall every year, many leading to hip fractures with a 24% mortality rate just within the first year. As a growing number of the US population approaches old age, these hip fractures are expected to cost the US over 25 billion annually. In the near future, physicians will need to not only improve the treatment for a larger patient population but also reduce the medical costs associated. The authors in this paper sought to determine whether specialized geriatric care positively impacted patient outcome compared to standard orthopaedic care for hip fractures. The study found that geriatric care significantly increased patient mobility within 4 months after hip fracture and will likely reduce overall medical costs. Similar studies have shown promising results as well. Moving forward, geriatric fracture programs need more prospective randomized trials to determine the effectiveness of these programs to increase patient quality while also reducing overall medical costs. This study in correlation with others further demonstrates the importance and need of specialized geriatric programs in the US.

Keywords: Hip fracture; geriatric fracture program; comorbidity; hospital costs

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One in three adults over the age of 65 falls every year, which is the leading cause of hospital trauma admissions (1). Hip fractures alone have a 24% mortality rate within the first year, many never regaining independence due to immobility (2). These fractures are projected to grow to over 3 million by 2025, a 50% increase expected to cost the United States over 25 billion annually (3). With the US government currently 18 trillion dollars in debt and a growing number of Baby Boomers approaching old age, many medical teams are seeking tailored treatment programs to increase patient quality of care and in turn lower costs due to postoperative complications. A proposed comprehensive geriatric program focuses on treating hip fractures along with comorbidities associated with geriatric patients and is intended to increase patient mobility and reduce overall medical costs associated with complications after surgery.

In this Norwegian study, the medical team focused on geriatric care *vs.* standard orthopaedic care for patients with hip fractures. Standard treatment consisted of fracture fixation by an orthopaedic surgical team and then transfer to the orthopaedic ward for post-operative care. Geriatric care treatment also consisted of fracture fixation by an orthopaedic surgical team; however, the patient was transferred to the geriatric ward for post-operative care, which focused on early mobilization and an overall medical assessment to include comorbidity treatment. The main measurement of patient outcome was mobility. After 4 months, they found those who received comprehensive geriatric care had significantly more mobility (P=0.010) than those who received standard care. They also found that comprehensive geriatric care is 99% more likely to be cost-effective than standard care (4). This study effectively shows that a geriatric program not only improves geriatric patient outcome but also significantly reduces costs associated with hip fractures.

In 2009, a similar study was conducted on the impact of a

geriatric fracture center in the United States. Complication rates for patients in the geriatric fracture center (31%) were much lower than patients under standard care (46%) (5), arguably leading to a shorter length of stay and lower costs. In 2012, a study showed that readmission due to complications also dropped 11% for those undergoing geriatric care (6). Concerning costs, one study showed that the geriatric fracture program saved more than $18,000 per fracture in hospital costs (7). However, there are limitations to a geriatric fracture program. In the Norwegian study, patients and staff were made aware of their treatment for ethical reasons. Also, the study was conducted at one site making reproducibility questionable as patient outcomes may vary due to cultural and socioeconomic status. Not all hospitals have access or the resources to implement such a program (7). There is also no standardized geriatric fracture program in the United States to follow, and there is a lack of physician leadership and case managers for programs at individual hospitals (8).

A geriatric fracture program requires a team of medical experts from various departments and physician leaders. Prospective randomized trials will be needed to further demonstrate the success and practicality of such programs. However, this study in conjunction with others shows that these programs increase the quality of patient care while also decreasing hospital costs. In a time when healthcare is moving towards bundled payments, efficiency and quality of patient care is impertinent to maintaining lower hospital costs as well as caring for the aging population in the United States.

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Editorial

Geriatric orthopedic co-management of older adults with hip fracture: an emerging standard

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Abstract: Hip fracture, a common complication of fall injuries in older adults, often results in high rate of mortality, increased debility, functional loss, and worse quality of life. The value of geriatric teams and model of care for the hip fracture patients have been examined in a number of studies, and even though most studies have demonstrated potential impact in improving outcomes for the hip fracture patients, they are often observational or quasi-experimental designs that are prone to bias. In this editorial, we review *the Lancet* article by Prestmo and colleagues, a randomized controlled trial that demonstrated improved outcomes for hip fracture patients managed in a geriatric unit.

Keywords: Geriatric; hip fracture; ortho-geriatric model of care

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Hip fracture is a potentially devastating illness for older adults which often results in high rate of mortality (1,2), substantial debility, functional loss (2-4), and poorer quality of life (5). Many studies have examined care factors associated with better outcomes for hip fracture, including anesthesia and orthopedic care for the surgical patient such as choice of anesthesia, timing of operation, but also peri-operative care elements that are perhaps best managed by medicine or geriatric specialties and interdisciplinary team such as pain control, early mobility, and delirium prevention. The value of geriatric teams and model of care for the hip fracture patients have been examined in a number of studies, and even though most studies have demonstrated potential impact in improving outcomes for the hip fracture patients, they are often observational or quasi-experimental designs that are prone to bias. The recent *Lancet* article by Prestmo and colleagues (6) provided a valuable addition to the evidence by studying the effect of hip fracture care in a geriatric unit in a randomized controlled trial.

In this single-centered randomized controlled trial of home-dwelling older adults with hip fracture (6), the authors demonstrated that those who were treated in a geriatric unit with comprehensive geriatric care had better physical performance at 4 months after hip fracture, better functional status and quality of life at 4 and 12 months when compared to those who were managed by orthopedic service for routine orthopedic care during the acute hospitalization period. The authors also found that those managed with geriatric care also had better cognitive status at 12 months after hip fracture and less fear of falling throughout the study period. The authors noted that although the mean length of hospital stay for the intervention group was longer, a difference of 1.7 days, a greater proportion of the older adults in the intervention group was discharged directly home (intervention 25%, control 11%), which perhaps suggests that the complexity of care coordination and discharge planning were possibly some of the reasons for the differences in hospital length of stay and discharge location. Overall, the study provides further evidence supporting the adoption of comprehensive geriatric care for the hip fracture patients which may lead to improved patient outcomes up to 12 months after hip fracture.

One important question that remains is what the

elements are in this model that made it effective in improving patient outcomes. Prestmo and colleagues (6) described the intervention as comprehensive geriatric care which uses various assessment tools, incorporates an interdisciplinary team with the focus on management of common geriatric syndromes, fall and delirium prevention, early mobilization, and early discharge planning. Previous studies on ortho-geriatric models of care for hip fracture suggest that there is substantial variability in how geriatric care is integrated in the management in hip fracture patients. Although a number of studies demonstrated the potential benefits of ortho-geriatric model of care in improving length of stay and readmission rate (7,8), reducing complication rate (8,9), mortality (8,9), and cost of care (10,11), a systematic review of these studies (12) commented on the substantial heterogeneity in both the implementation and components of the models of care and in their effects. In fact, a prior randomized controlled trial by Naglie and colleagues (13) that examined the effect of comprehensive geriatric care on hip fracture patients and employed similar components as described in the study by Prestmo *et al*. (6) failed to showed any significant differences in outcomes between those managed under geriatric care and those in usual care. The disparate findings may be the result of differences in the care components that are actually delivered in these models.

There are many elements of care that are important for management of hip fracture patients, and the challenges are often compounded by the multiple comorbid illnesses of the typical elderly hip fracture patient and the need to involve multiple disciplines in their care. Care elements that may have impact on patient outcomes are multiple, including pre-operative optimization and correction of serious medical abnormalities, early surgical intervention if possible, selection of anesthesia during operation and other standards for peri-operative care such as antibiotics, and prevention of venous thromboembolism using anticoagulants. Other elements that may have a significant impact on outcome include pain control, early mobilization, and tolerance of physical therapy. Another aspect of care that is important is delirium prevention which often involves a multi-component intervention that reduces the modifiable risks of delirium by eliminating catheters early, avoiding medications that may increase the risk of delirium, among other components (14,15). Other important disciplines include physicians who manage and optimize chronic medical problems during the peri-operative period, physical therapy and occupational therapy which have critical roles in assessing patients' functional status and providing therapy for rehabilitation, social workers or care managers who help to identify the psychosocial needs of the patients as well as the availability of the community resources. It is likely that Prestmo *et al*. (6) included most or all of these care elements in their intervention on the geriatric unit; however, careful tracking of certain processes of care, such as timing to first physical therapy, pain control, and incidence and duration of delirium, may help to elucidate how comprehensive geriatric care yields its benefits for hip fracture patients. A description of a standardized protocol to each area of intervention would be very helpful for future dissemination and implementation of this particular type of ortho-geriatric model of care.

Overall, the study by Prestmo and colleagues (6) contributes to the current evidence that supports the use of comprehensive geriatric care in a geriatric unit for hip fracture patients. It is clear that multiple care components are needed to achieve the outcomes seen in this study, and the study likely employed many of them in the geriatric unit. Future studies may benefit from detailed protocols that outline the different aspects of geriatric care and from the inclusion of process outcomes. Nonetheless, this study lays the groundwork for further multicenter studies that may tackle the issues of heterogeneity and generalizability, and ultimately lead to widespread transformation of care for hip fracture patients.

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Footnote

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Editorial

The Mkx homeoprotein promotes tenogenesis in stem cells and improves tendon repair

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Tendons are essential structures that transmit mechanical forces generated by skeletal muscles to bones to cause body motion. Acute tendon injury and tendinopathy are common pathologies of the musculoskeletal system. However, a poor understanding of tendon biology has impaired the design of efficient treatments for tendon repair following injury and tendinopathy (1). A recent paper by Liu *et al.*, published in *Stem Cells* in 2014 (2) highlighted an essential role for the Mohawk (Mkx) homeodomain protein in promoting tenogenesis in mouse stem cells and improving tendon repair in a mouse model for tendon injury.

Tendons are mainly constituted of extracellular matrix proteins and scattered tenocytes. Type I collagen is the main component of tendon matrix. It is constituted of α1 and α2 polypeptides encoded by the *Col1a1* and *Col1a2* genes. These peptides assemble in a parallel fashion to form collagen fibrils, fibrils associate to form fibers, that will in turn form fascicles, that finally assemble to form the tendon proper that is surrounded by external sheets (epitenon and paratenon) forming the peritenon. Together with type I collagen, other collagens and extracellular matrix proteins are part of the tendon-specific matrix (1). However, type I collagen is not a specific marker for tendons, as it is expressed in many types of fibroblasts. The lack of specific tendon markers has delayed tendon research for years. The first marker specific for tenocytes, the bHLH transcription factor Scleraxis (Scx), was described in mouse and chick models in 2001 (3). Scx is expressed in tendon (progenitors and differentiated) cells during development and in adult life (3-5). Scx has provided a unique tool to decipher the gene regulatory network controlling tenogenesis during normal and pathological conditions.

In addition to being an excellent tendon marker, Scx has been shown to be involved in tendon formation, to promote tenogenesis in stem cells and to improve tendon repair. *Scx* mutant mice display severe tendon defects (6). *Scx*-deficient tendons display a diminution of *Col1a1* expression and a disorganization of type I collagen fibrils (6). In addition, *Cola14a1* and *Tnmd* gene expression is lost in tendons from E16 in *Scx* mutant mice (6). Tnmd (Tenomodulin) is a type II transmembrane glycoprotein considered as a late tendon differentiation marker downstream of Scx (6,7). Ectopic application of Scx has been shown to activate tenogenesis in human stem cells, based on *Tnmd* expression (8-10), and grafts of Scx-producing stem cells have been shown to improve tendon repair in animal models for tendon injury (10).

In addition to Scx, two other transcription factors have been identified as being involved in tendon formation: the Mkx homeobox protein and the Egr1 zinc finger transcription factor. Although Mkx and Egr1 expression sites are not tendon-specific, Mkx and Egr1 mutant mice display tendon defects, mainly due to alteration of type I collagen production and organization (11-14). Egr1 has been shown to promote tenogenesis in stem cells and improve tendon repair in animal models of tendon injury (12,15). *In vitro* studies showed that when adding BMP12 to growth medium to promote tenocyte differentiation, mesenchymal stem cells (MSCs) isolated from equine umbilical cord blood (16) and bone marrow-derived mesenchymal stem cells (BMMSCs) (9) expressed *Mkx* together with other tendon genes (*Scx*, *Col1a1*, *Dcn*). However, until the publication of the study by Liu *et al.* (2), no data were available concerning a potential role of Mkx in tenogenesis induction in stem cells or during tendon repair

after injury.

Extracellular signals are also essential for tenogenesis. TGFβ is the main signaling pathway involved in tenogenesis during development and repair (1). TGFβ ligands have been shown to activate *Scx* expression in mouse stem cells (17,18). TGFβ ligands are released after tendon injury and the block of TGFβ signaling in the *Smad3* mutant mice impaired tendon healing (19). TGFβ ligands have been largely studied as putative candidates to improve tendon repair (1). Moreover, TGFβ signaling is also sufficient and required for *Scx* expression in tendons during mouse development (17,18). However, there is no clear picture of the regulatory network between extra cellular signals and transcription factors driving tenogenesis.

Liu and colleagues were the first to address Mkx function in tenogenesis in mouse stem cells and in tendon repair in a mouse model for tendon injury (2). *Mkx* was known to be expressed in progenitor cells of components of the musculoskeletal system, muscle, cartilage, bone and tendon (20,21). The Mkx homeobox protein, closely related to the Iroquois family, has been described as a potent transcriptional repressor and has been shown to block the myogenic conversion of 10T1/2 fibroblasts, to repress *MyoD* transcription in C2C12 cells and to repress *Sox6* transcription in satellite cells (22-24). Mkx also represses the expression of the cartilage marker *Sox9* in human anterior cruciate ligament cells (25). The transcriptional repression of specific muscle and cartilage markers by Mkx in cell cultures leads to the interesting hypothesis that Mkx promotes the tendon lineage by repressing the other lineages in mesodermal progenitors during development. However, *Mkx* mutant mice did not display obvious cartilage, bone or skeletal muscle defects, but showed severe tendon hypoplasia (13,14,26). In *Mkx*-deficient tendons, cell number was not changed but type I collagen production was reduced (transcripts and protein). Tendon defects were first observed in late developmental stages (from E16.5) and *Mkx*-deficient tendons also displayed reduced expression of *Tnmd* and of the extracellular matrix components Decorin (Dcn) and Fibromodulin (Fmd) (13,14).

Liu and colleagues observed that Mkx was present in rat Achilles tendons during postnatal tendon maturation (immuno-staining). Mkx expression was significantly decreased in human samples of tendinopathy tissues compared to normal tendon tissue (assessed by immuno-staining and computational analysis from Gene Expression Omnibus data sets). *Mkx* and *Scx* expression was also higher in human tendon stem/progenitor cells (TSPCs) compared to adipose stem cells and embryonic stem cell-derived mesenchymal stem cells. When *Mkx* expression was silenced by siRNA in mouse TSPCs, the expression of *Scx*, *Tnmd* and *Dcn* was decreased, suggesting a role for Mkx in the maintenance of tendon characteristics in these stem cells (2).

They tested the ability of Mkx to induce tenogenesis in stem cells by overexpressing *Mkx* in C3H10T1/2 cells, a mouse multipotent mesenchymal stem cell (MSC) line. They observed that Mkx decreased the clonacity of C3H10T1/2 cells using the colony-forming unit assay, and impaired the multi-differentiation potential of these MSCs towards adipogenesis and osteogenesis (2). Interestingly, MSCs expressing either *Scx* or *Egr1* transcription factor also displayed a minimal capacity to differentiate into adipocytes and osteocytes (8,10,12). The authors also compared the efficacy of Mkx with that of Scx to promote tenogenesis in MCSs cultured in a multilayered cell sheets adopting a tendon-like structure. Consistent with the Mkx requirement for correct type I collagen production (13,14), the levels of *Col1a1* mRNAs were increased in Mkx-MSCs and the collagen fibrils displayed higher diameters than those of control MSCs (2). The transcription of other tendon-associated collagens, *Col3a1*, *Col5a1*, *Col14a1* and other tendon-associated genes, *Tnmd*, *Dcn*, *Fmod* and *Tnc* was also strongly enhanced in Mkx-producing cells compared to control cells.

Interestingly, Liu *et al*. showed that Mkx induced *Scx* expression in mouse C3H10T1/2 cells and tail TSPCs (2). The *Scx* induction by Mkx in mouse MSCs differs from a concomitant study in which MKX did not activate the expression of *SCX* in human bone marrow MSCs (9). It is possible that ability of Mkx to induce *Scx* and other targets may differ between species and cell types. The ability of Mkx to induce *Scx* in mouse stem cells also differs from the developmental tendon process, where *Scx* is normally expressed in *Mkx* mutant mice (14,26). *Egr1* expression was not increased by Mkx in human bone marrow MSCs (9), and *Mkx* transcription was not increased by Egr1 in mouse C3H10T1/2 cells (12), suggesting independent pathways for the tendon-promoting effects of Mkx and Egr1 transcription factors. Liu and colleagues also observed that the tenogenic effect of Scx was less efficient than that of Mkx, based on smaller collagen fibril diameters and the absence of *Tnmd* activation in mouse Scx-C3H10T1/2 cells compared to Mkx-C3H10T1/2 cells in culture sheet systems that mimick tendon-like structures (2). However, Scx has been shown to activate *Tnmd* expression in human

bone marrow MSCs (9). Again, this discrepancy could be due to the use of different cell lines from different species. Collectively, these results show that in addition to being required for correct tendon formation (13,14,26), Mkx promotes tenogenesis in MSCs from different species (2,9).

To identify direct Mkx target genes during tenogenesis, Liu and colleagues used a chromatin immunoprecipitation sequencing approach to assess Mkx recruitment to regulatory regions in Mkx-C3H10T1/2 cells. No Mkx recruitment to the *Scx* promoter could be detected, but Mkx was recruited to the *Tgfb2* promoter. Furthermore, *Tgfb2* expression was increased in Mkx-C3H10T1/2 cells in 2-dimensional and in cell sheet culture systems, supporting a direct activation of *Tgfb2* transcription by Mkx (2). This result is somewhat surprising, since Mkx has been described as a potent DNA binding transcriptional repressor (23,24). However, one can speculate that Mkx has the ability to bind different partners, which would modify its transcriptional activity. For example, Smad3, a well-known transcriptional activator, was demonstrated to interact physically with Mkx in mouse C3H10T1/2 cells (27). Interestingly, the Egr1 transcription factor is also recruited to the *Tgfb2* promoter region in adult mouse tendons (12). The Egr1 recruitment to the *Tgfb2* promoter in tendons combined with the decrease of *Tgfb2* expression in injured tendons of *Egr1* mutant mice and the increase of *Tgfb2* expression Egr1-C3H10T1/2 cells, indicated a direct activation of *Tgfb2* transcription by Egr1 (12). Mkx and Egr1 are recruited to distinct regulatory regions of the mouse *Tgfb2* gene (2,12). Moreover, TGFβ2 only partially mediates the Egr1 and Mkx effects on tendon gene expression in MSCs, since TGFβ2 is not able to activate *Tnmd* expression, while Egr1 and Mkx are able to do so (2,12). Thus, it appears that *Mkx* and *Egr1* act at the same level in the genetic network controlling tenogenesis, upstream of *Tgfb2*. However, TGFβ pathway inhibition does not fully blocks Mkx and Scx effects on tenogenesis. It will thus be necessary in future work to characterize better the Mxk and Scx TGFβ-independent activities in this process.

Finally, Liu and colleagues tested the ability of Mkx-expressing MSCs to improve tendon healing after Achilles tendon injury *in vivo*. Mkx-expressing MSCs cell sheets were implanted after a complete transverse section of mouse Achilles tendon. Four weeks after implantation of Mkx-expressing cells, the typical structure of tendon was observed at the repaired sites, with a more mature collagen compared to the control tendons. Mkx-C3H10T1/2-grafted tendons had better biomechanical properties than those of GFP-C3H10T1/2-grafted tendons. These data showed that the application of Mkx-expressing MSCs improves tendon repair *in vivo*. This is the first experimental evidence that Mkx-cells promote tendon repair in animal models.

In conclusion, Scx, Mkx and Egr1 are three transcription factors involved in tendon development, and they all display the ability to induce tenogenesis in stem cells. The implantation of stem cells producing any of these transcription factors improves tendon repair in animal models for tendon injury. The genetic interactions between these transcription factors during tenogenesis are not fully understood and could be different between *in vitro* and *in vivo* systems and between species. However, the Mkx and Egr1 transcription factors were demonstrated to act upstream of *Tgfb2* during tenogenesis in mouse mesenchymal stem cells. This is an important step in the elaboration of the gene regulatory network orchestrating tenogenesis, even if other studies will still be needed to elucidate this network fully.

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Editorial

Lateral retinacular release and reconstruction

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In 1974, Merchant and Mercer published, "Lateral release of the patella: A preliminary report" (1). The operation rapidly became the answer for any type of anterior knee pain (2-6). This resulted in overuse of the procedure and use for inappropriate indications. As complications mounted, scientific analysis found the appropriate indications which were patellar tilt and excessively tight lateral retinacular tissues. In patients with patellar dislocations or hyperlaxity, lateral release alone has not been found to be as useful, but can be combined with medial patellofemoral ligament reconstruction.

The essential problem with the lateral release is that what makes it useful can also result in complications. The operation leads to decreased vastus lateralis strength and decreased lateral patella tracking. In patients without excessively tight lateral retinacular or with hyperlaxity, the result can be an unstable patella. This can be worse than the original problem. Patella instability or excessive medial tightening makes things worse by creating medial subluxation or even medial dislocation. Hughston and Deese first reported this in 1988 (7). Repair in these circumstances requires rebalancing the extensor mechanism, usually by restoring the lateral restraints.

In their recent paper, Sanchis-Alfonso *et al*. have described their results of recreating lateral stability with an ilio-tibial band (ITB) autograft (8). They used the technique of Andrich (9) utilizing a slip of ITB to reinforce the repair. They cite Teitge and Torga-Spak who showed that simple lateral retinaculum repair tends to fail over time (10). Medial subluxation following lateral release is an uncommon, but severe problem. The results of Sanchis-Alfonso *et al*. indicate that ITB autograft seems to be effective. This was the only reconstruction technique they tried, so it must be considered that other techniques using auto or allograft tissue to reinforce the lateral retinaculum are probably helpful in this situation as well.

While a solution to the problem of over-medialization is valuable, we are still struggling to understand the precise etiologies of patellofemoral pain. We know that the nociceptive fibers around the extensor mechanism include those in the subchondral patellar bone, the fat pad, the retinacular and the tendons. We also know that pain arising from patella instability is different from the pain arising from patella compression force overload. We do not understand why the pain is different, but we have learned that treating both problems with the same solution is not always successful.

It has been shown that in new onset patellofemoral pain, the majority of pain comes from subchondral patella bone nerves. This is followed by fat pad nerve fibers, then medial retinacular tissues (11). To their credit, Sanchis-Alfonso *et al*. noted a high percentage of fat pad pain in their subjects, performing partial fat pad resection in 13/17 subjects (8). One wonders how many failed lateral release procedures neglected addressing painful fat pads.

Until more details regarding the exact sources of pain (and the reasons for that pain) are known, we will continue to try new methods to change patellofemoral forces, both statically and dynamically. One thing is certain. The physical examination of the extensor mechanism in anterior knee pain must include examination of the fat pads, the retinacular (including the medial plica) and tests for hypermobility in addition to the standard tests for patellar tracking and compression pain.

For now, the hard indications for lateral retinacular release in adults are patellar tilt and an excessively tight lateral retinaculum. That is the conclusion after an extensive review of the literature by Clifton *et al*. (12). Dynamic

tracking issues, lateral patellar compression syndrome without tilt, lateral facet arthritis and instability issues may be soft indications in certain cases, but in these gray areas caution must be exercised as the solution of lateral release could be worse than the original problem. Repair for failed lateral release will always be necessary, but it is hoped that a rare operation can become even rarer.

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Editorial

When the capsule matters

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Hip arthroscopy can be considered an emerging technique that has been developed and is still developing rapidly. In recent years, the exponential increase in the number of arthroscopic hip surgery and continued development of technical variations push us to think about what and how, about the indications and techniques in addressing the hip pathology in young adults. Past difficulties to access and view the joint have given way to an increasingly advanced surgical refinement. In this new path, common sense should guide our steps, and the scientific evidence secures them.

Since before the explosion of hip arthroscopy, the anatomical and functional description of the hip joint and surrounding structures was performed exhaustively (1). However, the first steps in hip preservation surgery focused their efforts solely on the correction of bone deformities. Probably the technical difficulties were responsible for the initial capsulectomies that were performed to optimize the joint vision; in the same way, labral debridement was conducted to treat labral tears (2). Technology improvements and increased anatomical and functional knowledge of the labrum brought a change in the attitude of treatment; thus, more conservative measures have been imposed, improving functional outcomes of patients (3,4).

This is the same path that has been undertaken in more recent years to approach hip capsule: the way of preservation. In recent years it has increased the anatomical and functional knowledge of the capsule (5). We have to understand the joint as a whole organ, in which each of its parts plays a major role in joint function. One of the most relevant functions of capsule is to stabilize the joint that is accomplished through a multiple ligament complex (1); every part of it provides stability in the different planes of motion (6,7) being the most important the iliofemoral ligament. Moreover, this complex is the door of the joint vascularization and supports the synovium (8), which produces synovial fluid in order to maintain the cartilage homeostasis (9).

One of the problem emerged at the beginning of hip arthroscopy is that the capsule stood between the surgeon and the injury area, and correct vision was needed for proper correction of bone deformities, especially in CAM lesions. The easiest way to solve this obstacle was the partial excision of capsular tissue in the area of work or performed extensive capsulotomies. Frequently, bone deformities are often located in the anterolateral area, which corresponds to the capsular iliofemoral ligament, main hip stabilizer in extension. Consequently, this ligament was injured by the capsular defects created in this zone. Soon the results of such poor decisions were revealed. Several cases of macro-instability (10) and countless cases of micro-instability (11) (often underdiagnosed) roused the alarm. In addition, a complete view of the joint to achieve full correction of deformities was necessary. Therefore, the way was well defined: the view should be complete and the capsule preserved at maximum.

This premise has led to the current evolution of hip arthroscopic technique with two main trends in capsular handling: interportal capsulotomy and "T" capsulotomy. The former is little aggressive, but it is difficult to visualise extensive CAM-type deformities; hip flexion and rotation might help to improve the view in the peripheral compartment. However, in very large CAM deformities some degree of capsular debridement is needed, even if it is only performed in its deepest part and does not involve the full thickness. "T" capsulotomy provides an excellent view of the peripheral compartment but capsular repair, at least partially, needs to be performed to avoid iatrogenic instability (12,13). Nowadays most authors tend to repair

the interportal capsulotomy (14) and as more patients are treated and analysed in studies, it seems obvious that full capsule repair offers the best clinical results (15).

In spite of this, residual deformity remains the most common cause of revision hip arthroscopy, suggesting that the problem of correct deformity visualisation is not completely resolved (16). Novel developed conservative techniques tend to preserve the capsule at maximum (17). Understanding the capsular-ligamentous complex beyond a purely mechanical structure, these techniques promote a "no capsulotomy" intervention with maximum respect to the mechanical and biological functions of the capsule. They involve an enormous surgical effort for the experienced surgeon, but clinical results are promising.

Maintaining complete capsular integrity during surgery preserves the periarticular tissues from iatrogenic injuries as well as minimizes fluid leakage, diminishing postoperative pain. Postoperative mobilization is not restricted as capsule repair with sutures is not needed; postoperative adhesions and fibrosis, a natural tissue repair process, are reduced. Evidence is still scarce but medical intuition is strong: we must preserve the joint as much as possible and protect the most anatomical structures.

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Editorial

The arthroscopic Latarjet procedure: effective and safe

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Shoulder dislocation is the most popular dislocation of a major joint (1), which results in severe pain and possible complications such as fracture of the humerus, glenoid, injury to blood vessels or nerves (1). When the movement of the humeral head over the eroded surface of the glenoid is excessive and symptomatic, it is known as instability. Shoulder instability following dislocation is often seen in young people (1). Surgical intervention is necessary for the patients suffering from recurrent shoulder instability following the first episode of shoulder dislocation (1). Anterior shoulder instability (ASI) is the major direction of dislocation and also the most operated shoulder instability (1). The common surgical treatments of recurrent ASI include the Bankart procedure (open or arthroscopic), the Latarjet and the Bristow procedures (open or arthroscopic) (2). One of the major function outcomes after surgery is to evaluate recurrence of instability. A 20-year follow-up study in 68 Latarjet procedure-treated patients showed that the postoperative rate of recurrence was only 5.9%, which indicated that Latarjet procedures gave excellent long-term outcomes in the treatment of anterior glenohumeral instability (3). More recently, arthroscopic Bankart-Bristow-Latarjet procedures were performed in 47 patients with glenoid bone loss and capsular deficiency and the patients were followed up for average 16 months with the mean Rowe score as 88±16.7, and the mean Walch-Duplay score as 87.6±12.9; this study illustrated that arthroscopic Latarjet procedure is a safe and reproducible technique (4). A larger scale study with 180 arthroscopic Latarjet procedures found that patient-reported outcomes have 91% excellent scores and 9% good at 26 months (5). However, the long term outcomes of arthroscopic Latarjet procedure have not been fully studied previously.

Lately, Dumont *et al.* published an article entitled "The Arthroscopic Latarjet Procedure for Anterior Shoulder Instability: 5-year Minimum Follow-up" in the American Journal of Sports Medicine to investigate the long term outcomes of arthroscopic Latarjet procedure (2). This retrospective study was done with patients of a senior surgeon from Alps Surgery Institute, Clinique Générale, Annecy, France and all patients had undergone an arthroscopic Latarjet procedure before June 1, 2008. The information about whether the patient had experienced any dislocations, subluxations, or further surgery to the shoulder since the index procedure were obtained by phone calls, postal mails, or emails. All the participating patients also answered the Western Ontario Shoulder Instability Index (WOSI) questionnaire. The WOSI is a disease-specific, validated, quality-of-life measurement tools for patients with shoulder instability, which has 21 questions in four domains: physical symptoms, sports/recreation/work, lifestyle, and emotions. This study done by Dumont *et al.* followed up 62 patients (64 shoulders) for mean 76.4 months (6.4 years), ranging from 61.2 to 100.7 months. The mean age at having the procedure was 29.4 years and median age was 27.1 with a range from 17.1 to 57.4 years. The mean and median overall numbers of instability events (dislocations plus subluxation) before surgery were 8.6 and 7, respectively. Seven patients had the procedure after only 1 dislocation but their mean number of subluxation was 10. Among the 64 patients, 12 (18.8%) had undergone prior arthroscopic Bankart repairs on the shoulder with instability; the mean and median time between two procedures were 4.34 and 3.82 years. The remaining 52 (81.2%) patients had the index arthroscopic Latarjet procedure as the primary surgical treatment for their unstable shoulder. Overall only 1 of 63 (1.59%) shoulders had recurrent instability

after the arthroscopic Latarjet procedure. Also, 58 of the 62 patients reported postoperative participation in sports such as 34 patients in skiing/snowboarding, 18 patients in running/track and 18 patients in bicycling/motocross, *et al*. The WOSI score was as 90.6%±9.4% (mean ± standard deviation). Each domain of WOSI also showed high scores as follows: physical symptom 90.1%±8.7%; sports/recreation/work 90.3%±12.9%; lifestyle 93.7%±9.8%; and emotions 88.7%±17.3%.

Therefore, this study provided excellent results about the long term effectiveness of arthroscopic Latarjet procedure in treatment of ASI. The rate of recurrent instability is very low as 1.59% and the WOSI quality-of-life measurement showed good scores for an average 6.4 years of follow-up. However, there are several limitations of this study. First of all, the procedures were done by one senior surgeon in one facility, so the reproducibility of this study need to be tested with other similar studies. Second, as a retrospective study the o potential selection bias might exist. Third, no clinical evidences to evaluate the actual function of the shoulder and the answers were subject to the bias from the patients. At last, the WOSI scores were only determined after procedure, so no information available about change of pre- and post-operative scores.

In operative treatment of anterior recurrent instability of the shoulder, the two main procedures are arthroscopic or open Bankart repair and the open Latarjet procedure (6). Their short and long term outcomes have been studied extensively. A meta-analysis done by Harris *et al*. with 26 studies (1,781 patients) and a minimum of 5 years' follow-up analyzed the long-term outcomes of arthroscopic and open Bankart repair (7). This analysis showed that the mean age of patients were 28 years with majority as male (81%). Most patients had unilateral dominant shoulder (61%) and the mean number of recurrent ASI prior surgery was 11 without significant glenoid bone loss. They found that the clinical follow-up time for arthroscopic repair is significantly shorter than that for open repair (9.1 *vs*. 13.1 years, P<0.001); the recurrent dislocation rate was 11% for arthroscopic versus 8% for open procedures but the difference was not statistically significant (P=0.063); the recurrent subluxation rates are 5% for both; the time of recurrent instability is 2.5 years for arthroscopic versus 3.7 years for open procedures (P<0.01); rate of return to sport at pre-injury levels was 74% for arthroscopic versus 89% for open procedures (P<0.01) (7). Another systematic study done by Bhatia *et al*. about open Latarjet procedure demonstrated good results of open Latarjet procedure regarding recurrent instability (8). Among the ten studies included in this review, 5 of them showed none of recurrence with follow-up range from 6 months to 14.3 years; another two studies had 5% recurrence rate with mean follow-up as 21 months and 59 months; one study had 8% recurrence rate with follow-up range from 23 to 65 months (8). The 20-year follow-up study for open Latarjet procedure showed that the postoperative rate of recurrence was 5.9% (3). A recent study compared 93 patients undergoing open Latarjet procedures to 93 patients undergoing arthroscopic Bankart repairs and found that 10% (9 of 93) in the Latarjet group and 22% (20 of 93) in the Bankart group demonstrated recurrent instability (P=0.026; odds ratio, 0.39; 95% CI, 0.17-0.91) over a mean 6-year followup (6). Therefore, they concluded that the open latarjet procedure is superior to arthroscopic bankart repair regarding to shoulder stability (6).

Compared to arthroscopic or open Bankart repair and the open Latarjet procedure, the study done by Dumont *et al*. illustrated that the arthroscopic Latarjet procedure had a much lower rate of recurrent instability for long term. The arthroscopic Bankart repair was originally described by Morgan *et al*. in 1987 (9), while the arthroscopic Latarjet procedure was first described by Lafosse in 2007 (10). As a relative new procedure, the available clinical evidence regarding the long term outcomes of arthroscopic Latarjet procedure is still limited. However, considering the benefits of arthroscopic surgeries over open surgeries and the excellent results of the current study, arthroscopic Latarjet procedure could be a preferable procedure for recurrent ASI although more clinical studies are needed.

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Editorial

Bone marrow edema and results after cartilage repair

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Bone marrow edema (BME) has been described in several areas of both knee pathology and treatment, with the first reports dating back more than two decades ago. However, even though a very long time has passed since the first description by Wilson *et al*. in 1988 (1), BME remains a controversial entity not only in terms of clinical impact, but also for its still unknown significance in etiopathological processes.

BME is an MRI finding, defined as an alteration of the signal intensity of the bone marrow, seen on T1-weighted and T2-weighted images and best seen with fat suppression and short tau inversion recovery (STIR) sequences (2). However, although the imaging appearance is highly suggestive of an edema condition, very little true edema has been actually detected histologically, and conditions characterized by BME have instead been found to present non-characteristic abnormalities including bone marrow necrosis, bone marrow fibrosis, and trabecular alterations (3). Thus, in recent years, the more general term "bone marrow lesion" (BML) has been preferred (4-7) to describe the MRI findings and their heterogeneous underlying pathological elements.

BMLs are associated with multiple pathological conditions, both traumatic (bone contusion, osteochondral fracture, insufficiency and stress fractures, etc.) and atraumatic (avascular necrosis, spontaneous osteonecrosis, osteoarthritis-associated BML, etc.) (8). Whereas little is known about their exact physiopathological aspects, a common element among these pathologies presenting BML is likely to be a disequilibrium between the pathological stimulus and the ability of the bone to remodel and restore the physiological condition.

Although several studies have attempted to explore the meaning of BML for joint homeostasis and evolution of both osteonecrosis and osteoarthritis, more attention has been recently placed on the meaning of BML after cartilage treatments, due to an increasing awareness of the role played by the subchondral bone in cartilage lesions. In fact, understanding the importance of focusing on the entire osteochondral unit has led to the development of new osteochondral procedures (9) on one hand, whereas on the other it has increased attention on the imaging evaluation of the BML observed after cartilage treatment.

A recent study published by Niethammer *et al*. (10) documented prospectively the BME observed after third-generation autologous chondrocyte implantation (ACI). They followed 38 knees in 30 patients, by a standardized MRI examination performed at 1.5, 3, 6, 12, 24, and 36 months. BME was seen in 78.9% of defects over the postoperative course. It was more common in femoral than patellar defects, but no correlation with the clinical outcome could be found in this series. This strong prospective study on a homogeneous cohort of patients supported similar findings previously suggested by other reports. In fact, other authors also found a high rate of bone marrow alterations after cartilage surgery. Takahashi *et al*. (11) showed a link between BML and 47% of the implants, and a similar rate was also reported by the studies of Henderson *et al*. (12), Dhollander *et al*. (13), and Tetta *et al*. (14), with half of the patients presenting MRI subchondral alterations. The evolution of post-surgical BML is less clear, with both evidence of reduction or increase over time. With regards to this, a recent study on a large cohort of patients shed some light on a possible explanation for these controversial findings. Filardo *et al*. (15) evaluated the MRIs of 116 patients treated with hyaluronic acid-based ACI, making a total of 248 exams performed from 6 to 108 months postoperatively. The high number and wide follow-up range of the MRIs studied enabled a specific trend to be found: BML was present in the first postoperative phases, markedly reduced at 2 and 3 years, and then again increased and steadily present at mid/long-term follow-up. The initial

reduction may be explained by a maturation phase, which for such cartilage treatments is commonly acknowledged to stabilize at around 2 years with a parallel reduction of the MRI signal. On the other hand, the hyaline-like cartilage found as a result of ACI procedures may be not sufficient to protect the subchondral bone from mechanical forces, and thus lead to progressive bone marrow stimulation. The importance of the abnormal load applied seems to be supported by the distribution of BML, which was found to be more common in femoral condyles than in trochlea and patellae, or in joint compartments with combined meniscus damage and therefore further increased abnormal mechanical stress.

Worthy of note, no correlation was found between BML and the clinical outcome, as confirmed by the previously mentioned study by Niethammer *et al.* (10). The high MRI sensitivity might allow early changes to be detected, which may be a tissue reaction that is abnormal but still not severe enough to affect the clinical outcome, even at mid/long-term follow-up. Thus, although BML is a common finding after cartilage surgery, the interpretation of MRI abnormalities remains to be clarified. Prospective well designed studies with multiple evaluations at long follow-up are still needed for a better understanding of the evolution of post-surgical BML over time, as well as its importance as a prognostic factor at long-term follow-up, in order to better evaluate the potential of cartilage procedures and improve the management of patients undergoing surgery for the treatment of the articular surface.

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Editorial

The epidemiology and health care burden of tennis elbow: a population-based study

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What we have learned

Epidemiology is not an easy discipline to assess a large patient population. In their epidemiology article, Dr. Sanders and his associates have taken a manageable approach using a relatively homogeneous and small community (Olmstead County Minnesota) (1). This community is the home of the Mayo Clinic, and as such, adds the Mayo resources to a highly efficient county government. Mayo Clinic's Dr. Morrey, one of the authors, is, as well, a world expert in the diagnosis and treatment of elbow disorders.

Up to this point in history, the epidemiological data concerning tennis elbow has been based primarily on the written articles from tertiary care centers reflecting their emphasis on diagnosis and treatment and empirical observations regarding epidemiology. As an example in our center, we did a limited study of five very active tennis clubs and found that 50% of 194 tennis players, average age 43, who played 4 times a week for at least 1 year, or more, had a tennis elbow incidence of 50% over their tennis playing years. This limited study was, of course, a small sample and a very specific patient sports population.

In contrast, Dr. Sanders' study was of a general population of 144,000. Over a period of 13 years, 5,867 persons were identified with tennis elbow, an overall incidence rate of 4.5 per 1,000 in the year 2000 reducing to 2.4 per 1,000 in the year 2012. Of the 5,867, a 10% random group of 576 patients were chosen for closer evaluation. Out of the group of 5,867, 1.6% or 89 patients came to lateral elbow surgery. Fifty five of the 89 (61.8%) had open, and 34 (38.2%) had an arthroscopic technique.

A main stated goal of the study was to determine the natural history of the lateral tennis elbow and identify, if possible, a clear indicator to proceed to surgery. In this regard, the study suggested that patients with symptoms persisting for over six months were more likely to come to surgery.

Nirschl Orthopaedic Center experience

This author has operated on approximately 1,500 patients with lateral tennis elbow over a period of 40 years. As our expertise and experience expanded, many patients presented to our center requesting surgery, having failed both non-operative and operative treatment at other institutions. In our 1979 original clinical series of 1,213 patients, 88 elbows came to surgery (0.73%). There were 38 women, average age 41.5 and 44 men, average age 45. The average time from symptom onset to surgery was 51 months for the women and 21.6 months for the men. The dominant arm was involved in 75 patients and 13 non-dominant (16%). Three of these patients had bilateral surgery (2). The thousands of patients that followed did not substantially deviate statistically from the 1979 group with one exception, our surgical incidence. Over the years, as our confidence increased and the sophistication of our technique progressed to a mini-open incision, our percentage of surgical cases increased to approximately 25%. This occurred because our center became a tertiary center for failed cases by both operative and non-operative approaches. Many of these patients had multiple cortisone injections with decreasing

Table 1 Nirschl pain phase scale for athletic overuse injuries
Phase 1: stiffness or mild soreness after activity, usually gone within 24 hours
Phase 2: stiffness or mild soreness before activity that is relieved by warm-up. Symptoms are not present during activity but return after, lasting up to 48 hours
Phase 3: stiffness or mild soreness before specific sport or occupational activity. Pain is partially relieved by warm-up. It is minimally present during activity but does not cause athlete to alter activity
Phase 4: pain is similar to but more intense than phase 3 pain. Phase 4 pain causes athlete to alter performance of the activity. Mild pain may also be noticed with activities of daily living
Phase 5: significant (moderate or greater) pain before, during, and after activity, causing alteration of activity. Pain occurs with activities of daily living but does not cause a major change in them
Phase 6: phase 5 pain that persists even with complete rest. Phase 6 pain disrupts simple activities of daily living and prohibits doing household chores
Phase 7: phase 6 pain that also disrupts sleep consistently. Pain is aching in nature and intensifies with activity

effectiveness of pain control.

The Sanders' study noted that patients with symptoms greater than 6 months were more likely to come to surgery but did not comment further on other potential surgical indicators (1). Our experience is similar regarding symptoms over 6 months but we noted other indicators. As noted above, our first series time to surgery was 21.6 to 51 months (male to female). As our surgical technique (Nirschl open resection and repair) was first developed in 1975, we were initially quite careful not to move to surgery too quickly. As the experience and sophistication (mini-open) with the new technique grew, we were much more confident to recommend surgery earlier (now approximately 15 months). It would be rare for us to proceed to surgery in less than 1 year. Besides the 6-month time frame noted, we have found that 2 or more failed cortisone injections and the patient suffering Nirschl pain scale phases 6 and 7, are also strong indicators for surgery (*Table 1*).

The Sanders' study noted the preponderance of persons getting tennis elbow were office workers and nurses and that the dominant arm was more likely. Our experience is similar that these groups are involved (e.g., much computer work or lifting in patient care). Our experience also noted an even higher incidence of upper extremity sport and blue collar groups (e.g., carpentry, plumbing, tennis, golf, racquet ball, baseball, and squash). To understand the high incidence of the malady in these groups, one must understand the histopathology of tendinopathy.

In our 1979 report (2), we not only reported a new surgical technique, but what the technique was predicated upon. For the first time we clearly identified that the full body of the extensor carpi radialis brevis (ECRB), and the anterior medial edge of extensor digitorum communis (EDC) tendons were grossly abnormal (gray, friable, edematous) in comparison to normal surrounding tendon (firm and shiny). Microscopic evaluation of this tissue, also revealed very abnormal findings (e.g., dysfunctional vascular and immature fibroblastic elements with disruption of collagen). These anatomical regions also have minimal blood supply (3). There were also no inflammatory cells. Since there are no inflammatory cells the common term tendinitis is a misnomer and we called the tissue angio-fibroblastic hyperplasia. In 1976, Paddu, in Italy, noted a similar histological pattern in achilles tendons and he named this achilles tissue tendinosis (4). The subsequent terminology we now use is angio-fibroblastic tendinosis and the term has been widely accepted. It should be noted that this same histological appearance is similar in all tendinopathies (e.g., rotator cuff, elbow tendons lateral, medial, and triceps, quadriceps, patellar, Achilles and planta fascia).

With understanding the histopathology, we now had a clearer picture of the causation of the tendon failure. The history is almost always the same (e.g., repetitive overuse). In a few cases, a direct blow to the epicondyle adds another dimension to pathological findings (namely the formation of a bony exostosis at the tip of the epicondyle). Bony exostosis has also been caused by an ill-placed injection needle against the epicondyle. In the huge majority, however, high repetitive activity is the key factor in tendon failure.

In 1969, we noted another important factor, a subset of patients had not only unilateral tennis elbow but bilateral, and also had associated symptoms in the medial elbow, rotator cuff, the cubital and carpal tunnels and hip bursitis. It was clear that this subset of patients added another dimension to causation (namely a generalized tendon

durability deficiency). We theorize this deficiency as a collagen defect and have named this malady "mesenchymal syndrome" (5,6). We note that Dr. Sanders' study noted, of the 576 patients, 67 had bilateral symptoms (a 11.29% incidence). Presence of medial elbow, and carpal or cubital tunnel symptoms was not cited in the Sander study, but I suspect their subgroup of bilateral lateral symptoms also included some of these symptoms but were not recognized or discussed. The 11.29% incidence of bilateral lateral elbow symptoms is consistent with our observation of "The Mesenchymal Syndrome".

The Sanders' study included review of the 576 patients for non-operative and operative treatments. The study concluded there were no standard non-operative treatment protocols in the patient's studied. This noted lack of treatment consistency suggests that multiple prescribers with a relative small amount of cases had limited experience. Patients referred into our center also often had wide variation of treatments, in large part ineffective. In contrast to this wide variation of non-operative protocol, we developed a consistent protocol with the following concepts (7,8):

(I) Enhance collateral vascular infiltration and collagen production with controlled eccentric rehabilitation exercise associated with the modalities of physical therapy (heat, cold, and high voltage electrical stimulation).

(II) Control repetitive overuse by counter force bracing, proper technique modification of high demand activity, proper equipment, and control of frequency intensity and duration of activity. The concept and term counter force bracing was initially introduced in our clinic in 1976, with the function of diffusing excess concentration of forces (9).

(III) Pain control is not curative but important to allow efficient rehab exercise. Pain control can include anti-inflammatory medication including cortisone injections to control inflammatory chemical mediators which are adjacent to but not in the pathological angio-fibroblastic tissue.

Surgical concepts

If the above three non-operative approaches prove ineffective, surgical intervention is considered. The Nirschl mini-open surgical technique like non-operative treatment is as also precise. To be successful, the technique must accurately identify the painful pathological tissue in the ECRB and EDC tendons and cleanly remove it (6,10). On occasion (5%), an intra-articular synovial plica or an epicondyler spur is present and these additional elements are addressed when present. The success of the Nirschl mini-open technique with total pain relief for activities of daily living is 97%. About 93% of patients have returned to the sport level (tennis, golf, etc.) that they enjoyed prior to surgery (2). A long range review of our patients at 10 to 14 years post-op revealed the above noted success rate was maintained (11).

There are also many surgical candidates who have not only lateral elbow but medial elbow and cubital tunnel symptoms concomitantly. We reviewed a group of these patients in 2011 and found the success rate of all three areas was 95% (12). We note the Sanders' study did not report surgicalS success rates from their patient population but did report success of a literature report comparing arthroscopy versus open techniques. The reported success rate was 78% for arthroscopic and 67% for the open technique utilized by these surgeons (13). Such success would not be acceptable by our standard of 97% success. Our center has, as well, had the opportunity to do salvage procedures from prior failed open and arthroscopic surgery at other institutions. The reason for failure is almost always the same (namely failure to clearly identify and remove the ECRB and EDC pathological tissue (14). This is especially true of arthroscopic procedures, and by our observation of a high failure rate arthroscopy is not recommended. It is also necessary to do the open procedure correctly. In this regard, it needs to be emphasized that the Nirschl procedure is not a release operation but is dedicated to clear identification and removal of the pathological tissue which is extra-articular (6,10).

There are a few cases (5%) which have an additional intra-articular component (namely synovial plica) and in these cases a small intra-articular incision is made and the plica removed.

Summation

The Sanders' study confirms what we have known empirically, but it is always helpful to have confirmation. Lateral tennis elbow does not threaten quantity of life, but is a major impediment to quality of life. As noted in the Sanders' report, the malady is also statistically significant and I agree with the Sanders' estimation of approximately 1,000,000 cases per year in America. Dr. Sanders and his colleagues are to be congratulated for a job well done. I

trust my editorial comments will add deeper understanding to a very bothersome malady.

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Footnote

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Editorial

Intra-articular platelet-rich plasma injections were not superior to viscosupplementation for early knee degeneration

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This report commend Filardo *et al.* on their recent research entitled "Platelet-rich plasma intra-articular knee injections show no superiority versus viscosupplementation: a randomized controlled trial" (1). The aim was to assess the benefit provided by platelet-rich plasma (PRP) injections to treat early knee joint degeneration in comparison with hyaluronic acid (HA) injections. The authors conducted a randomized (allocation concealed), blinded (clinician, patients, and outcome assessors), controlled trial with 12 months of follow-up in a specialized center for orthopedics. It was a well-designed study with proper statistical analysis. A total of 192 patients with unilateral knee pain of minimum 4 months and imaging findings of chondropathy or osteoarthritis (Kellgren-Lawrence score of ≤3) were allocated to PRP injections (n=96, mean age 53.3 y, 63.8% women) or HA injections (n=96, mean age 57.5 y, 58.4% women). The patients received 3 weekly intra-articular injections of PRP or high-molecular-weight HA. There was no additional rehabilitation program following injections except the instructions for a short rest and cold therapy. Main outcome measure was the International Knee Documentation Committee (IKDC) subjective score. Secondary outcome measures were the Knee injury and Osteoarthritis Outcome Score, EuroQol visual analog scale, and Tegner score. Two patients from PRP group and seven patients from HA group were excluded from statistical analysis due to lack of complete data at final evaluation. The study had 80% power to detect a clinically relevant 6.7 points difference between groups in IKDC subjective score at the 12-month follow-up. The PRP and HA groups both improved from baseline in all the clinical scores used, with no statistically significant differences between groups. The authors concluded that the injections of PRP did not improve pain and knee function more than HA in patients with knee cartilage degeneration and osteoarthritis.

The study by Filardo is very useful in the care of patients with knee osteoarthritis. No significant differences were identified in any outcome measures at any time point after injections of PRP in comparison with HA injections. Both groups improved similarly, and significantly, from baseline. This study provides invaluable data regarding the use of PRP in these patients. Of the randomized controlled trials investigating the efficacy of PRP in knee osteoarthritis, the present one has ever been conducted on the largest cohort of patients with the longest follow-up period. The results of this study are in contrast with the prior studies (2-5) that suggested benefit with PRP treatment in knee osteoarthritis. It is suggested that PRP injections should not be preferred to HA injections for patients with knee cartilage degeneration.

Pain and disability caused by knee osteoarthritis is a growing problem exerting a large economic burden in terms of health care and loss of productivity (6). The early management of knee osteoarthritis is still challenging and the investigation continues for novel treatments. Biologic treatment offers a new and exciting possible avenue for cartilage degeneration. Promising results obtained with previous studies have led to high interest in using PRP in this field. However, as the study by Filardo indicates, there is a need for more well-designed studies with large sample size to make a true judgment for the role of PRP injections in the management of osteoarthritis.

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Editorial

Intraarticular hyaluronate injection for knee osteoarthritis—reconsider the rationale

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Intraarticular hyaluronate injection, also referred as viscosupplementation, stands as a popular nonsurgical therapy commodity for patients suffering osteoarthritis (OA) of knee. Despite the currently wide use of hyaluronate injection for knee OA treatment, there are still controversies and uncertainties on this supplementation therapy.

The idea of hyaluronate injections comes from the direct understanding that OA derives from excessive mechanical stress applying to osteochondral surfaces (1). Hyaluronan is a naturally occurring polysaccharide of high viscosity in the extracellular matrix of most kinds of tissues, particularly in soft connective tissues. It acts as a major component of the synovial fluid and of cartilage. Exogenous intraarticular hyaluronate injection stands as a nonsurgical treatment of knee OA (2). In the traditional view, therapeutic goals of intraarticular hyaluronate can be divided into short term and long term effects. Instant hyaluronate injection provides an intraarticular lubrication, which improves the viscoelastic properties of synovial fluid (3). It is also claimed that hyaluronate may exert anti-inflammatory, analgesic and chondroprotective influences on cartilages in a longer run (4). The clinical benefits of treatment with intraarticular hyaluronate, which may persist well beyond the intraarticular residence time of the product, have been suggested to be caused by an increase in the endogenous production of hyaluronate that persists long after the exogenous injected material has left the joint (5). Some experimental studies indicate that hyaluronate may exert its action through mechanisms of enhancing prostaglandin synthesis and suppressing proinflammatory mediators. Histological evidence shows that hyaluronic acid (HA) prevents the degradation of cartilage and may promote its regeneration although its mechanism is largely unknown (5). Still more, the lower incidence of adverse effect of hyaluronate injection makes doctors more apt in using this therapy. Concerning the local and general tolerance of hyaluronate, it shows a relatively satisfactory result as a disease modifying treatment when compared with other drugs with cardiovascular and gastrointestinal complications like NSAIDs or opioids (6,7). Several institutions also did comparative studies to evaluate cost effectiveness between hyaluronate and NSAIDs or other nonsurgical therapies. The results indicated that hyaluronate may be more favorable in economic concerns generally (8) and even save the cost from cancellation or delayed surgical procedures in some knee OA patients (9).

Despite numerous trials and meta-analyses, the efficacy of hyaluronate-related agents in patients with knee OA remains debated and uncertain. As in many of the other trials of hyaluronates, there was a large placebo effect in this trial. A range of systematic reviews and meta-analyses showed discrepant results in term of the efficacy of hyaluronate injection, possibly caused by different search strategies and selection criteria to identify trials for inclusion in these analyses (2). Clinical effects of hyaluronate injections, however, may still be uncertain in several concerns. Although several clinical studies reveal a significant outcome in patients' pain relief, other trials and meta-analyses show a pessimistic result in reduction of knee joint space and uncertainties in its long term chondroprotective effects (10,11). Still, considerable therapeutic heterogeneity exists from study to study. Some of the minor side effects include pain and skin reaction at injection area. More serious side effects like pseudo-septic

reactions and joint infections have both been detected, but with a relatively lower incidence (12,13). Some researches raised concerns about risk of hyaluronates in adverse events gastrointestinal and cardiovascular adverse events, but still with lower incidence than that of NSAIDs (13). Discordances even exist among different brand of product concerning the molecular mass of hyaluronate. Some researches highlighted high molecular mass hyaluronate and some indicated intermediate molecular mass performed better (14), but the overall effectiveness were modest to non-distinguishable from the placebo (2).

Since a range of pooled analyses and trials raised uncertainties in the therapeutic effects of hyaluronate injection, international guidelines for OA started to put it in a secondary priority. The latest version of the evidence from the Osteoarthritis Research Society International (OARSI) in 2014 does not recommend for the treatment of either knee or multiple joint OA (15). Similarly, the American Academy of Orthopaedic Surgeons (AAOS) clinical practice guideline and 2012 American College of Rheumatology recommendations do not act for or against hyaluronate injections. It is conditionally recommended only when patient do not have a significant to medical therapies, especially in patients over 75 years old (16). The British National Institute for Health and Care Excellence (NICE) do not recommend HA in knee OA either (6). Consensus of these guidelines for OA patients in early or moderate conditions is to lose weight and undertake suitable exercises.

In brief summary, although some clinical doctors observe that intraarticular hyaluronate may have some instant effects, current evidence based facts are non-sufficient to distinguish that effect from placebo. So that the majority of most updated international guidelines do not recommend hyaluronate as a regular nonsurgical treatment for early to moderate knee OA. Experimental investigations on chondroprotective mechanisms and larger sample RCTs with longer following durations of intraarticular hyaluronate injections are needed to further clarify its therapeutic indication and effect.

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Editorial

A bone to pick with Fc gamma receptors

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Bone formation is a dynamic process, in which the bone structure is constantly remodeled. Osteoclasts and osteoblasts play critical but opposing roles in bone formation and resorption. While osteoclasts promote bone resorption, osteoblasts drive bone formation. Both processes are intertwined and tightly regulated to ensure the integrity of the bony skeleton. In particular, bone mass, strength and mineral homeostasis depend on balanced osteoclast and osteoblast function. Enhanced osteoclast activity leads to massive bone loss as exemplified in autoimmune diseases like rheumatoid arthritis (RA) or systemic lupus erythematosus (SLE). Osteoclasts and osteoblasts originate from different precursors. Whereas osteoblasts derive from mesenchymal stem cells, osteoclasts originate from multinucleated progenitors of the monocyte/macrophage family. Two critical factors that regulate osteoclastogenesis are macrophage colony-stimulating factor (M-CSF) and receptor for activation of nuclear factor kappa B (NF-κB) (RANK) ligand (RANKL). RANKL is expressed by T cells, endothelial cells and osteoblasts. Although activation of the RANKL pathway is essential to initiate osteoclastogenesis, an immunoreceptor tyrosin based activation motif (ITAM) co-stimulatory pathway is required for calcium-mediated activation of nuclear factor of activated T-cells, cytoplasmic 1 (NFATc1), which serves as an important factor in osteoclast differentiation (1). The ITAM co-stimulatory pathway is activated in response to ligation of immunoglobulin-like receptors such as osteoclast-associated receptor (OSCAR), triggering receptor expressed on myeloid cells (TREM-2) or paired Ig-like receptor A (PIR-A), and the phosphorylation of the adaptor molecules containing ITAM motifs. Such ITAM motif-containing proteins are DNAX activation protein of 12 kDa (DAP12) and the Fc-receptor γ subunit (FcRγ) Importantly, the γ-chain not only facilitates FcγR signaling but is also required for the transport of IgG Fc receptors to the cell surface (2,3). The critical role of FcRγ and DAP12 for osteoclast activation was first demonstrated in mice suffering from severe osteopetrosis when both factors were lacking. Importantly, the phenotype was less pronounced in mice lacking only DAP12, whereas FcRγ-deficient mice showed no disease phenotype (2). These data suggest that FcRγ plays an important role in osteoclastogenesis in concert with DAP12.

In mice, four different FcγRs have been described: FcγRI, FcγRIIB, FcγRIII and FcγRIV (4). FcRγ acts as the common subunit of the activating FcγRs, whereas the only inhibitory FcγR, FcγRIIB, signals independent of FcRγ. Despite the availability of knockout-mice for the distinct FcγRs, a detailed understanding of the individual roles of IgG Fc receptors in osteoclastogenesis has been lacking. Negishi-Koga *et al*. provide now detailed insights into the role of activating and inhibitory FcγRs in bone homeostasis at steady state and under inflammatory conditions (5).

The first and surprising finding was that naive FcγRIII-deficient mice showed an osteoporotic phenotype, which was associated with an increased number of osteoclasts. In contrast, osteoblast numbers were not altered. *In vitro* experiments confirmed this observation. FcγRIII-deficient bone marrow-derived monocyte/macrophage cells (BMM) stimulated with RANKL and M-CSF showed enhanced osteoclast formation. These results suggest that FcγRIII has an inhibitory effect on osteoclastogenesis under homeostatic conditions, even when IgG1 immune complexes (IC), the dominant ligand of FcγRIII, are missing. The authors explain this unexpected suppressive role of FcγRIII on

osteoclast activity by a sequestering effect of FcRγ that is associated with the highly expressed FcγRIII under physiologic conditions. In the absence of FcγRIII, more FcRγ is available resulting in increased surface expression of OSCAR and PIR-A. As a consequence, mice lacking FcγRIII showed hyperactivation of PLCγ2 and increased intracellular calcium release. In support of this finding, the authors showed that FcγRIII is inversely correlated with the surface expression of OSCAR and PIR-A.

In autoimmune disorders, auto-antibodies form either soluble or cell-bound IC, serving as ligands for FcγRs. Depending on their subclass, they bind with different affinities to the four FcγRs. IgG1 antibodies are the most dominant subclass in mice. IgG1 IC bind predominantly to FcγRIIB and FcγRIII, both of which are expressed on osteoclasts. Importantly, the affinity of IgG1 IC for FcγRIIB is tenfold higher than for FcγRIII. Consequently, IgG1-mediated osteoclast activation is mainly regulated by the relatively low binding affinity to activating FcγRIII and the high binding affinity of IgG1 IC to inhibitory FcγRIIB resulting in an A/I ratio of 0.1 (4). In line with these considerations, FcγRIIB-deficient mice suffer from enhanced inflammation in various IgG1-mediated autoimmunity models (6), which are often associated with enhanced bone resorption. Accordingly, the authors demonstrate that IgG1 IC induce osteoclast formation in cells from mice lacking the inhibitory FcγRIIB but not in wildtype cells. This phenotype could be rescued by the additional deletion of FcRγ or reduction of FcγRIII expression by shRNA, demonstrating a critical role for FcγRIIB and FcRγ activation downstream of FcγRIII for bone homeostasis under inflammatory conditions. The *in vivo* relevance of IgG1 IC for the regulation of bone resorption was underscored by experiments, in which the authors injected IgG1 IC locally into the calvarial bone. Recapitulating the *in vitro* findings, bone loss occurred only in FcγRIIB-deficient but not in wild type mice. Of note, the impact on bone dynamics was not associated with any signs of cellular inflammation.

During the course of experimental RA or SLE, auto-antibodies of the IgG2a/c and IgG2b subclasses develop that can bind with high to moderate affinities to FcγRI, FcγRIV and FcγRIII, when complexed with their antigens. Importantly, the A/I ratios of IgG2a/c and IgG2b are 70 or 7 and thus much higher than the A/I ratio for IgG1. Consistent with this notion, inflammation models using IgG switch variants confirmed the higher inflammatory potency of IgG2a/c or IgG2b as compared with IgG1 antibodies (7). Here, the authors demonstrated that IgG2a/c and IgG2b antibodies induce strong osteoclast formation even in wild type cells that was markedly suppressed in response to shRNA-mediated knock-down of FcγRI or FcγRIV. The *in vivo* relevance of this observation was highlighted using sera from mice suffering from collagen-induced arthritis (CIA). Such sera induced strong osteoclastogenesis, whereas sera from control mice did not. Depletion of IgG abrogated this effect. Mechanistically, BMM from CIA mice upregulated activating FcγRIII and FcγRIV and downregulated inhibitory FcγRIIB.

This reciprocal regulation of activating and inhibitory FcγRs may result from classical and/or alternative pathway activation of the complement system by IgG2a/c and IgG2b IC. In fact, the cleavage fragment of the complement component 5 (C5), i.e., C5a, can set the threshold for FcγR activation by upregulation of activating and downregulation of inhibitory FcγRs on macrophages in the lung (8) and the peritoneum (9) through activation of C5a receptor 1 (C5aR1). Of note, C5aR1 is expressed in osteoclasts and drives osteoclastogenesis in response to C5a, even in the absence of RANKL and M-CSF (10), suggesting that IgG2a/c IC can induce osteoclast formation directly through the activation of FcγRI, FcγRIII and/or FcγRIV and indirectly through the activation of the complement system.

Another important part of IgG Fc that the authors identified as a regulator of osteoclast activation is the glycan fraction within the CH2 region of the heavy chain. IgG Fc harbors a complex biantennary glycan structure at Asn297 that either terminates with N-acetyl-glucosamine, galactose or sialic acid. IgG lacking Fc-sialylation bind with higher affinity to activating FcγR than their sialylated counterpart (11). Interestingly, the authors identified a higher frequency of desialylated IgG in sera from FcγRIIB-deficient mice as compared with wildtype controls. The purified IgG from FcγRIIB-deficient mice stimulated osteoclastogenesis more efficiently than those from wild type mice. This is an important finding, as sera from RA patients suffering from acute flares show a high frequency of auto-antibodies lacking terminal sialylation and galactosylation (12). In fact, the decrease in terminal Fc-glycosylation precedes the onset of RA, suggesting that bone resorption may already start prior to clinical signs of autoimmune disease. In addition to terminal sialic acid, galactose may also impact on bone homeostasis. Highly galactosylated IgG1 IC suppress C5a-mediated cell activation through a pathway that cross-links FcγRIIB and the C-type lectin receptor dectin-1 (13),

thereby potentially interfering with the direct and indirect effects of C5a on osteoclastogenesis, as outlined above. In light of these findings, the impact of the glycan composition on bone resorption needs to be considered in the design of therapeutic antibodies that are administered in autoimmune diseases or cancer. In these settings, IC formation might provide ligands for osteoclasts and induce therapy-related bone loss, in particular after long-term administration.

In addition to specific immunotherapy by IgG antibodies, patients suffering from autoimmune diseases are often treated with intravenous immunoglobulin (IVIG). IVIG is composed of pooled serum of many thousand donors. The IgG fraction is the main component of IVIG. The findings of Negishi-Koga *et al*. suggest that IVIG treatment will reduce the bone loss in autoimmune disease. Among the many proposed immunomodulatory pathways of IgG within IVIG, C5a scavenging, modulation of activating and inhibitory FcγR expression, blockade of activating FcγRs and saturation of neonatal FcR may limit auto-antibody-induced increase in osteoclastogenesis (14).

Finally, it will be important to delineate how the data obtained in the mouse system translate into the human situation. First findings are promising and support the view that the observations by Negishi-Koga *et al*. may also apply to the regulation of human bone homeostasis. For example, RA patients carrying the high affinity FcgRIIIA158V allele suffer from more severe bone erosion when compared to patients carrying the less affine FcgRIIIA158F allele (15). Also, the levels of IgG- or citrullinated peptide-specific antibodies in RA patients correlate with the incidence and the extent of bone destruction (16). However, as not only the IgG subclasses and FcγR composition differ between mice and humans but also the potency of individual IgG subclasses to activate the complement system, future research will need to address in more detail the impact of the different IgG subtypes and their Fc-glycan structures on the multiple FcγR-complement axes and also the activation of C-type lectin receptors.

In summary, Negishi-Koga *et al*. identified an unexpected inhibitory role for FcγRIII in osteoclastogenesis under physiological conditions and provide important novel insights into FcγR-mediated mechanisms that lead to bone resorption in IC-mediated diseases (5). Their data provide evidence that the IgG isotype determines the activation of the downstream pathways that eventually result in osteoclast differentiation and activation. For IgG1 IC driven osteoclast activation, the A/I ratio between FcγRIII and FcγRIIB is critical. In contrast, IgG2a/c or IgG2b IC mediate osteoclast activation mainly through FcγRI and FcγRIV aggregation. Further, the complement-activating properties of IgG isotypes and their Fc-glycan composition need to be taken into account, as they drive important feedback loops that impact on FcγR expression, define the binding affinity of IgG Fc to FcγRs and can activate osteoclasts independent of FcγRs through complement and C-type lectin receptors.

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Footnote

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Editorial

Why arthroscopic partial meniscectomy?

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Abstract: "Arthroscopic Partial Meniscectomy versus Sham Surgery for a Degenerative Meniscal Tear" published in the *New England Journal of Medicine* on December 26, 2013 draws the conclusion that arthroscopic partial medial meniscectomy provides no significant benefit over sham surgery in patients with a degenerative meniscal tear and no knee osteoarthritis. This result argues against the current practice of performing arthroscopic partial meniscectomy (APM) in patients with a degenerative meniscal tear. Since the number of APM performed has been increasing, the information provided by this study should lead to a change in clinical care of patients with a degenerative meniscus tear.

Keywords: Meniscus tear; arthroscopic meniscectomy; osteoarthritis; knee pain

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Attributed to two controlled trials (1,2), showing a lack of efficacy of arthroscopic surgery, the number of arthroscopic surgical procedures performed to treat established knee osteoarthritis has decreased dramatically in the past 15 years. However, the number of arthroscopic partial meniscectomy (APM) performed has concurrently increased by 50%, with annual direct medical costs estimated at $4 billion in the United States alone (3,4). Nevertheless, APM has been shown to be of no benefit to patients with concomitant knee osteoarthritis (5,6). Since the optimal treatment of a degenerative meniscus tear in patients with mild or no knee osteoarthritis is unknown, the objective of this target paper (7) was to argue against the current practice of performing APM in patients with a degenerative meniscal tear. The results of this randomized, sham-controlled trial show that arthroscopic partial medial meniscectomy provides no significant benefit over sham surgery on pain and function in patients with a degenerative meniscal tear and no knee osteoarthritis. This demonstration should lead to a change in clinical care of patients with a degenerative meniscus tear.

Since 1980, arthroscopic technique has become the standard method of treatment if patients require meniscectomy (8-11). However, according to a prospective study using validated questionnaires to assess patient-relevant outcomes after APM (12), despite significant improvement was seen with only minor pain and other symptoms remained postoperatively, significant physical disability and handicap were reported. Technically, APM can be complicated by excessive resection, damage to articular cartilage, neurovascular injury, persistent drainage from portals, and infection; the procedure can be rendered more difficult, and the outcome less certain, if the surgeon fails to recognize concomitant injuries, malpositions the portals, or misidentifies the components of a meniscus tear (13). Moreover, people following APM are at increased risk of developing knee osteoarthritis (14). Studies to clarify the long-term clinical and radiological consequences of APM found that greater articular cartilage degeneration assessed at surgery, greater size of meniscal resection, greater laxity of the anterior cruciate ligament, and prior surgery on the index knee were the strongest predictors of worse functional outcomes (15,16) and will lead to significantly increased osteoarthritic change in the long-term (17-19). There is also evidence that high impact loading and a higher external peak knee adduction moment is believed to be a contributor for the development of osteoarthritis after APM (20-22).

Why we perform APM for a patient? Is it for symptoms relief? Prevention of cartilage degeneration? Or just for the removal of the torn meniscus itself? Significant variation

exists among practicing orthopaedic surgeons with regard to decision making for APM. The three clinical factors that most influenced a surgeon's decision to recommend APM were normal radiographic findings, failed non-operative treatment, and the presence of positive physical examination findings (i.e., positive McMurray test, joint line tenderness, and effusion) (23). Knee pain is usually the main reason that patients seek for help. APM is typically advocated for patients with knee pain in whom a tear is confirmed by MRI, particularly those without concomitant knee osteoarthritis. However, increasing evidence suggests that a degenerative meniscal tear may be an early sign of knee osteoarthritis rather than a separate clinical problem requiring meniscal intervention (24-27). For example, one study showed no significant association between the presence of meniscal damage and the development of frequent knee pain in middle-aged and older adults, once the co-occurrence of osteoarthritis at baseline was taken into account (28). Another recent study (29) suggested a neglected cause of knee pain called "medial abrasion syndrome" might be intermingled with medial meniscus tear and could be successfully treated by arthroscopic medial release. These findings proclaim against the current practice of performing APM in patients with an accidentally found degenerative meniscal tear. More possibilities should be taken into consideration before making this decision.

In conclusion, more and more evidence suggests that patient-relevant outcomes after APM provide additional information and preoperative evaluation for the meniscectomy patient should include a realistic expected functional outcome. Knee pain, as the main concern of patients, should be carefully evaluated for its possible causes before performing APM.

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Editorial

Editorial: Functional testing in the assessment of return to sports after anterior cruciate ligament reconstruction

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Abstract: The paper entitled "Functional testing differences in anterior cruciate ligament (ACL) reconstruction patients released versus not released to return to sport" published in the *American Journal of Sports Medicine* (*AJSM*) assessed Functional Movement Screen (FMS) and the Lower Quarter Y Balance Test (YBT-LQ) as possible objective tools for evaluating a patient's readiness to return to sports after ACL reconstruction. The results suggest that many patients clinically cleared continue to have measurable function deficits and that both FMS and YBT-LQ may be used as additional tools for return to sports clearance.

Keywords: Anterior cruciate ligament (ACL); reconstruction; functional test

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The goal of anterior cruciate ligament (ACL) reconstruction is often to aid patients in returning to high level activities. No objective criteria exists in assessing a patient's readiness to return to play after ACL reconstruction, so clearance is still largely dependent on the clinical encounter and physical examination. The most frequently used criterion for return to sport is time from surgery (60%) (1,2). Usually, athletes are cleared to return to sport between 6 and 12 months after ACL reconstruction (1,3,4).

A recent *American Journal of Sports Medicine* (*AJSM*) paper entitled "Functional testing differences in anterior cruciate ligament reconstruction patients released versus not released to return to sport" compared the performance of such patients with regards to two functional tests—FMS and YBT-LQ. A total of 98 patients were included in this study. Clinical examinations were performed between 5 and 9 months postoperatively. Pain scores, presence of an effusion, range of motion, Lachman and pivot-shift test were recorded. Additionally, graft laxity and isokinetic quadriceps strength was tested. FMS and the YBT-LQ functional tests were then administered. The FMS testing included the deep squat, hurdle step, in-line lunge, shoulder mobility, active straight leg raise, trunk stability/push up, and rotary stability tests (5,6). The whole score and the number of asymmetries between the operative and nonoperative leg were calculated. YBT-LQ testing data were recorded for anterior, posteromedial, and posterolateral reaches for both the operative and nonoperative legs (7). The average normalized reach score for each leg was calculated as well as the reach symmetry for each reach direction.

All patients were grouped based on whether they had been cleared to return to sports. This was determined by the treating surgeon and was based on both clinical and objective measures. If patients had progressed through the standard rehabilitation program and had no effusion, range of motion within 5 of the contralateral leg, a Lachman test with less than 5 mm of translation and a firm endpoint, a negative pivot-shift test, a KT-1000 arthrometer test within 5 mm of the contralateral limb, and isokinetic testing demonstrating no or mild quadriceps strength deficits, they were cleared to return to sports.

This study showed that results on the FMS test and YBT-LQ tests were not statistically different between patients cleared for athletics and those who were not. This suggests that current return to sport criterion does not clearly identify patients with poor neuromuscular function

and may place them at risk of future injury.

The retrospective nature of the study introduces inherent bias. There was significant heterogeneity in the decision process due to three treating surgeons and multiple therapists. The difference in age between the cleared and noncleared group, with the cleared group being older, contrary to currently accepted clinical impression, is another limitation.

Recent research has identified functional tests that may assist in identifying athletes at risk for future injury. Postural stability, flexibility, and neuromuscular control are all key components of ACL rehabilitation (8,9). The traditional return-to-sport criterion that focuses only on the Lachman, pivot-shift, KT-1000 test and isokinetic testing is inadequate and will lead to higher reinjury risk. Patients' neuromuscular control and lower extremity function should also be assessed before returning to athletics. Besides the FMS and YBT-LQ tests, there are other tests for neuromuscular control evaluation such as the single-leg squat test, gait analysis or other core strength measures that can also be used (10,11).

In our opinion, there is currently no "in office" test or examination that can accurately "clear" an athlete to return safely to sports. Parameters that we use to assess readiness include ROM within 5 degrees, no effusion, good stability, and thigh circumference measured 15 cm above patella that is within 2 cm of the contralateral side. Next, static strength testing should be at least 90% of opposite side. However, the best testing is "dynamic" or "functional" testing, in which an athlete is asked to perform sports specific activities/maneuvers and his/her mechanics and performance is assessed. In addition, different sports/positions typically return athletes at different times. While some football players can return safely at 6 months with a brace, many basketball players (who don't like to wear braces) often take 8-10 months.

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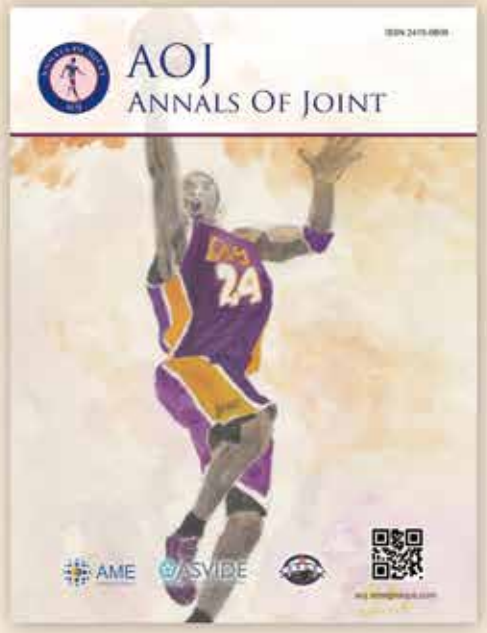

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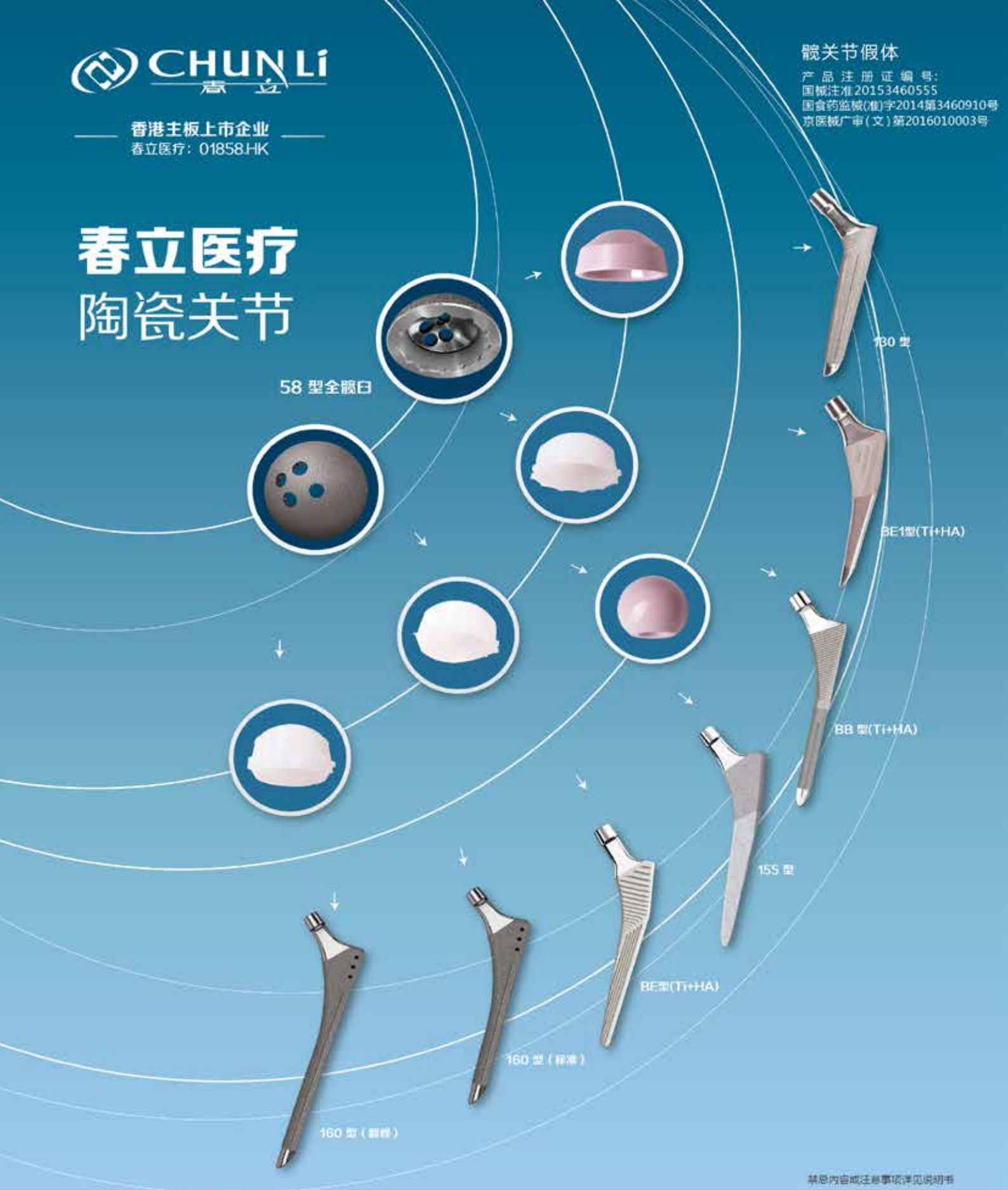

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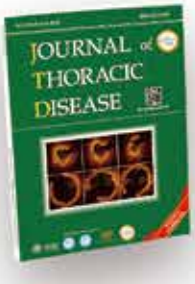

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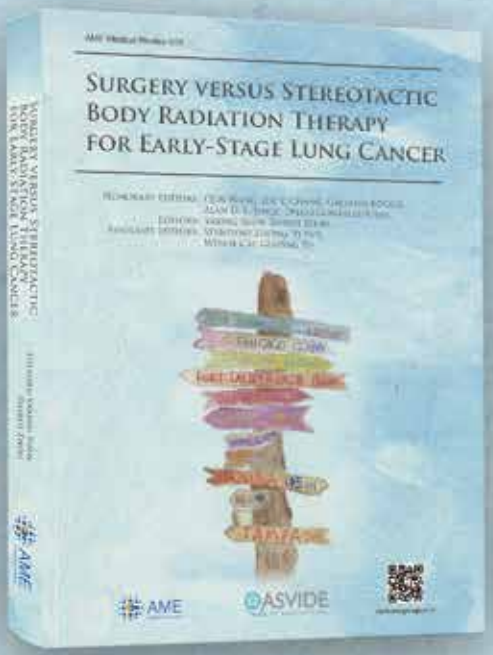

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